Tricuspid valve dysfunction and surgery after orthotopic cardiac transplantation

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Abstract

Objective: The study examines the prevalence of tricuspid regurgitation and biopsy-induced flail tricuspid leaflets after orthotopic heart transplantation and evaluates the results of the tricuspid valve surgery. Methods: By a computerized search of the databases 647 of 889 patients who survived heart transplantation for more than 30 days were identified for this study. The primary tool for rejection monitoring in our institution is the daily observation of intramyocardial ECG (IMEG) based on day-by-day changes of the maximal QRS complex amplitude. Endomyocardial biopsy with 45-cm-long sheath bioptome was performed only in doubtful IMEG and echocardiographic data and at times of annual routine heart catheterization. Tricuspid regurgitation was diagnosed clinically and by echocardiography as mild, moderate and severe. Eleven patients received prosthetic valve replacements (four bioprostheses and seven mechanical valves) and six patients underwent valve reconstruction. The choice of xenograft valve was dictated by the condition of renal function. Patient survival and incidence of tricuspid regurgitation and freedom from operation for severe tricuspid regurgitation were analyzed with Kaplan–Meier method. Results: The prevalence of tricuspid regurgitation was 20.1%. Mild and moderate tricuspid regurgitation was seen in 14.5 and 3.1% of the patients, respectively, who were responsive to medical therapy and remained clinically stable in NYHA class I±II. Severe tricuspid regurgitation was seen in 16 (2.5%) patients who presented signs of an acute right heart dysfunction. Tricuspid valve pathology at operation revealed biopsy-induced rupture of the Chordae tendineae at various valve segments mostly the anterior and posterior leaflets. There was one hospital death (<30 day) and five late deaths due to infection, arrhythmia and trauma and no procedurally related or directly cardiac related death. Ten patients (62.5%) are alive at a mean follow-up time of 29.9 months (range 4–81 months) and nine survivors are in NYHA class I–II and one in class III. Conclusions: Severe tricuspid regurgitation in transplanted hearts is associated mainly with biopsy-induced injury or endocarditis. Other regimes of rejection monitoring may help to eliminate this complication. Apart from our preference of valve repair, the choice of valve substitute may be influenced by the presence or the prospect of chronic renal failure. Heart transplant patients can safely undergo valve surgery with acceptable mortality, low morbidity and excellent intermediate-term clinical results. Mild to moderate functional tricuspid regurgitation is responsive to medical therapy and non-progressive and occur in 17.6% of orthotopic transplanted hearts without having a detrimental effect on the right ventricular performance. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Heart transplantation; Tricuspid valve surgery

1. Introduction

The remarkable advances and success in orthotopic heart transplantation (HTx) has fortunately resulted in a limited number of patients that subsequently require cardiac valve or coronary artery procedures due to infective or traumatic valve and coronary artery diseases [1–6]. At our institution the immunologic monitoring and immunosuppressive therapy (classic triple therapy) are individualized based on non-invasive day-by-day telemetric bipolar pacemaker for monitoring the amplitude of the QRS-complex (IMEG: intramyocardial electrocardiography) during the sleeping phase through a normal telephone system at home [7]. Tricuspid regurgitation (TR) after orthotopic HTx has been described as early as in the 1980s [8] and a wide range of causes have

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been described, including (1) distortion of the tricuspid annulus due to disturbed geometry of the right atrial anastomosis with subsequent impairment of the functional unit of the valvular apparatus, (2) ischemic injury to the papillary muscles at the time of transplantation, (3) biopsy-induced injury to the tricuspid valve apparatus [1,3,5], (4) size mismatch of the donor heart and the pericardial cavity, and (5) endocarditis. Most of the TR which developed after orthotopic HTx is asymptomatic or less symptomatic and decreases under medical management [9,10]. Severe tricuspid regurgitation in the transplanted heart occurs rarely and is refractory to medical management [1,3] and therefore requires surgical therapy.

This study examines the prevalence of TR in our cardiac transplant recipients and evaluates the results of the surgical procedures on the tricuspid valve in the transplanted hearts.

2. Material and methods

2.1. Patients demographics

Our experience at the Deutsches Herzzentrum Berlin is based on 1124 orthotopic cardiac transplantations in 1095 recipients since April 1986 [11]. Overall 1-, 5-, 10- and 13-year survival of our patients are 80, 59, 50 and 50%, respectively [11]. Thirty-day survival of all patients was 81% (n = 889). The study population consisted of 647 heart transplanted patients (486 male and 161 female) surviving more than 30 days, excluding children (n = 63) and external outpatients with incomplete echocardiographic data (n = 179). The mean age at transplantation was 45.23 ± 14.9 years and the mean donor age was 33.3 ± 14.1 years. Freedom from graft sclerosis at 1, 5 and 10 years after HTx was 92, 69 and 59%, respectively. Eight patients underwent coronary artery bypass grafting due to severe intractable angina at a mean of 69 months (range 6–128 months) after cardiac transplantation, with four in whom previous angioplasty was unsuccessful [12]. At a mean of 54 months (range 6–96 months) after the initial HTx eight patients underwent retransplantation for severe graft coronary disease and worsening end-stage heart failure [13]. All the patients received orthotopic bi-atrial cardiac transplantation according to the technique of Lower and Shumway [14]. Generous atrial cuff was used at the heart transplantation to facilitate the atrial anastomoses with 3-0 prolene without creating a tension between the anastomoses and the tricuspid annulus. Furthermore, a pericardial reduction closure was employed to prevent axial displacement of the right atrium-tricuspid annulus-right ventricle alignment as well as a size mismatch of the donor heart and the pericardial cavity.

2.2. Follow-up

The patients who all received classical triple immunosuppressive therapy underwent routine surveillance echocardiography and annual right heart catheterization. Rejection was monitored by telemetric intramyocardial electrocardiography (IMEG) based on day-by-day changes of the maximal amplitude of the QRS-complex. Endomyocardial biopsy was performed only in doubtful IMEG and echocardiographic data. Since 1986, 45-cm sheath biopom has been used for endomyocardial biopsy. The average rate of biopsies per patients during the first two years after orthotopic HTx from 1986–1990 was 14.36 vs. 4.8 in the period 1991–1999. The degree of TR was assessed on the basis of the maximal area of the color Doppler regurgitant jet to the atrial area [9] and pulsed-wave evidence of systolic reversal of flow in the hepatic veins: trace <10%, mild 10–24%, moderate 25–50%, severe >50% [10,15]. The ratio of the regurgitant jet area to the atrial areas manifests the severity of TR.

Maximum follow-up from orthotopic heart transplantation was 13 years and minimum was 1 year. Maximum follow-up after tricuspid valve operation was 81 months and the minimum was 1 month.

2.3. Statistical analysis

Patient survival, incidence of TR and freedom from operation for severe TR were analyzed with the Kaplan–Meier actuarial curves method. Tricuspid valve dysfunction was diagnosed when there was onset of postoperative evidence of clinically mild, moderate or severe valve incompetence. The time of censoring for significant or severe TR due to structural or non-structural deterioration of flail tricuspid leaflets was the date of tricuspid valve operation and explant if necessary.

3. Results

3.1. Prevalence of tricuspid valve dysfunction

The overall prevalence of TR after orthotopic cardiac transplantation was 20.1% (130 patients) among 647 follow-up patients during the period between 31 days and 13.3 years (mean: 5.1 years) after orthotopic HTx. Ninety-four (14.5%) patients had evidence of mild, 20 (3.1%) moderate and 16 (2.5%) severe tricuspid regurgitation and 80% of the patients showed absent or no trace of tricuspid regurgitation. The patients with mild and moderate TR have remained stable and are in NYHA class I and II.

On actuarial analysis 90, 60.2, 40 and 40% of cardiac transplant survivors are expected to be alive with severe TR at 1, 5, 10 and 13 years, respectively (Fig. 1).

3.2. Severe tricuspid regurgitation

Sixteen patients, in which severe tricuspid regurgitation was detected 12.7–160.7 months (mean: 105 months) after orthotopic HTx, were scheduled for tricuspid valve surgery.
Ten patients were males and six were females and their mean age was 56.8 years (range: 46–68 years). The diagnoses at the time of orthotopic HTx were: dilating cardiomyopathy in 14 patients, ischemic cardiomyopathy in one patient and acute myocarditis in one patient who was bridged to orthotopic heart transplantation with biventricular assist device for 39 days. The mean age of the donors was 37.9 years (range: 17–60 years).

All the 16 patients presented clinical signs of acute right heart failure with fatigue and decreased exercise tolerance associated with hepatomegaly, jugular venous distension and lower extremity edema. They were all in NYHA class III–IV. They showed elevated right atrial pressures but presented good right ventricular function with a mean ejection fraction of 59%. The hemodynamic assessment of the patients before the tricuspid valve surgery are demonstrated in Table 1.

Preoperatively in 15 patients non-infectious related TR was diagnosed. In one patient the tricuspid regurgitation was associated with *Staphylococcus aureus* infection 42 months after orthotopic HTx preceded by biventricular assist device for 39 days due to acute myocarditis.

The average frequency of biopsies was 11.9 (range 11–20) between 1986 and 1990 and 2.3 (range 1–3) between 1991 and 1999.

Co-morbidity of the patients is summarized in Table 2.

### 3.3. Surgical management

Time of tricuspid valve operation after the heart transplantation was 105 months (range: 2–160.7 months) with five patients being more than 10 years after HTx. Eleven patients received prosthetic valve prosthesis (seven mechanical and four xenografts) with preservation of the subvalvular apparatus, one of them had a previous tricuspid valve repair. The other six patients underwent tricuspid valve repair; five DeVega and one Kay–Whooler annuloplasty without supporting rings. The choice of xenograft valve was dictated by renal function of the patient. Ten concomitant procedures were performed: pericardectomy, *n* = 3; coronary bypass grafts, *n* = 2; closure of right coronary artery fistula, *n* = 2; closure of atrial septum defect secundum type, *n* = 1; and ventricle septum defect, *n* = 1; resection of the right lower lobe and installation of extracorporeal membrane oxygenation (ECMO), *n* = 1.

At surgery biopsy-induced flail tricuspid leaflet due to injury of the Chordae tendineae was seen in 15 patients (2.3%) of whom 12 patients received their heart transplants between 1986 and 1993 at the time short sheath biopompe was used for biopsy. This findings reflect the higher rate of biopsies during the first two years after orthotopic HTx in this period (14.4 biopsies/patient/year) compared to exclusively IMEG-period (4.8 biopsies/patient per year).

Presence of prior endocarditis in one patient (0.15%) was also associated with rupture of the Chordae tendineae leading to flail leaflets and perforation of the anterior leaflet. The intraoperative tricuspid valve pathology and the tricuspid valve concomitant procedures are summarized in Table 3.

Overall there were four major postoperative complications, bleeding leading to an uneventful rethoracotomy in

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**Table 1**

Preoperative cardiac hemodynamic data of patients undergoing tricuspid valve surgery for biopsy-induced flail tricuspid leaflet

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>Range</th>
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<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>12.7</td>
<td>5–18</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>24</td>
<td>17–40</td>
</tr>
<tr>
<td>PAd (mmHg)</td>
<td>17</td>
<td>10–30</td>
</tr>
<tr>
<td>PVR (dyn/sec per cm$^5$)</td>
<td>300</td>
<td>140–561</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>59.4</td>
<td>53–69</td>
</tr>
<tr>
<td>RV-EDVI (ml/m$^2$)</td>
<td>75.1</td>
<td>35.4–127</td>
</tr>
</tbody>
</table>

*RAP, right atrial pressure; PAR, pulmonary artery pressure; PAd, pulmonary artery diastolic pressure; PVR, pulmonary vascular resistance; RVEF, right ventricular ejection fraction; RV-EDVI, right ventricular end-diastolic volume index.*
two patients, acute renal failure leading to hemodialysis in two patients, pulmonary failure necessitating an ECMO in one patient, atrial fibrillation in five patients which were managed medically.

3.4. Early mortality

One patient died 3 days postoperatively in pulmonary failure on an ECMO following prosthetic tricuspid valve replacement and right lower lobe resection for cancer.

3.5. Late mortality

Five patients died 4–29 months (mean 13 months) after tricuspid valve operation (four tricuspid valve replacements and one tricuspid valve repair). Two patients died of sepsis and multiple organ failure four months after surgery. Two other patients had sudden deaths and another in severe shock after a femur fracture. None of the deaths were attributable to the tricuspid valve procedure or directly related to a cardiac cause.

3.6. Follow-up

Ten patients (62.5%) are alive and enjoying normal life. Six patients are in NYHA class I, three in class II and one in class III. The mean follow-up time was 29.9 months (range 4–81 months). One patient who had a previous tricuspid valve repair underwent a reoperation 6 months later due to recurrent tricuspid regurgitation and received a prosthetic valve replacement. She survived the operation and is doing well in NYHA class II. The other five patients with tricuspid valve repair are clinically in stable condition and with mild regurgitation in NYHA class I and II. Patients with mechanical valves are under long-term anticoagulation therapy. Neither thrombembolic episodes nor prosthetic or native valve infections were observed during the follow-up period.

4. Comments

All our patients underwent the same implantation technique of Lower and Shumway yet the severity of the TR was heterogeneous, implying that at least there were six causes for TR in our series: implantation technique, biopsy technique, frequency of biopsy, infection, ischemic injury, and size mismatch of the donor heart and the pericardial cavity. However, the incidence of functional TR after Lower and Shumway technique of orthotopic heart transplantation is very low and responsive to medical therapy. Apart from our preference for valve repair which is our first procedure in AV valve operations, the choice of prosthesis for replacing valve in a transplanted heart will be influenced by the presence or the prospect of chronic renal failure [1,2,16,17]. Valve replacement is performed with preservation of the subvalvular apparatus which was employed in our series. In longitudinal studies with color Doppler trivial to mild TR has been observed in 15–83% and moderate TR in 5% of normal subjects [9,12,18].

In echocardiographic studies similar observation has been made in orthotopic transplanted hearts with a prevalence of TR of 67%-85% [3,10]. We found a 3.1 and 2.5% prevalence of moderate and severe TR in our transplant recipients as compared to 5–32% in other series [3,5,10,15,19]. It appears that the low incidence of severe TR in our series is associated with our non-invasive rejection monitoring system (IMEG) and low rate of endomyocardial biopsy with a long sheath biop tome, however the incidence does not differ much from that of the bicaval orthotopic transplantation technique [20]. They are mild to moderate and do not require surgical intervention unless there is an additional chordal damage by infection or by mechanical means which will cause flail leaflets.

Our hemodynamic data did not reveal any relationship between TR and pulmonary hypertension or pulmonary vascular resistance which confirm reports by other authors [3,5]. The patients were well monitored for rejection by IMEG and had good right ventricular pump function. Biopsy is only performed when there is doubt in the IMEG or echocardiographic data which are not consistent with the clinical condition of the patients, hence the frequency of biopsy is low (7–10%). Reduc tion pericardial closure has been suggested by Haverich and co-workers [21] to minimize functional tricuspid regurgitation due to a size mismatch of the donor heart and the pericardial cavity. A control of posttransplantation pulmonary hypertension as well as meticulous control of rejection with IMEG, has prevented development of severe tricuspid regurgitation. Since we did not observe severe functional tricuspid regurgitation but rather a biopsy-induced severe TR in our series, we assume that (1) tensionless atrial anastomosis, (2) reduction pericardial closure to match donor heart size to the pericardial cavity, (3) control of posttransplantation pulmonary hypertension and (4) other regimes of rejection monitoring to reduce the frequency of biopsies are the surgical and non-surgical factors which might prevent the development of hemodynamic relevant tricuspid regurgitation after heart transplantation.

The biopsy-induced chordal injury has no preferential

<table>
<thead>
<tr>
<th>Injured leaflet chordae</th>
<th>n</th>
<th>Time from HTx to tricuspid valve operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>2</td>
<td>9 months–9.8 years</td>
</tr>
<tr>
<td>Posterior</td>
<td>3</td>
<td>5.4 months–12 years</td>
</tr>
<tr>
<td>Ant/post</td>
<td>8</td>
<td>2 months–12 years</td>
</tr>
<tr>
<td>Ant/post/septal</td>
<td>2</td>
<td>10.6 months–13.2 years</td>
</tr>
<tr>
<td>Post/septal</td>
<td>1</td>
<td>9.7 years</td>
</tr>
<tr>
<td>Septal</td>
<td>1</td>
<td>9.9 years</td>
</tr>
</tbody>
</table>
site, and it could occur at every segment of the leaflet chordae; anterior posterior, posterior/septal or anterior/posterior and septal leaflet chordae. Mild to moderate functional TR even if it is related to geometric abnormality of the tricuspid annulus through the technique of atrial anastomosis yet has not been detrimental to the functional performance of the transplanted heart in our series. Mild to moderate TR might develop to severe TR when chordal injury by mechanical means such as bioprome or by infection results in a flail leaflet.

Forty percent of the heart transplant patients who would undergo tricuspid valve operation are expected to be alive 10 years after their heart transplantation. Therefore heart transplant patients can safely undergo tricuspid valve surgery with acceptable mortality and low morbidity and excellent intermediate-term clinical results.

Acknowledgements

We thank Ms Diana Kendall and Tonie Derwent for their help in preparing the manuscript.

References


Appendix. Conference discussion

Dr R. DeSimone (Heidelberg, Germany): Did you find any difference between patients operated with the Shumway technique and patients operated with the bicaval anastomosis? Because you mentioned that the major etiology of tricuspid regurgitation in transplantation is the endomyocardial biopsy. We published a work in the Annals of Thoracic Surgery (DeSimone et al. Ann Thoracic Surg 1995;60:1686–1693) that, by the way, you didn’t mention, and we found that the mechanism of the tricuspid regurgitation is correlated to the dysfunction and distortion of the annulus which may occur in the conventional Shumway technique. This finding has been confirmed by other works (Blanche et al.). You can observe tricuspid regurgitation just after the transplantation. Thus it seems that endomyocardial biopsy is not the most important etiology of tricuspid regurgitation after heart transplantation.

Professor Yankah: Well, as I mentioned at the beginning of my talk, 15–83% of the normal population have tricuspid regurgitation. That means this prevalence is also valid for heart donors. Functional tricuspid valve regurgitation, which occurs also in heart transplant patients, are grade II–III and can be treated medically without having any hemodynamic effects. It is postulated that tension on the atrial anastomosis as well as mismatch of the size of the donor heart and pericardial cavity, which creates an axial malalignment between the right atrium, tricuspid annulus and the right ventricle, might result in early functional tricuspid regurgitation. In our hands the use of generous atrial cuff for the atrial anastomosis and pericardial reduction closure have been our routine surgical technique at biautal–orthotopic heart transplantation. All those patients who have to undergo surgery in our series
are those with severe tricuspid valve incompetence, and all of them were biopsy-induced with the exception of one patient with tricuspid valve endocarditis.

*Dr C. Campbell (Cheshire, UK)*: I should just add a final comment. In Manchester we found approximately the same. The incidence is much higher with repeated biopsies, but the incidence of tricuspid regurgitation is also much more prevalent with the standard technique compared to the bicaval.