Background: Long-term echocardiographic data on quantitative assessment of tricuspid and mitral regurgitation after heart transplantation are scarce.

Methods and Results: From November 1992 to December 2008, the medical records for 201 patients (mean age, 42.8±12.4 years, 47 females) who underwent heart transplantation were reviewed. Quantitative assessment of mitral and tricuspid valve function was performed using transthoracic echocardiography through long-term follow-up. A total of 196 (97.5%) patients were evaluated with echocardiography for more than 6 months postoperatively. During a mean echocardiography follow-up duration of 89.9±54.3 months, 23 (11.4%) patients showed either tricuspid regurgitation (TR >mild; n=21, 10.4%) or mitral regurgitation (MR >mild; n=6, 3.0%); 4 (2.0%) patients experienced both significant TR and MR. Freedom from moderate-to-severe TR at 10 years was 85.5±5.1% and 93.4±2.2% for the standard and bicaval techniques, respectively (P=0.531). Freedom from moderate-to-severe MR at 10 years was 96.0±2.7% and 98.6±1.0%, respectively, for the 2 techniques (P=0.252). In multivariate analysis, older-age donor emerged as the only independent predictor of significant TR (hazard ratio 1.06, 95% confidence interval 1.01–1.12, P=0.012).

Conclusions: The long-term results of atrioventricular function after heart transplantation in adults were excellent regardless of anastomotic technique. Older-age donor was significantly associated with the development of postoperative TR. (Circ J 2014; 78: 1654–1660)

Key Words: Heart transplantation; Mitral regurgitation; Tricuspid regurgitation
tion at Asan Medical Center, Seoul, South Korea. Of these, patients undergoing re-transplantation (n=0) or multi-organ transplantation (n=2; no heart-lung transplantation, 2 heart-kidney transplantations) were excluded. We reviewed the data for the remaining 201 patients and of them, 53 (26.4%) underwent heart transplantation using a standard anastomosis technique and 148 (73.6%) received a bivacal anastomosis. All echocardiographic data of these patients were acquired to evaluate tricuspid and mitral valve function. The long-term incidence of moderate-to-severe TR and MR was assessed quantitatively using the transthoracic echocardiographic images. This study was approved by the institutional review board, which waived the requirement for informed consent based on the retrospective nature of the study.

Surgical Procedures
A median sternotomy approach with ascending aorta and selective vena cava cannulation was used. Protection of the donor heart was achieved with infusion of 2L of 4°C Custodiol® HTK solution and hypothermia. The harvested heart was rinsed in HTK solution and transported on ice. Donor-recipient heart anastomosis was completed using a standard or bivacal anastomotic technique. Before January 1999, standard anastomosis was performed but since then, all heart transplantations have used a bivacal anastomosis. The details of the heart transplantation surgical procedure have been described previously.12 The donor left atrium was sutured first to the recipient left atrium, followed by anastomosis of the great arteries (main pulmonary artery, aorta) and venae cavae with continuous 4-0 prolene suture in the usual fashion. Intraoperatively, solumedrol 500 mg IV was routinely administrated before releasing the aortic cross-clamp.

Postoperative Management of Transplant Recipients
After heart transplantation, all recipients were managed according to protocols that included immunosuppression, infection prophylaxis, endomyocardial biopsy (EMB), and coronary angiography (CAG), the details of which have been described previously.12 In brief, from November 1992 to June 1999, the preoperative immunosuppressive protocol consisted of induction with cyclosporine 5 mg/kg and azathioprine 4 mg/kg per os (PO). Postoperatively, cyclosporine was maintained around 400 ng/ml during the first year and then 250–300 ng/ml. Azathioprine was 1.0–2.0 mg·kg⁻¹·day⁻¹ to maintain the white blood cell count (WBC) >4,000/mm³. After June 1999, the preoperative immunosuppressive protocol consisted of anti-interleukin-2 receptor monoclonal antibody (anti-IL2R mAb), mycophenolate mofetil 1.5–2.0 g PO, and administration of cyclosporine 3–4 mg/kg PO (not used after January 2007). Cyclosporine was withheld if the serum creatinine (Cr) concentration was >1.5 mg/dl. Intraoperatively, methylprednisolone 500 mg intravenous (IV) was used with same method. Postoperatively, patients were treated with mycophenolate mofetil 1–2 g/day and anti-IL2R mAb to maintain a WBC of 4,000–6,000/µl. Cyclosporine trough levels were maintained during the first year at 300–400 ng/ml by an enzyme-multiplied immunoassay (EMI) method and at 150–200 ng/ml thereafter. FK 506 has been used since January 2007 and trough levels of 10–15 ng/ml are maintained during the first year and 6–8 ng/ml thereafter. Methylprednisolone 125 mg was injected every 8 h for 3 injections. The initial postoperative dose of prednisone was 1 mg·kg⁻¹·day⁻¹, decreasing to 0.25 mg·kg⁻¹·day⁻¹ at 1 month and to 0.1 mg·kg⁻¹·day⁻¹ at 1 year. If possible, prednisone was discontinued at 1 year of transplantation. For infection prophylaxis, patients negative for HBsAg and HBsAb received hepatitis B virus vaccination preoperatively. All patients also received pneumococcal and influenza vaccinations routinely. Positive recipients for cytomegalovirus IgG received ganciclovir IV for 4 weeks as prophylaxis. Surveillance EMB was performed using a percutaneous right internal jugular approach on a scheduled basis, every week for 1 month, every month for 3 months, and at 6 months and 1 and 2 years. In the event of clinical suspicion of rejection, further biopsy was performed. The International Society of Heart and Lung Transplantation grading system was used to determine the severity of acute cellular rejection. Evaluation of cardiac allograft vasculopathy (CAV) was performed by CAG and intravascular ultrasonography.

Follow-up
Long-term echocardiographic data of all patients were obtained from hospital records through to January 2012. Follow-up transthoracic echocardiographic evaluations were generally performed immediately postoperative at 1-week intervals in the 1st, 2nd, 3rd and 6th months, then 6-month intervals in the first year and every year thereafter. Postoperatively, rhythms in patients were monitored daily using standard 12-channel surface ECG and follow-up ECGs were performed at 3–6-month intervals during the first year and every year thereafter. Episode of atrial fibrillation (AF), atrial tachycardia, or atrial flutter beyond the initial blanking period of 3 months were defined as a late AF event if the duration was ≥30 s by monitoring.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Heart Transplantation Patients</th>
<th>n (%) or mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>201</td>
</tr>
<tr>
<td>Recipient age, years</td>
<td>42.8±12.4</td>
</tr>
<tr>
<td>Donor age, years</td>
<td>29.9±9.7</td>
</tr>
<tr>
<td>Recipient female sex</td>
<td>47 (23.4)</td>
</tr>
<tr>
<td>Donor female sex</td>
<td>43 (21.4)</td>
</tr>
<tr>
<td>Recipient BMI (kg/M²)</td>
<td>22.2±2.9</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>III</td>
<td>99 (49.3)</td>
</tr>
<tr>
<td>IV</td>
<td>100 (49.8)</td>
</tr>
<tr>
<td>Significant pulmonary hypertension</td>
<td>63 (31.3)</td>
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<td>Underlying condition</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>17 (8.5)</td>
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<tr>
<td>Hypertension</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>16 (8.0)</td>
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<tr>
<td>Cause of heart failure</td>
<td></td>
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<tr>
<td>Dilated cardiomyopathy</td>
<td>146 (72.6)</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>22 (10.9)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>9 (4.5)</td>
</tr>
<tr>
<td>Other</td>
<td>24 (11.9)</td>
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<tr>
<td>Anastomotic technique</td>
<td></td>
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<tr>
<td>Standard</td>
<td>53 (26.4)</td>
</tr>
<tr>
<td>Bicaval</td>
<td>148 (73.6)</td>
</tr>
<tr>
<td>Ischemic time (min)</td>
<td>139.7±57.9</td>
</tr>
<tr>
<td>Postoperative late AF</td>
<td>16 (8.0)</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; BMI, body mass index; NYHA, New York Heart Association; SD, standard deviation.
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Echocardiography
Two-dimensional and Doppler echocardiographic examinations were performed using HP Sonos 5500 (Hewlett-Packard, Andover, MA, USA), Philips iE33 (Philips Medical Systems, Bothell, WA, USA) and GE vivid 7, E9 (GE Medical System, Horten, Norway). Preoperative echocardiography was performed in all patients less than 2 months prior to surgery. The grade of MR was classified as none, trace (barely detected regurgitation), mild (PISA radius <4 mm), moderate (PISA radius 4–8 mm) and severe (PISA radius >8 mm). TR was evaluated using the apical 4-chamber view, and graded as none, trace, mild, moderate and severe when the jet area occupied 0%, <10%, 10–20%, 20–33%, and >33% of the right atrial area, respectively. Regurgitation scoring was: 0, no regurgitation; 1, trivial; 2, mild; 3+, moderate; 4+, severe. Significant pulmonary hypertension was defined as a TR peak velocity >3.4 ms⁻¹, equivalent to a pulmonary artery pressure >50 mmHg. Postoperative significant TR or MR were defined as: (1) TR >mild or (2) MR >mild.

Statistical Analysis
Categorical variables are presented as frequencies and percentages while continuous variables are expressed as mean ± standard deviation, or as median and range. Kaplan-Meier curves were used to delineate freedom from moderate-to-severe TR and MR. Stratified curves were plotted to determine unadjusted differences for donor-recipient heart anastomotic technique (log-rank test). For multivariate analyses, the Cox proportional hazards model was used to determine the association of baseline characteristics with time to significant TR or MR. Prespecified covariates (Table 1) were included in this analysis. Variables with P<0.20 in the univariate analyses were candidates for analyses with the multivariable Cox proportional hazards model. P<0.05 was considered significant. SPSS version 18.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

Results
Baseline Characteristics (Table 1)
The mean age of recipients at surgery was 42.8±12.4 years, and 76.6% (n=154) were male; 99% (n=199) of the patients were categorized as New York Heart Association (NYHA) functional class III or IV, and preoperative significant pulmonary hypertension was seen in 31.3% (n=63) of the recipients. The most common diagnosis requiring heart transplantation was dilated cardiomyopathy. Heart anastomotic technique was standard in 53 patients (26.4%) and bicaval in 148 (73.6%).

Endomyocardial Biopsy and Acute Cellular Rejection (Table 2)
The number of EMBs performed postoperatively was 8.1±2.1 per patient, 32 (15.9%) patients experienced no rejection (Grade 0R) and moderate or severe acute cellular rejection (Grade 2R or 3R) occurred in 40 (19.9%) patients.

CAG and Significant CAV
Of the 201 patients, 149 (74.1%) underwent CAG within the first postoperative month and the findings were normal in all of them. However, during a mean CAG follow-up duration of 10.4±4.0 years (no. of CAG performed postoperatively: 3.7±1.4 per patient), 10 (6.7%) patients showed significant (≥70% stenosis) CAV and of these 10 patients, percutaneous coronary intervention was performed in 5.

TR and MR: Long-Term Incidence and Risk Factors
A total of 196 (97.5%) patients were evaluated with echocardiography for more than 6 months postoperatively. The echocardiographic data are summarized in Table 3. During a mean echocardiography follow-up duration of 89.9±54.3 months, 23 (11.4%) patients showed either significant TR (≥mild; n=21, 10.4%) or significant MR (≥mild; n=6, 3.0%), and 4 (2.0%) patients experienced both significant TR and MR. A detailed review of the 21 patients with significant TR postoperatively revealed that it was observed in 10 patients at 0–3 months and in 11 patients at 6–120 months after heart transplantation. Clinically, the NYHA status was class III or IV in 6 (28.6%) patients at the last follow-up. Most patients (81.0%) with significant TR were managed with diuretic therapy: 6 patients were improved, but the others experienced persistently significant TR. Of the patients with significant TR, 7 patients died (infection in 5 patients, heart failure after pericardiectomy in 1, unknown in 1). The mechanism of MR in 6 patients with significant MR included tethering in 4, incomplete leaflet closure in 1, and prolapse of the anterior mitral leaflet in 1. During the follow-up period, among the patients with significant MR, 3 died of chronic rejection and left ventricular dysfunction and 1 patient died of heart failure after pericardiectomy for constrictive pericarditis. The long-term incidence of TR or MR after heart trans-
Valve Function of Transplanted Heart

Moderate to Severe TR

Moderate to Severe MR

Discussion

In the present study of 201 patients who underwent heart transplantation, moderate-to-severe TR developed in 10.4% of the recipients and moderate-to-severe MR developed in 3.0% of the recipients. We demonstrated that current long-term outcomes of atrioventricular valve function following heart transplantation were excellent regardless of anastomotic technique. In our multivariate analysis, older donor age was the only independent risk factor of moderate-to-severe TR.
Heart anastomosis technique has been proposed as a risk factor of TR. Previous studies reported that the bicaval technique was associated with a lower incidence of TR, better right atrial contraction and improved hemodynamics.\textsuperscript{8,14-16} However, another study demonstrated that the standard technique also resulted in a lower incidence of TR and conduction anomalies.\textsuperscript{17} The present study found an incidence of moderate-to-severe TR that seemed to be slightly lower for bicaval anastomosis than for standard anastomosis but there was no statistically significant difference between the 2 groups.

The number of EMBs has a direct correlation with the severity of TR. Nguyen et al demonstrated that a cutoff of less than 31 EMBs reduced the risk of severe TR\textsuperscript{18} and Lo et al demonstrated a correlation between EMBs >10 and iatrogenic damage to the tricuspid valve.\textsuperscript{19} In the present study, the number of EMBs performed postoperatively was 8.1±2.1 per patient. This low number of EMBs might have contributed to the low incidence of moderate-to-severe TR in our study.

In this study, the most interesting finding was that older donor age was the only significant independent risk factor for moderate-to-severe TR. Previous studies have identified that older donor age is associated with lower survival.\textsuperscript{20-22} Donor age >40 years represents an important risk factor for survival after heart transplantation and the use of a donor age cutoff point of 40 years may be a useful clinical criterion.\textsuperscript{20,22} In our study, older donor age as a continuous variable was associated with the incidence of significant TR (P=0.012) and donor age >40 years as a categorical variable also affected the incidence of significant TR (P=0.008). The aged myocardium is known to undergo structural and functional changes. At the level of DNA, mutation and telomere shortening might be associated with limited regenerative capacity.\textsuperscript{23} Also, the expression and/or activity of protein kinases, which play a critical role in cardioprotection, are altered in the aged heart. Furthermore, with ageing, the chance of having comorbidities such as atherosclerosis and diseased coronary arteries increases. Thus, these changes may be associated with increased vulnerability to poor cardioprotection. In the present study, the older donor age might have contributed to the development of postoperative TR because of poor myocardial protection related to the structural

\begin{table}[h]
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\begin{tabular}{|l|c|c|}
\hline
\textbf{Table 4. Univariate and Multivariate Analysis of Risk Factors for Significant Tricuspid Regurgitation in Heart Transplantation Patients} & \textbf{HR (95\% CI)} & \textbf{P value} \\
\hline
\textbf{Univariate} & & \\
Preoperative factors & & \\
Recipient age & 0.566 & \\
Donor age & 0.010 & \\
Recipient female sex & 0.948 & \\
Donor female sex & 0.193 & \\
Recipient BMI (kg/m\textsuperscript{2}) & 0.656 & \\
NYHA functional class >II & 0.791 & \\
Diabetes mellitus & 0.624 & \\
Hypertension & 0.830 & \\
Cerebrovascular accident & 0.657 & \\
Previous cardiac surgery & 0.313 & \\
Cause of heart failure & 0.239 & \\
Operative factors & & \\
Bicaval technique vs. standard technique & 0.532 & \\
Ischemic time & 0.257 & \\
Preoperative echocardiographic data & & \\
LV ejection fraction, % & 0.462 & \\
Significant pulmonary hypertension & 0.324 & \\
Postoperative factors & & \\
Postoperative late AF & 0.358 & \\
Endomyocardial biopsy* & 0.138 & \\
Significant acute cellular rejection** & 0.936 & \\
\hline
\textbf{Multivariate} & & \\
Preoperative factors & & \\
Donor age & 1.06 (1.01–1.12) & 0.012 \\
\hline
\end{tabular}
\begin{flushleft}
*No. of endomyocardial biopsies performed postoperatively; **moderate to severe acute cellular rejection including Grade 2R and Grade 3R. *P<0.05. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,3.
\end{flushleft}
\end{table}
Valve Function of Transplanted Heart

Conclusions

In the present study of patients after heart transplantation, the incidence of moderate-to-severe TR was 10.4% and moderate-to-severe MR occurred less frequently than TR. The long-term results of atrioventricular function after heart transplantation in adults were excellent regardless of anastomotic technique. Older donor age was the important factor associated with development of postoperative moderate-to-severe TR.

Ultramini Abstract

In analysis of 201 patients who underwent heart transplantation, the long-term results of atrioventricular function after heart transplantation in adults were excellent regardless of anastomotic technique. Donor older age was significantly associated with development of TR postoperatively.

References