ELSEVIER

Tricuspid Valve Regurgitation and Endomyocardial Biopsy After Orthotopic Heart Transplantation

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ABSTRACT

Objective. Tricuspid valve regurgitation (TR) after heart transplantation (HTx) has been reported to be caused by endomyocardial biopsy (EMB), acute cellular rejection (ACR), or atrial anastomosis. We performed a prospective study of this problem among our HTx cohort.

Methods. From 1988 to 2006, we performed 274 HTx. Excluding cases within 1 year (2006), there were 178 patients in whom we had records of EMB dates, ACR grades (International Society for Heart and Lung Transplantation [ISHLT], 1990), echocardiography-measured TR, and time-to-TR. Statistical analyses were performed using nonparametric comparisons, Spearman correlation, Kaplan-Meier time to failure curves, and Cox regression model.

Results. All 178 patients underwent a biatrial anastomosis and underwent 2631 EMB (median, 15 times per patient; range, 0–42). The median follow-up duration was 66 months (range 2 days–194 months). Up to December 31, 2006, there were 47 patients (47/178 = 26.4%) who developed moderate-to-severe TR, which differed significantly from the prevalence rate (24/39 = 61.5%) reported by another cardiac team ($P = .001$) that performed bicaval anastomoses in half of the cases (20/39 = 51%). Our 1-, 3-, and 10-year Kaplan-Meier incidence rates of remarkable TR were 14.7% (10.2%–20.8%), 19.4% (14.2%–26.2%), and 36.3% (27.2%–47.3%), respectively. A positive correlation was shown between each patient's EMB times and ACR but not TR grades, in terms of mean, maximum, or minimum over time (all $P < .001$ for null hypothesis of noncorrelation). Each patient's EMB times and number of definite ACRs (≥ISHLT grade II) did not differ significantly between the two groups of remarkable versus nonremarkable TR. Remarkable TR was negatively predicted by each patient's EMB times (hazard ratio = 0.93; $P = .010$) but not by the ACR grades or the numbers of definite ACRs.

Conclusion. Our cohort demonstrated that biatrial anastomosis, ACR, or EMB were not associated with the risk of remarkable TR. The protective effect of EMB on remarkable TR needs further investigation.

HEART transplantation (HTx) has become one of the best treatments for irreversible end-stage heart disease over the decades, with revised surgical techniques[1,2] and postoperative care, accompanied by improved clinical outcomes.[3] Since the first case in Taiwan, in 1987, we have performed more than 500 HTx up to 2003 with comparable clinical outcomes to Western countries.[4] There have been more than 700 cases as reported by the Taiwan Organ Registry and Sharing Center in 2007 (http://ots.doh.gov.tw).

Tricuspid valve regurgitation (TR) is not uncommon. It causes morbidity after HTx.[5,6] It may result from endomyocardial biopsy (EMB),[5,7–13] acute cellular rejection (ACR),[10] and biatrial approaches.[14–17] Some reports have favored a bicaval anastomosis for a lower incidence of TR;[18–21] whereas, other reports did not show supporting evidence.[22] In addition our cohort all with biatrial anastomosis showed

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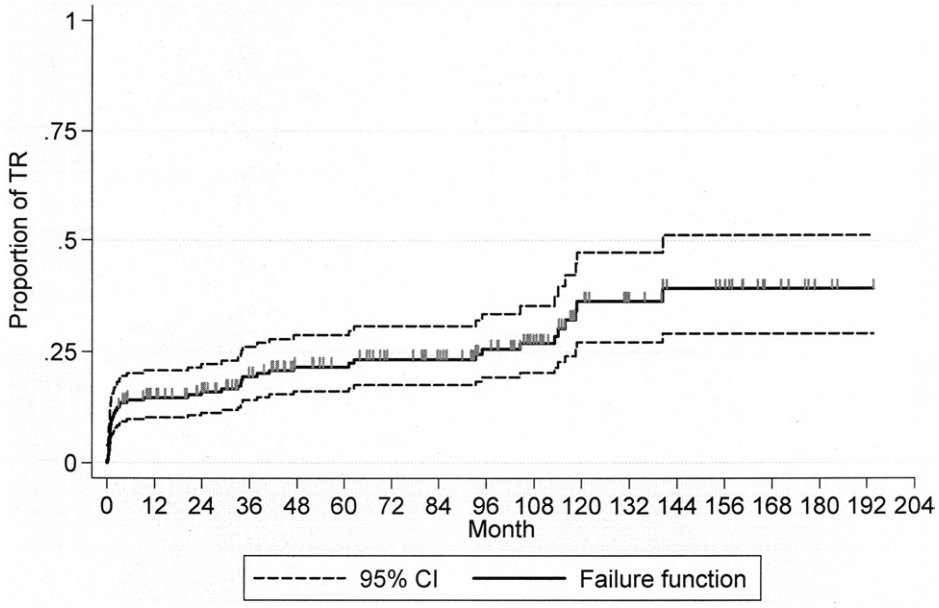

Fig 1. Kaplan-Meier failure curve for post-HTx TR, with pointwise Greenwood 95% confidence bands. Abbreviation: CI, confidence interval.

a relatively low incidence of TR[23] compared with another institute that used both bicaval and biatrial approaches.[11] In association of EMB and post-HTx TR has also been reported in Chinese patients.[23,24] Although EMB is the standard procedure to obtain a specimen to detect ACR, Doppler echocardiography may be used to assess TR severity in post-HTx patients.[25] To examine the effects of EMB as well as ACR on TR, we reviewed our HTx cohort.

METHODS

This prospective study was performed from 1988 to December 31, 2006, namely the first to the 274th HTx. We recorded their EMB dates, ACR grades (International Society for Heart and Lung Transplantation [ISHLT], 1990)[26] at each EMB, echocardiography-measured TR grades, and time-to-TR. Excluding those patients who underwent transplantation within the past year (2006) with incomplete data, 178 survivors entered the analysis.

The EMB specimens were obtained via the right internal jugular vein by an experienced interventional cardiologist at the cardiac catheterization laboratory. ACR was graded by certified pathologists according to the ISHLT 1990 guidelines.[26] Definite ACR was defined as a grade not less than ISHLT (1990) grade II. TR was graded by qualified cardiologists with 2-dimensional and Doppler echocardiography according to previous recommendations.[27] Remarkable TR was defined as a severity not less than moderate to severe. Each patient had the repeated measurements of ACR grade over time. The ACR grades were characterized as the mean, the standard deviations (SD), the maximum, and the minimum over time for every patient. The number of definite ACR episodes (≥ISHLT-1990, grade II) was also counted for each patient.

Each patient's EMB times, ACR grades, TR grades, and time-to-TR were analyzed with nonparametric comparisons, Spearman correlations, Kaplan-Meier failure curves, and Cox regression models. To compare the scale and ordinal variables, a Mann-Whitney test was used for the 2 groups and a Kruskal-Wallis test was used for multiple groups. To compare nominal variables, we used Fisher exact test. Correlations assessed by the nonparametric, Spearman correlation coefficient ρ (rho) were tested for P values with the null hypothesis of noncorrelation (rho = 0). With the ending date of December 31, 2006, the end-point of remarkable TR, and the time-to-remarkable, Kaplan-Meier failure curve for remarkable TR were plotted with pointwise Greenwood confidence bands for TR. Cox regression model was used to assess the hazard ratio and to identify predictors for remarkable TR. Significance level was set to $P < .05$. Statistical software used in the analysis was Stata 9.2 (StataCorp, College Station, Tex, USA).

RESULTS

All of the 178 HTx patients had biatrial anastomoses (standard Lower and Shumways technique). There were 2631 EMB procedures, with the median of 15 (range, 0–42 times per patient). The median follow-up duration was 66 months (range, 2 days –194 months).

Up to December 31, 2006, there were 47 patients (47/178 = 26.4%) who developed remarkable TR. The TR prevalence rate differed significantly from the rate reported by another medical center (24/39 = 61.5%) [11] (P = .001 by Fisher exact test) where biatrial anastomoses were only performed in about half of their cases (19/39 = 49%).

A Kaplan-Meier failure curve was plotted with the pointwise Greenwood 95% confidence bands for the incidence rates of remarkable TR (Fig 1). The 1-, 3-, 5-, and 10-year Kaplan-Meier incidence rates of remarkable TR were 14.7% (10.2%–20.8%), 19.4% (14.2%–26.2%), 21.6% (16.1%–28.8%), and 36.3% (27.2%–47.3%), respectively, with a plateau incidence rate of 39.2% (29.1%–51.3%).

A Spearman correlation matrix for the TR grades, the EMB times, the time-averaged ACR grades, the SD-over-

time ACR grades, the maximum-over-time ACR grades, the minimum-over-time ACR grades, and the numbers of definite ACR did not correlate with the EMB times or the ACR means, SDs, maximums, minimums, or definite episodes. However, the EMB times correlated significantly with the ACR means (Spearman rho = 0.22; $P = .003$); SDs (Spearmen rho = 0.48; $P < .0001$); maximums (Spearman rho = 0.62; $p < .0001$); minimums (Spearman rho = −0.32; $P < .0001$); or definite episodes (Spearman rho = 0.69; $P < .0001$). The definite ACR episode counts correlated with the ACR means-over-time (Spearman rho = 0.45; $P < .0001$), SDs-over-time (Spearman rho = 0.80; $P < .0001$), and maximums-over-time (Spearman rho = 0.89; $P < .0001$).

Comparing the 2 groups of remarkable versus nonremarkable TR, we failed to observe a significant difference in EMB times ($P = .69$ by Mann-Whitney test) or number of definite ACR episodes ($P = .47$ by Mann-Whitney test).

To identify predictors for remarkable TR, we built a multiple Cox regression model with stepwise selection observing the only significant predictor to be EMB times (hazard ratio = 0.93; $P = .010$), but not ACR grades (mean, SD, maximum, or minimum-over-time) or numbers of definite ACRs. Our data showed more EMBs were associated with a decreased risk of remarkable TR, which was paradoxical to the belief that EMB induces TR.

DISCUSSION

In our post-HTx cohort with biatrial anastomoses, the prevalence rate of TR with regular EMBs was 26.4%, which was relatively low compared with results of other cardiac teams who reported 33.6%[11] and 61.5%.[24] With the sample size of 178 patients and 2631 EMBs, our study did not show a significant association between TR and ACR. It also failed to demonstrate a positive association between TR and EMB. Instead, we showed that more EMBs predicted a decreased risk of TR over time. One plausible explanation may be the expertise of our interventional cardiologists to avoid iatrogenic injury to the tricuspid valve during EMB.

EMB times associated significantly with ACR grades. Generally speaking, worse ACR status might need more EMBs. Thus, higher EMB times were associated with more definite ACR episodes, and higher ACR grade averages over time (mean), worst status over time (maximum), and variations over time (SD), but lower ACR grade best status over time (minimum). Definite ACR episodes showed similar patterns of association with ACR grades. These results illustrated the phenomenon that fluctuating or unstable ACR grades (higher SD) or worse ACR grades (higher mean or maximum) may mandate more EMBs for physicians to adjust the immunosuppressants.

A limitation of our study was the assumption that TR progression was irreversible, which was not validated. In contrast, ACR grades could go both up and down in response to the therapy. Thus, ACR progression was reversible. Therefore, our dataset had repeated measurements of ACR grades over time, but only one measurement of remarkable TR for each patient. The Kaplan-Meier failure curve and Cox regression model both treated remarkable TR as an irreversible outcome similar to mortality. The consequence of this assumption of TR irreversibility has not yet been evaluated. Another limitation of our study was the use of summary statistics (mean, SD, maximum, and so on) for the TR grades that were repeated measurements over time. For longitudinal data, more complex and advanced statistical models may be used, such as generalized estimating equations (GEE).

Nevertheless, to avoid the potential adverse influence of EMB, an alternative method of remote noninvasive rejection monitoring has been used by the German Heart Institute (Berlin): intramyocardial ECG (IMEG). Excellent clinical outcomes have been reported.[28] Studies may be done to compare TR prevalence and incidence rates between conventional EMB and novel non-EMB groups.

In conclusion, our cohort provided preliminary evidence that EMB, ACR, and bicaval anastomoses did not increase the risk of post-HTx TR under the circumstances that experienced cardiac surgeons and interventional cardiologists are available in the team.

REFERENCES

1. Blanche C, Valenza M, Aleksic I, et al: Technical considerations of a new technique for orthotopic heart transplantation. Total excision of recipient's atria with bicaval and pulmonary venous anastomoses. J Cardiovasc Surg (Torino) 35:283, 1994

2. Trento A, Czer LS, Blanche C: Surgical techniques for cardiac transplantation. Semin Thorac Cardiovasc Surg 8:126, 1996

3. Magliato KE, Trento A: Heart transplantation--surgical results. Heart Fail Rev 6:213, 2001

4. Wei J, Chang CY, Chuang YC, et al: Heart transplantation at Cheng Hsin General Hospital in Taiwan: 15-year experience. Transplant Proc 36:2374, 2004

5. Stahl RD, Karwande SV, Olsen SL, et al: Tricuspid valve dysfunction in the transplanted heart. Ann Thorac Surg 59:477, 1995

6. Williams MJ, Lee MY, DiSalvo TG, et al: Biopsy-induced flail tricuspid leaflet and tricuspid regurgitation following orthotopic cardiac transplantation. Am J Cardiol 77:1339, 1996

7. Wiklund L, Caidahl K, Kjellstrom C, et al: Tricuspid valve insufficiency as a complication of endomyocardial biopsy. Transpl Int 5(suppl 1):S255, 1992

8. Huddleston CB, Rosenbloom M, Goldstein JA, et al: Biopsy-induced tricuspid regurgitation after cardiac transplantation. Ann Thorac Surg 57:832, 1994

9. Tucker PA, 2nd, Jin BS, Gaos CM, et al: Flail tricuspid leaflet after multiple biopsies following orthotopic heart transplantation: echocardiographic and hemodynamic correlation. J Heart Lung Transplant 13:466, 1994

10. Hausen B, Albes JM, Rohde R, et al: Tricuspid valve regurgitation attributable to endomyocardial biopsies and rejection in heart transplantation. Ann Thorac Surg 59:1134, 1995

11. Chan MC, Giannetti N, Kato T, et al: Severe tricuspid regurgitation after heart transplantation. J Heart Lung Transplant 20:709, 2001

12. Mielniczuk L, Haddad H, Davies RA, et al: Tricuspid valve chordal tissue in endomyocardial biopsy specimens of patients with significant tricuspid regurgitation. J Heart Lung Transplant 24: 1586, 2005

13. Nguyen V, Cantarovich M, Cecere R, et al: Tricuspid regurgitation after cardiac transplantation: how many biopsies are too many? J Heart Lung Transplant 24(7 suppl):S227, 2005

14. Blanche C, Valenza M, Czer LS, et al: Orthotopic heart transplantation with bicaval and pulmonary venous anastomoses. Ann Thorac Surg 58:1505, 1994

15. Deleuze PH, Benvenuti C, Mazzucotelli JP, et al: Orthotopic cardiac transplantation with direct caval anastomosis: is it the optimal procedure? J Thorac Cardiovasc Surg 109:731, 1995

16. Forni A, Faggian G, Chiominto B, et al: Avoidance of atrioventricular valve incompetence following orthotopic heart transplantation using direct bicaval anastomosis. Transplant Proc 27:3478, 1995

17. Laske A, Carrel T, Niederhauser U, et al: Modified operation technique for orthotopic heart transplantation. Eur J Cardiothorac Surg 9:120, 1995

18. Traversi E, Pozzoli M, Grande A, et al: The bicaval anastomosis technique for orthotopic heart transplantation yields better atrial function than the standard technique: an echocardiographic automatic boundary detection study. J Heart Lung Transplant 17:1065, 1998

19. Koch A, Remppis A, Dengler TJ, et al: Influence of different implantation techniques on AV valve competence after orthotopic heart transplantation. Eur J Cardiothorac Surg 28:717, 2005

20. Park KY, Park CH, Chun YB, et al: Bicaval anastomosis reduces tricuspid regurgitation after heart transplantation. Asian Cardiovasc Thorac Ann 13:251, 2005

21. Marelli D, Silvestry SC, Zwas D, et al: Modified inferior vena caval anastomosis to reduce tricuspid valve regurgitation after heart transplantation. Tex Heart Inst J 34:30, 2007

22. Grande AM, Rinaldi M, D'Armini AM, et al: Orthotopic heart transplantation: standard versus bicaval technique. Am J Cardiol 85:1329, 2000

23. Wei J: Tricuspid valve regurgitation induced by endomyocardial biopsy after heart transplantation. J Chin Med Assoc 70:183, 2007

24. Lo CY, Chang HH, Hsu CP, et al: Endomyocardial biopsy-related tricuspid regurgitation after orthotopic heart transplantation: single-center experience. J Chin Med Assoc 70:185, 2007

25. Rees AP, Milani RV, Lavie CJ, et al: Valvular regurgitation and right-sided cardiac pressures in heart transplant recipients by complete Doppler and color flow evaluation. Chest 104:82, 1993

26. Billingham ME, Cary NR, Hammond ME, et al: A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. The International Society for Heart Transplantation. J Heart Transplant 9:587, 1990

27. Zoghbi WA, Enriquez-Sarano M, Foster E, et al: Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 16:777, 2003

28. Warnecke H, Muller J, Cohnert T, et al: Clinical heart transplantation without routine endomyocardial biopsy. J Heart Lung Transplant 11:1093, 1992