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Original article

Donor age is a predictor of early low output after heart transplantation

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ABSTRACT

Background: Using hearts from marginal donors could be related to increased risk of primary graft dysfunction and poor long-term survival. However, factors associated with delayed myocardial recovery after heart transplantation (HTx) remain unknown. We sought to clarify risk factors that predict early low output after HTx, and investigated whether early low output affects mid-term graft dysfunction.
Methods: We retrospectively analyzed patients who had undergone HTx at The University of Tokyo Hospital. We defined early low output patients as those whose cardiac index (CI) was <2.2 L/min/m^2 despite the use of intravenous inotrope at 1 week after HTx.
Results: We included 45 consecutive HTx recipients, and classified 11 patients into early low output group, and the others into early preserved output group. We performed univariable logistic analysis and found that donor age was the only significant factor that predicted early low output (odds ratio 1.107, 95% confidence interval 1.034–1.210, $p = 0.002$). CI of early low output patients gradually increased and it caught up with that of early preserved output patients at 2 weeks after HTx (2.4 ± 0.6 L/min/m^2 in early low output group vs 2.5 ± 0.5 L/min/m^2 in early preserved output group, $p = 0.684$). Plasma B-type natriuretic peptide concentration of early low output patients was higher (1118.5 ± 1250.2 pg/ml vs 526.4 ± 399.5 pg/ml; $p = 0.033$) at 1 week, 703.6 ± 518.4 pg/ml vs 464.6 ± 509.0 pg/ml ($p = 0.033$) at 2 weeks, and 387.7 ± 231.9 pg/ml vs 249.4 ± 209.5 pg/ml ($p = 0.010$) at 4 weeks after HTx, and it came down to that of early preserved output patients at 12 weeks after HTx.
Conclusions: Donor age was a predictor of early low output after HTx. We should be careful after HTx from old donors. However, hemodynamic parameters of early low output patients gradually caught up with those of early preserved output patients.

Introduction

Heart transplantation (HTx) is an established procedure that shows a satisfying long-term outcome for end-stage heart failure (HF) patients. However, this therapy is limited by donor organ shortage. In particular, in Japan, the donor shortage has been more severe than in other developed countries. By October 31, 2014, only 215 hearts had been procured for HTx in Japan since Japanese organ transplantation law was issued in 1997. A mean waiting time for HTx was extraordinarily long, namely 981 days in 2013 [1]. Therefore, ventricular assist devices (VADs) had to be implanted in most patients as a bridge to transplant [2]. The organ shortage and long waiting time have forced Japanese transplant programs to consider the use of hearts from donors who were considered to be marginal.

Regarding the use of marginal donors, we should be careful about the occurrence of primary graft dysfunction (PGD) and/or poor long-term survival. From a consensus conference at the 33rd Annual International Society of Heart and Lung Transplant (ISHLT) meeting, PGD was defined as heart failure without secondary

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reasons developing within 24 h after HTx [3]. PGD is the major cause of early death after HTx, and there have been many reports about risk factors for the development of PGD, including donor age [4], recipient age [5], ischemic time of donor heart [6], female donor [7], donor-to-recipient weight mismatch [8], small donor heart [9], and so on. Therefore using marginal donors could be related to increased risk of PGD. Long-term survival after recovery from PGD remains unknown, but some reports have shown that the long-term survival of patients who had suffered from PGD and survived was similar to non-PGD patients [10,11].

On the other hand, risk factors for delayed myocardial recovery after HTx, which may be different from those of PGD, have not been fully understood. In this study, we sought to clarify risk factors in our institute that predict early low output at 1 week after HTx, meaning delayed myocardial recovery. We also investigated whether early low output affects long-term graft dysfunction or not.

Materials and methods

Patient selection

We retrospectively included 49 consecutive recipients, who had received HTx between May 2006 and October 2014 at The University of Tokyo Hospital. Four recipients were excluded because of data insufficiency, and we finally included 45 HTx recipients in this study. All grafts were harvested from beating-heart brain-dead donors, preserved using a cold crystalloid heart preservation solution (Celsior) and stored in cold condition during transportation. All recipients except one had received VAD before HTx. HTx was performed according to the standard procedure with Lower–Shumway or modified bicaval anastomosis technique. All patients were treated with a standard immunosupression regimen including one of calcineurin inhibitors, mycophenolate mophetil, and prednisolone. Some recipients received everolimus with/without discontinuation of mycophenolate mophetil and reduction of calcineurin inhibitor doses. Doses of immunosuppressant were controlled under the scheduled monitoring of trough concentration as described previously [12]. Written informed consent was obtained from all patients and family members before HTx.

According to our facility criteria for donor selection, in this study we have not used donors with age >66 years. Also we did not use donors with inotrope score >20, and left ventricular ejection fraction (LVEF) <50%.

Cardiac catheterization

Scheduled serial right heart catheterization and endomyocardial biopsy from right ventricular septal wall were performed at every week until post-HTx 4 weeks, every 2 weeks until post-HTx 12 weeks, and every 4 weeks until post-HTx 24 weeks. In this study we collected data at 1, 2, 4, 12, and 24 weeks after HTx [12].

For hemodynamic evaluation, a Swan-Ganz catheter was introduced from the femoral or jugular vein. Then, the hemodynamic parameters, including mean right atrial pressure (mRAP), right ventricular pressure, mean pulmonary capillary wedge pressure (mPCWP), and mean pulmonary arterial pressure (mPAP) were determined [13]. Cardiac index (CI) was measured by the thermodilution method, because no patients had severe tricuspid valve regurgitation after HTx. Stroke volume (SV) was calculated from cardiac output and heart rate (HR). Endomyocardial biopsy was performed as previously described [14].

Echocardiographic examination

Transthoracic echocardiography was performed sequentially after HTx. Routine echocardiographic parameters including left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), LVEF, interventricular septum thickness (IVS), posterior wall thickness (PW), and color Doppler parameters were obtained [15]. We collected data at about 1, 2, 4, 12, and 24 weeks after HTx. Left ventricular hypertrophy (LVH) was defined as IVS or PW wall thickness >11 mm at parasternal long-axis view [16]. Small donor heart was defined as LVDd <36 mm as previously described [9].

Variables evaluated

Preoperative parameters including donors/recipients' demographics, surgical procedures and donor–recipient relationships were obtained. High dose inotropes were defined as inotrope score >10, which was defined as dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) with each drug dosed in μg/kg/min [3]. As doses of inotropes for donor change by time, we selected the latest doses at the time when the donor information was given to us. As for donors' echocardiographic data, we also selected the latest data before the harvest. Donor–recipient sex mismatch was defined as female donor to male recipient.

In this study, we defined early low output group as patients whose CI <2.2 L/min/m^2 despite the use of intravenous inotrope at 1 week after HTx. We defined early low output as the primary endpoint. We also defined the other patients as early preserved output group.

Statistical analysis

Categorical variables were summarized as frequencies and percentages, and compared using Chi-square test or Fisher's exact test as appropriate. Continuous variables were represented as mean ± standard deviation (SD) unless otherwise specified, and compared using unpaired *t*-test or Mann–Whitney test as appropriate. Logistic regression analyses were performed to find significant predictors among baseline parameters. Kaplan–Meier survival analysis was performed to evaluate survival after HTx on two groups, and survival among these groups was compared by log-rank test.

The cut-off point of the variable was determined based on receiver-operating characteristic (ROC) analysis with JMP9 (SAS Institute Inc., Cary, NC, USA). All tests reported were two-tailed, and used a p-value <0.05 as significant. All statistical analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA) except for the ROC analysis with JMP9 [2].

Results

Baseline characteristics

Table 1 shows the baseline characteristics of all patients. Forty-five patients were included. Regarding donor characteristics, the donor age was 44 ± 14 (11–66) years, and 49% were male. Cerebrovascular causes for the brain death were found in 53% of the donors. A history of cardiopulmonary resuscitation >5 min was found in 44%. High-dose catecholamine of inotrope score >10 was found in 22%, but inotrope score >20 was found in no patients. Also donors who were >66 years and with LVEF <50% were not selected for HTx.

Regarding recipient characteristics, the recipient age was 41 ± 14 (13–62) years and 69% were male. Ischemic cause for HF was found in 16% of the patients. Twenty-four patients (53%) had paracorporeal VAD implanted before HTx and 20 patients implantable VAD. One patient had been managed with continuous intravenous infusion of inotropes.

During the perioperative period, total ischemic time was 248 ± 40 (156–331) min and pump time for surgical procedure