Effect of Therapeutic Modification on Outcomes in Heart Transplantation Over the Past Two Decades
— A Single-Center Experience in Japan —

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Background: During these 2 decades (1999–2019), many therapeutic strategies have been developed in the field of heart transplantation (HTx) to improve post-HTx outcomes. In the present study, 116 consecutive HTx adults between 1999 and 2019 were retrospectively reviewed to evaluate the influences of a therapeutic modification on post HTx outcomes.

Methods and Results: Patient survival, functional status and hemodynamics after HTx and modification of therapeutic strategies were reviewed. The overall cumulative survival rate at 10 and 20 years post-HTx was 96.4 and 76.7%, respectively. There were no significant differences in survival rate or exercise tolerance after HTx between extracorporeal and implantable continuous flow-LVAD.

Post-HTx patient survival in patients, irrespective of the donor risk factors such as donor age, low LVEF, history of cardiac arrest, was equivalent across cohorts, while longer TIT and higher inotrope dosage prior to procurement surgery were significant risk factors for survival. In 21 patients given everolimus (EVL) due to renal dysfunction, serum creatinine significantly decreased 1 year after initiation. In 22 patients given EVL due to transplant coronary vasculopathy (TCAV), maximum intimal thickness significantly decreased 3 years after initiation.

Conclusions: The analysis of a 20-year single-center experience with HTx in Japan shows encouraging improved results when several therapeutic modifications were made; for example, proactive use of donor hearts declined by other centers and the use of EVL in patients with renal dysfunction and TCAV.

Key Words: Heart transplantation; Immunosuppression; Left ventricular assist device; Marginal donor

The Japanese Organ Transplant Act came into effect in October 1997 and the first heart transplantation (HTx) under this Act was performed at Osaka University Hospital in February 1999 and the second and third ones at the National Cerebral and Cardiovascular Center (NCVC). The annual number of HTx procedures increased steadily to ~10, but rose sharply to 84 in 2019 after a revision of the Act in July 2010, and the total HTx exceeded 500 at the end of 2019. One hundred and thirty-three HTxs of them have been performed at the NCVC.

During these 2 decades (1999–2019), many therapeutic strategies have been developed in the field of HTx to improve pre- and post-HTx outcomes. For those patients waiting for HTx, the Japanese insurance coverage was extended to the continuous flow-type of implantable left ventricular assist device (CF-LVAD) in April 2011; the total number of CF-LVAD implantation patients enrolled in the Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) increased to nearly 1200 at the end of 2019, of which were implanted at the NCVC. Before approval of CF-LVAD, most HTx recipients were bridged with the Nipro-Toyobo extracorporeal LVAD (E-LVAD; Nipro Co., Ltd, Osaka, Japan) at the NCVC as well as at other centers. Regarding donor selection, we...
started to proactively use a marginal donor heart declined by other HTx centers due to medical reasons since April 2016 to increase the chances of our marginal recipients to undergo HTx.

Regarding the immunosuppressive regimen, since 2007, we have primarily considered converting from mycophenolic molestil (MMF; Cellcept®, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) with standard-dose calcineurin inhibitors (CNIs) to everolimus (EVL; Certican®, Novartis Pharma Co., Ltd., Tokyo, Japan) with low-dose CNIs for the recipients with impaired renal function, those with increases in or an initially large maximal intimal thickness (MIT) on routine intravascular ultrasound (IVUS) examinations and those with MMF-related leukopenia. Basiliximab has been used since 2006 as an alternative for muronomab-monoclonal CD3 in de novo heart transplant recipients with impaired renal function, high anti-HLA antibodies, and recipient- and donor-related risk factors.6

In the present study, 116 consecutive HTx cases were retrospectively reviewed to evaluate the influences of these therapeutic modifications on outcomes of HTx for 20 years after HTx was initiated in 1999 in Japan.

Methods

Study Design

This was a single-center, retrospective, observational analysis to assess the influence and interdependence of immunologic and non-immunologic risk factors on the outcomes after HTx. Overall, 122 consecutive patients who received HTx between May 1999 and June 2019 at the NCVC were included in this study. Of these, 7 recipients aged <18 years were excluded. The primary endpoint of this study was overall survival for 20 years after HTx. The secondary endpoints were post-HTx patient survival by bridge-to-transplant (BTT) strategies; post-HTx patient survival and peak oxygen consumption (VO2) by donor decline number and marginal donor score; acute cellular rejection (ACR)-free survival by type of CNI; serum creatine level and MIT before and after initiating EVL; and viral loads of Epstein-Barr virus (EBV) before and after a decrease in steroid dosage. Patient characteristics, such as recipient status, donor status, waiting status and period, immunosuppressive therapy regimen, and survival rates were collected.

The study protocol was approved by the Institutional Review Board (IRB) of the NCVC (IRB number M30-026-2). Informed consent was obtained from all participants.

Bridge-to-Transplantation Strategies

After insurance coverage was extended to CF-LVAD in April 2011, the most commonly used LVAD for BTT at the NCVC changed from E-LVAD to CF-LVAD, in accordance with other centers in Japan. However, even now, we still use E-VAD including pulsatile and centrifugal pumps for initial short-term ventricular support, as a bridge-to-decision or candidacy treatment, in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) levels 1 and 2 patients. After the patient is determined as a HTx candidate, E-VAD was exchanged to CF-LVAD, which is known as the bridge-to-bridge (BTT) strategy, which can provide a safer BTT.

Donor Assessment and Management, and Donor Heart Selection

Although the Organ Transplant Act was revised in July 2010,7 brain-dead donor organ donation (50 cases in a year) in Japan has still been significantly lower than that for other developed countries. To increase organ availability, special strategies to assess and manage donors; that is, the medical consultant (MC) system, have been established since 2002.8 Briefly, cardiac transplant surgeons or physicians are sent to a donor hospital to evaluate which organ can be transplanted, and stabilize hemodynamics and respiratory function using anti-diuretic hormones and frequent bronchoscopes in collaboration with physicians at the donor hospital.

The decline in the number of suitable donor hearts has led to an increasing interest in the use of previously unacceptable donors. In Japan, if 1 candidate declines a donor heart, it may be offered to other candidates. Since April 2016, we have started to proactively transplant marginal donor hearts declined by other institutes. Regards to old donor age, the immunosuppressive regimen was not different between patients transplanted with hearts from donors aged ≥50 and <50 years. But in patients transplanted with hearts from donors aged ≥60 years, the expected transport time limit was set within 120 min. Regardless of donor age, if donor coronary artery disease was suspected as a result of chest CT findings or examination by touch, a coronary artery angiogram was conducted in the first week after HTx to confirm whether there were coronary artery lesions requiring therapeutic intervention.

Immunosuppressive Protocol After HTx

All de novo HTx recipients at the NCVC received triple immunosuppressive therapy consisting of CNIs (i.e., cyclosporine A [CsA] or tacrolimus [Tac]), MMF, and corticosteroids.6 We regulated immunosuppressive drug dosage based on blood trough concentrations. Target trough levels of CsA (Neoral®; Novartis Pharma Co., Ltd., Tokyo, Japan) and Tac (Prograf®; Astellas Pharma Inc., Tokyo, Japan) were controlled, as previously described.6 Tac was used as an alternative to CsA as the primary immunosuppressant since 2005.6

At the beginning of our HTx program, methylprednisolone 500 mg intravenous (IV) was given at the initiation of surgery and the time of aortic unclamping intraoperatively, and tapered daily to 70 mg at the 7th postoperative day. This was followed by oral prednisolone (PSL) 1 mg/kg daily. This was gradually tapered to 5 mg/day at 6 months after HTx. Due to improvement in the immunosuppressive regimen, the dose of steroid given was decreased. Currently, methylprednisolone 500 mg IV is given at the time of aortic unclamping intraoperatively, followed postoperatively at 125 mg IV every 8 h for three doses. This was tapered down in increments of 0.125 mg · kg⁻¹ · day⁻¹ every 2 days to 0.25 mg · kg⁻¹ · day⁻¹ at the 12th post-HTx day and then it was switched to oral PSL at a dose of 20 mg/day. If endomyocardial biopsy revealed no treat-need rejection, PSL was tapered down to 15 mg/day at 5 weeks after HTx and the patient was discharged. PSL was gradually tapered off during 6–12 months after HTx if there was no rejection episode. Since April 2016, the declining speed of PSL administration has been increased to avoid post-HTx infection, especially viral infections.

MMF was given at 1.000 mg per oral dose twice daily postoperatively and increased with a target dose of 2 g daily.
Once target trough levels of EVL (6–8 ng/mL) were achieved, the CNI dose was reduced to obtain target trough levels, as previously described.\(^6\) Induction therapy has been considered for recipients with impaired renal function, high anti-HLA antibodies, and those with increases in or an initially large MIT on routine IVUS examinations, and those with MMF-related leukopenia.

Since 2007, we have primarily considered converting from MMF with standard-dose CNIs to EVL with low-dose CNIs for the recipients with impaired renal function, those with increases in or an initially large MIT on routine IVUS examinations, and those with MMF-related leukopenia.

### Table 1. Pretransplant Condition of Heart Transplant Recipients Before and After Approval of CF-LVAD

| Pretransplant condition | Total (n=115) | Before approval (n=52) | After approval (n=63) |
|-------------------------|--------------|------------------------|----------------------|
| Inotrope                | 7 (6)        | 3 (6)                  | 4 (6)                |
| NIPRO-TOYOBO            | 48 (42)      | 41 (79)                | 7 (11)               |
| HeartMate XVE           | 2 (2)        | 2 (4)                  | 0 (0)                |
| Novacor                 | 1 (1)        | 1 (2)                  | 0 (0)                |
| EVAHEART                | 12 (10)      | 1 (2)                  | 11 (17)              |
| DuraHeart               | 7 (6)        | 0 (0)                  | 7 (11)               |
| Jarvik2000              | 6 (5)        | 1 (2)                  | 5 (8)                |
| HeartMateII            | 28 (24)      | 1 (2)                  | 27 (43)              |
| HVAD                    | 1 (1)        | 0 (0)                  | 1 (2)                |

The pretransplant conditions of heart transplant recipients before and after approval of CF-LVAD in Japan (April 2010) are shown. Data are presented as n (%). The pretransplant conditions between the groups were significantly different in the Pearson's \(\chi^2\) test \(P<0.05\). CF-LVAD, implantable continuous flow left ventricular assist device.
Diagnosis and Treatment of Acute and Chronic Rejection

ACR was defined as either biopsy-proven, as defined by ISHLT grade 3R (3A or 3B) or higher histology, suspected and subsequently treated rejection in the presence of hemodynamic compromise, or grade 1A or 1B with symptoms or signs.

Treatment of ACR typically consisted of intravenously administered methylprednisolone 500 g to 1,000 g for 3 days. Grade 2 rejection or symptomatic low grade (1A or 1B) rejection used to be treated with a 50–80 mg prednisone tapering dose. Since April 2015, oral steroid pulse therapy (PSL 100 mg/day for 3 days) has been given, even in patients with more than a grade 3A rejection, if the rejection episode occurred after 3 months of HTx and asymptomatic to avoid post-HTx infection, especially viral infections.

Endomyocardial Biopsy and Intra-Coronary Ultrasound

Scheduled endomyocardial biopsies were performed at 1, 2, 3, 5, 7, and 11 weeks, 4.5, 6, 9, 12 months, then every 6 months until 5 years, annually after 5 years after transplant or whenever ACR or antibody-mediated rejection (AMR) was clinically suspected. Histopathologic results were based on the International Society of Heart and Lung Transplantation (ISHLT) standardized cardiac biopsy grading.\textsuperscript{10,11} Additionally, AMR was monitored by checking the panel reactive antibody test, presence of donor-specific antibody, and pathological findings on endomyocardial biopsy. Coronary angiography and IVUS were performed within the first week to 11 weeks, at 12 months and annually thereafter after HTx.

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patients with asymptomatic rejection with low grade 1B
and grade 2, no steroid pulse therapy was applied and the
doses of CNI and MMF were not modified or slightly
increased.

Prophylaxis and Therapy Protocol for Infectious Diseases
We selected peri-operative antibiotics based on microbi-
ologic sensitivities. Prophylaxis for bacterial infections
include broad-spectrum drugs against gram-positive
organisms and gram-negative bacilli. For fungal infections,
IV antifungals are administered. Regarding EBV infection,
EBV deoxyribonucleic acid (DNA) is routinely monitored
in polymerase chain reaction (PCR) tests.

Myocardial Protection Fluids and HTx Procedures
For myocardial protection, St. Thomas was used in the
initial 7 cases and Celsior has been used until now. After
a modified bicaval technique was introduced by Kitamura et
al,12 this method was used in 114 cases, with the exception
of 2 cases who had a congenital heart anomaly.

Statistical Analysis
Continuous variables are expressed as mean±standard
deviation or as median (interquartile range), as appropriate.
Adverse events are presented as both percentages and event
rates (events per patient-year of support [EPPY]). The 2
groups were compared using an unpaired t-test for data with
normal distribution or a Mann-Whitney U-test for data with
normal distribution. Categorical variables are expressed as
number and frequency. Kaplan-Meier analysis was used to
evaluate overall survival and transplantation. Statistical analysis was performed using JMP version 10
(SAS Institute Inc., Cary, NC, USA).

Results

Demographics and Pretransplant Condition
Initially, there were approximately 2 or 3 HTx cases per
year at the NCVC after the Organ Transplantation Act was
issued in 1997, but the revision of the Act caused a sharp
rise in HTxs to over 10 per year, and in 2017, the figure
reached 19 (Figure 1). Of the 116 adult HTx recipients, 89
(76.7%) are male. The age of recipients ranged from 17 to
66 years, with an average age of 40.4±13.2 years. Underlying
diseases among HTx recipients were: dilated cardiomyopathy
in 76 (66%), dilated phase hypertrophic cardiomyopathy
in 12 (10%), ischemic cardiomyopathy in 7 (6%), muscular
dystrophy in 6 (5%), post-myocarditis in 4 (3%), sarcoidosis
in 4 (3%), arrhythmogenic right ventricular cardiomyopathy
in 2 (2%), congenital heart disease in 1 (1%) and others.

Of the 116 procedures, 108 cases were on BTT with a
LVAD. No cases were implanted with bilateral ventricular
VAD. After approval of CF-LVAD, mostly implanted
LVAD was changed from E-LVAD to CF-LVAD, which
is currently HeartMate II (Figure 1A, Table 1), as previously
described.13 Mean Status 1 waiting time was 300 days
between 1999 and 2001, increasing to 1,038 days at the time
of revision of the Act, once decreasing to 894 days between
2009 and 2011 and rising again to 1,271 days (Figure 1B).

Overall Outcomes After HTx
The cumulative survival rate at 5, 10, 15 and 20 years
after HTx were 96.4, 96.4, 92.0 and 76.7%, respectively
(Figure 2A). Interestingly, there were no significant differ-
ences in the cumulative survival rate at 2, 6, and 10 years
between E-LVAD and CF-LVAD (97.9, 93.6 and 93.6% in
p-LVAD vs. 100, 100 and 100% in CF-LVAD, respectively,
P=0.337) (Figure 2B). As none of the recipients supported
with CF-LVAD died during 10 years after HTx, there
were no differences in the cumulative survival rate among
the type of CF-LVAD used, such as EVAHeart (N=12),
DuraHeart (N=7), Jarvik2000 (N=6), HVAD (N=1) and
HeartMate II (N=32).

Although it is possible that compared to patients with
primary CF-LVADs, the BTT patients are more likely to
develop complications and have decreased patient survival
after HTx, and there were no significant differences in the
cumulative survival rate at 2 and 4 years between BTT
patients and non-BTT patients (100 and 100% [N=9] vs.
100 and 100% [N=60], respectively) (Figure 2C).

Demographic Characteristics of the Heart Donor and Their
Effect on Survival Rate After HTx
To elucidate the role of this donor evaluation and manage-
ment system, 115 consecutive HTx recipients until the end
of June 2019 were reviewed.

Patient survival at 2, 6 and 10 years who had a donor
aged <50 years (N=76) was not significantly different from
the survival of those who had a donor aged ≥50 years
(N=39) (Figure 3A). Patient survival at 2, 6 and 10 years
who had a donor within <240 min of total ischemic time
(TIT) (N=111) was significantly higher than those who had
a donor with ≥240 min of TT (N=4) (100, 97.1 and 97.1
% vs. 75.75 and 75.75%, respectively; P=0.035) (Figure 3B).
Patient survival at 2, 6 and 10 years who had a donor without
a history of cardiac arrest (N=54) was not significantly different
from those who had a donor who experienced
a cardiac arrest (N=61) (Figure 3C). Patient survival at 2,
6 and 8 years who had a donor heart with >50% left
ventricular ejection fraction (LVEF) (N=112) was not
significantly different from those who had a donor who had
≤50% LVEF (N=3) (Figure 3D). There was no significant
difference among patient survival at 2, 6 and 10 years
where the donor died of: subarachnoid hemorrhage (N=37),
head trauma (N=13), subdural hematoma (N=4), asphyxia
(N=40), cerebral infarction (N=3), brain tumor (N=2) and
other stroke (N=16) (Figure 3E). However, patient survival at
2, 6 and 10 years who had a donor who was given with
<10 µg·kg⁻¹·min⁻¹ of inotropic agents or epinephrine
(N=100) was significantly higher compared with patient
survival for those who had a donor who was given ≥10 µg·
kg⁻¹·min⁻¹ of inotropic agents or epinephrine (N=15)
(100, 100 and 100% vs. 93.3, 76.4 and 76.4%, respectively;
P<0.0001) (Figure 3F).

Effects of the Donor’s Risk Factor on the Exercise Capacity
of Recipients Early on After HTx
Although previous studies have shown that the recipients
exhibit improvements in exercise capacity and performance
after HTx, the recipients often have a lower exercise capacity
than normal healthy age and gender-matched controls in
the early period or long after HTx. In the present study, the
effects of the recipient and donor risk factors on the patient’s
exercise capacity early on after HTx were investigated.

We retrospectively reviewed the medical records of 50
HTx recipients who received a transplantation from April
2010 to November 2016 at the NCVC in Japan. Three
weeks after a HTx, if patients have had no episodes of
rejection or other adverse events, a 3-month program of
rehabilitative exercise under the supervision of experienced
Figure 3. Cumulative patient survival after heart transplantation at the National Cerebral Cardiovascular Center between May 1999 and June 2019. Each figure shows (A) by donor age, (B) by TIT, (C) by history of cardiac arrest; (D) by LVEF; (E) by cause of brain death; and (F) by usage of high-dose inotropes. TIT, total ischemic time; LVEF, left ventricular ejection fraction.
Outcomes in HTx Over the Past Two Decades

Effect of CNI on Acute Cellular Rejection Early After HTx
Tac was used as an alternative to CsA as the primary immunosuppressant beginning in 2005. ACR-free survival at 1, 2 and 3 years in patients who were given Tac (N=102) were significantly higher compared with those given CsA (N=18) (96.9, 96.9 and 96.9% vs. 94.4, 83.3 and 83.3%, respectively; P<0.001) (Figure 4).

Mid-Term Effectiveness of EVL on Heart Transplant Recipients With Renal Dysfunction or Transplant Coronary Artery Atherosclerosis
In the present study, EVL efficacy on renal dysfunction and TCAV were assessed. Of 69 patients in whom MMF was converted to EVL, 21 patients who were initiated EVL due to renal dysfunction with a longer than 1-year follow up of serum creatine and 22 patients with TCAV with a longer than 3-year follow up of annual MIT measurement

Table 2. Changes From Baseline to the 3-Month Follow up in Cardiopulmonary Exercise-Test Measurement Results Compared by Recipient and Donor Risk Factors

| Recipient risk factors         |  |  |  |  |
|-------------------------------|--|--|--|--|
| Recipient age (years)         |  |  |  |  |
| <50              | 30 | 19.1±4.0 | 24.2±5.4 | <0.01 |
| ≥50              | 11 | 15.4±3.2 | 18.6±3.5 | 0.019 |
| P-value between 2 groups     | <0.01 | <0.01 |  |
| Underlying heart disease     |  |  |  |  |
| DCM               | 21 | 18.6±4.0 | 23.0±5.9 | <0.01 |
| dHCM              | 10 | 17.8±4.2 | 21.8±6.2 | <0.01 |
| Others            | 10 | 17.4±3.3 | 22.8±4.4 | 0.05 |
| P-value between 2 groups   | 0.72 | 0.85 |  |
| LVAD type          |  |  |  |  |
| E-LVAD            | 16 | 19.4±4.8 | 25.6±5.9 | <0.01 |
| CF-LVAD           | 24 | 17.3±3.6 | 20.6±4.3 | 0.019 |
| P-value between 2 groups | 0.30 | 0.011 |  |
| Donor risk factors   |  |  |  |  |
| Donor age (years)     |  |  |  |  |
| ≥50               | 13 | 16.6±3.3 | 20.8±4.8 | <0.01 |
| <50               | 28 | 18.8±4.4 | 23.5±5.7 | <0.01 |
| P-value between 2 groups | 0.12 | 0.14 |  |
| LVEF (%)           |  |  |  |  |
| <55               | 5  | 20.8±5.9 | 28.2±5.7 | <0.01 |
| ≥55               | 36 | 17.8±3.8 | 21.9±5.1 | <0.01 |
| P-value between 2 groups | 0.13 | 0.015 |  |
| History of cardiac arrest |  |  |  |  |
| Yes               | 25 | 17.9±4.0 | 21.5±4.5 | <0.01 |
| None              | 16 | 18.4±4.6 | 24.5±6.5 | <0.01 |
| P-value between 2 groups | 0.73 | 0.09 |  |
| TIT (min)         |  |  |  |  |
| ≥240             | 2  | 16.6±0.2 | 23.2±6.9 | <0.01 |
| <240             | 39 | 18.2±4.2 | 22.6±5.6 | <0.01 |
| P-value between 2 groups | 0.59 | 0.88 |  |
| High dose requirement of inotropes |  |  |  |  |
| Yes               | 4  | 16.2±1.4 | 22.1±2.8 | 0.022 |
| None              | 37 | 18.3±4.3 | 22.7±0.9 | <0.01 |
| P-value between 2 groups | 0.34 | 0.85 |  |

DCM, dilated cardiomyopathy; dHCM, dilated phase of hypertrophic cardiomyopathy; E-LVAD, extracorporeal LVAD; CF-LVAD, implantable continuous flow LVAD; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; TIT, total ischemic time.

personnel was initiated. Each recipient underwent a symptom-limited cardiopulmonary exercise test at the start and at the end of the 3-month program.

The peak oxygen consumption (VO2) was significantly increased in patients after the 3-month program, irrespective of recipient factors, such as recipient age, underlying heart disease and type of LVAD and donor risk factors, such as donor age, low LVEF of the donor heart, history of cardiac arrest, long TIT and high inotrope dosage prior to procurement surgery. Younger recipient age was significantly associated with higher peak VO2 at the start and at the end of the 3-month program. However, the peak VO2 at the start and end of the 3-month program was equivalent between patients with and without main recipient or donor risk factors predictive on heart recipient survival, which included the type of LVAD and marginal donor heart factors (Table 2).
by IVUS, were enrolled in this study.

In 21 patients given EVL due to renal dysfunction, serum creatinine was significantly decreased from initiation of EVL to 1-year after initiation (1.44±0.32 vs. 1.23±0.36 mg/dL; P=0.0004), but that did not significantly change since then (Figure 5A). In 22 patients given EVL due to TCAV, MIT was significantly decreased from initiation of EVL to 3 years after initiation (1.20±0.38 mm vs. 1.00±0.40 mm, P<0.001; Figure 5B).

**Effects of Steroid Tapering on EBV Load**

As described above, the tapering speed of oral PSL after 6 months of HTx has increased since April 2016. Therefore, the dose of PSL at 26 weeks post-HTx after April 2016 was not significantly different from that at before April 2016 (8.79±3.26 vs. 8.18±3.04 mg, respectively); however, at 52 weeks post-HTx after April 2016, the dose was significantly lower than that used before April 2016 (4.73±0.52 vs. 3.41±0.55 mg/day, respectively). The positive rate of EBV-PCR over 1 year after HTx, after April 2016, was significantly lower than that before April 2016 (10/43 [23.2%] vs. 25/37 [67.6%], respectively; P=0.003).

**Discussion**

The Japanese Organ Transplant Act came into effect in October 1997 and the first HTx procedure was performed in February 1999. The number of procedures increased steadily to ~10 per year, but then rose sharply to 84 in 2019 after a revision of the Act in July 2010. However, the number of HTx procedures remains low in international terms, and the mean waiting period exceeded 1,310 days at the end of 2018. These changes are very similar to those in the present study. The long waiting times have not improved despite higher rates of HTx procedures performed since the legislative amendments, probably because of the rapid increase in patients listed as a HTx candidate and improvement of survival during waiting by use of CF-LVAD. Therefore, the use of CF-LVAD may have a greater role in prolonging patient survival and improving activities of daily living (ADL) while patients wait for a HTx, as previously described. However, the effects of LVAD type on patient survival and ADL have not been elucidated.

In the present study, patient survival after HTx in patients with E-LVAD was not significantly different from that in patients with CF-LVAD. Moreover, peak VO2 after HTx...
in patients with E-LVAD was also not significantly different from that in patients with CF-LVAD. Only recipient age and several nutrition factors at the start of the 3-month exercise training program were associated with peak VO₂: at the start or the end of the 3-month program,¹⁴ and these data suggested that nutrition management and rehabilitation at the bedside between the time of HTx and the start of the 3-month program play a significant role in increasing peak VO₂ at the start of the rehabilitation program. Although E-LVAD required a significantly longer hospital stay during the wait for a HTx and had higher risk for cerebral events than CF-LVAD, well-maintained patients with E-LVAD had a similar prognosis and exercise tolerance after HTx as patients with CF-LVAD.

Although it is easily speculated that compared to patients with primary implantable LVADs, the BTB patients are more likely to develop complications after HTx, in our experience, there was no significant differences in the cumulative survival rate after HTx between BTB and non-BTB patients in the present study. Although the second official report of J-MACS⁸ reported that survival rate of patients with primary CF-LVAD was significantly higher than that of patients undergoing BTB (93% vs. 86% at 360 days and 91% and 82% at 720 days; P=0.0499), a change from E-VAD to CF-LVAD, known as the BTB strategy, can provide a good post-HTx prognosis, as well as a safer BTT.

As a consequence of the severe shortage of donor organs in Japan, marginal donor organs have been utilized as much as possible in many countries. However, only 3,408 hearts of 8,589 brain-death donors (39.6%) were transplanted in Japan and the cumulative survival rate at the end of August 2019, and because of the very strict Japanese Organ Transplantation Act, only 264 HTx would be considered marginal. Therefore, an original and innovative program consider the use of donor organs that would be considered marginal. Therefore, an original and sophisticated donor evaluation and management system has been established in Japan; for example, MC and pre-procurement meetings as described above.⁸ By these efforts, 476 hearts of 625 brain-dead donors (76.2%) were transplanted in Japan and the cumulative survival rate at 5, 10, 15 and 20 years after HTx was 92.8, 89.8, 83.7 and 77.7%, respectively.⁴ In the present study, the cumulative survival rate at 5, 10, 15 and 20 years after HTx at the NCVC were 96.4, 96.4, 92.0, 91.6% and 76.7%, respectively. These data were equivalent to that found in the national NCVC were 96.4, 96.4, 92.0, 91.6% and 76.7%, respectively.

Outcomes in HTx Over the Past Two Decades

As previously reported, by these efforts, 287 (75%) of 384 donor hearts (including 3 heart–lung transplantations) were transplanted. Although 20 heart grafts from donors aged 260 years at the time of the procedure were transplanted, there was no significant difference in patient survival by donor age group. The most common cause of brain death of the donor was: subarachnoid hemorrhage (95), followed by anoxia (58), head trauma (53), cerebral hemorrhage (29), post-resuscitation (19), cerebral infarction (5) and others. Interestingly, there is no significant difference in patient survival by cause of brain death of the donor. These data suggest that the MCs may play a greater role in increasing donor heart availability and in improving the outcomes of cardiac recipients from older donors or donors who died of post-resuscitation and anoxia in Japan.

In the present study, post-HTx patient survival in patients, irrespective of the donor risk factors, such as donor age, low LVEF, history of cardiac arrest, were equivalent across cohorts, while longer TIT and higher inotrope dosage prior to procurement surgery were significant risk factors for survival. Regarding longer TIT, there were only 4 cases and only 1 died early post-HTx. This patient had dextrocardia, which would increase operative complexity and TIT. Therefore, it was difficult to conclude that longer TIT was a risk factor for survival. In contrast, inotrope dosage prior to procurement surgery might be a considerable risk factor. Regarding ADL after HTx, the peak VO₂ was significantly increased after the 3-month exercise program in patients irrespective of donor risk factors, such as donor age, low LVEF of the donor heart, history of cardiac arrest, TIT and inotrope dosage prior to procurement surgery. Moreover, the peak VO₂ at the start and end of the 3-month exercise program were equivalent between patients with and without main recipient or donor risk factors predictive of heart recipient survival, which included the type of LVAD and marginal donor heart factors. These data suggested that an appropriately selected donor heart can provide good prognosis and improved ADLs for the recipient after HTx.

As reported in the ISHLT registry report, Tac was used as an alternative to CsA as the primary immunosuppressant since 2003 in the NCVC, and ACR-free survival for patients treated with Tac was significantly lower than that in patients treated with CsA, even though patient survival between patients treated with Tac and CsA was equivalent at the NCVC as well as those in the ISHLT registry. Several investigators reported that de novo HTx patients randomized to receive either EVL and low-dose CNI followed by CNI-free therapy maintain significantly better long-term renal function as well as significantly reduced TCAV than patients randomized to receive standard CNI treatment. However, the effects of conversion from MMF to EVL on renal function or TCAV were not well elucidated. In the present study, conversion to EVL with low-dose CNI resulted in short-term improvement in renal function and TCAV in heart transplant patients. The MANDELA study showed that conversion from CNI to EVL with MMF (CNI-free) and reduced CNI with EVL (EVL/redCNI) improved and stabilized renal function based on 18 months post-HTx, with superiority of the CNI-free vs. EVL/redCNI patients, but there were higher rates of biopsy-proven acute rejection (BPAR). In total, 6/15 episodes in CNI-free patients occurred with a EVL concentration <5ng/mL. But in our experience, no BPAR was observed after MMF was converted to EVL, probably because the serum concentration of EVL and Tac was closely monitored. As mentioned above, once the target trough levels of EVL (6–8ng/mL) were achieved, the CNI dose was reduced and most patients tolerated the 6–8ng/mL EVL target level despite controllable mouse soars or leukopenia in some patients. But 6 of 69 patients who converted to EVL discontinued EVL because of moderate leukopenia in 2, interstitial pneumonia in 1, hemorrhagic intestinal ulcer in 1 and eosinophilic myocarditis in 1. In 4 of these 6 patients, adverse events disappeared after converting to MMF again, but 2 of them still had adverse effects after conversion to MMF (leukopenia in 1 and interstitial pneumonia in 1). Therefore, close monitoring of gastrointestinal ulcer including mouse soar, leukopenia.
and interstitial pneumonia is important when using EVL. EBV-seronegative recipients of HTx are at risk for the development of post-transplant lymphoproliferative disease (PTLD) following primary EBV infection, due to the ongoing treatment with immunosuppressive drugs. Therefore, an immunosuppressive regimen to prevent positivity of EBV-DNA is clinically important. In the present study, the increased tapering speed of oral PSL after 6 months of HTx resulted in a lower positive rate of EBVPCR over 1 year after HTx compared when the conventional protocol was used. This modification may play a role in reducing PTLD as well as EBV infection.

Conclusions

Our 20-year HTx analysis of a single-center experience in Japan shows encouraging improved results after several pre- and post-HTx therapeutic modifications. E-VAD exchanged to CF-LVAD, known as the BTB strategy, can provide a good post-HTx prognosis as well as a safer BTT. Proper donor selection for each particular recipient may increase heart availability without a decrease in patient survival. The conversion of MMF to EVL with reduced dose of CNI for patients with renal dysfunction and TCAV was effective to increase serum creatine and to reduce MIT, respectively.

Disclosures

H.O. is a Senior Advisory Editor of the Circulation Journal. Other authors have no conflicts of interest to declare. The de-identified participant data will not be shared.

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