Heart Transplantation in Endstage Rheumatic Heart Disease
– Experience of an Endemic Area –

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Background: Rheumatic heart disease (RHD) remains a significant cause of cardiovascular disease in developing countries. The nonsuppurative cardiovascular sequel of group A streptococcal infection is sustained inflammatory and immune reactions toward the myocardium and valves. This study attempted to determine the long-term outcome of heart transplantation in endstage RHD patients.

Methods and Results: The 23 patients with endstage RHD at National Taiwan University Hospital between June 1987 and March 2012 were enrolled. In the same period, 226 dilated cardiomyopathy (DCM) patients were enrolled as the control group. The RHD group experienced more right ventricular failure and higher central venous pressure than the control group, which resulted in impaired liver and kidney function. The RHD patients had a lower 15-year survival rate than the DCM patients after transplantation (22.7% vs. 45.7%, P=0.038) and higher incidence of tricuspid regurgitation than the control group (32.2% vs. 11.4%). No differences existed between the groups for the mitral regurgitation rate (RHD 37.7% vs. DCM 29.4%, P=0.562).

Conclusions: Preoperatively, the RHD patients suffered more tricuspid regurgitation than the control group. The aortic and mitral valves in both groups functioned well over the long term. Heart transplantation for endstage RHD had a long-term survival rate that was inferior to that for DCM patients. (Circ J 2014; 78: 1900–1907)

Key Words: Rheumatic heart disease; Transplantation; Valvular diseases

Rheumatic fever and rheumatic heart disease (RHD) remain significant causes of cardiovascular diseases worldwide.1,2 Despite a documented decrease in the prevalence of RHD in industrialized nations over the past 5 decades, the nonsuppurative cardiovascular sequelae of group A streptococcal infection remain medical and public health problems in both industrialized and developing countries century.3,4

Molecular mimicry between streptococcal antigens and human proteins, mainly heart tissue proteins, has been implicated as the mechanism leading to autoimmunity in RHD patients.5-10 These T-cell-dependent immunological mechanisms lead to progressive heart damage in RHD patients.5,7-9,11-14 As a result of the immune and inflammatory response targeting the myocardium and valve, some patients eventually develop mitral valve disease and will undergo mitral valve surgery for mitral stenosis and mitral regurgitation. Some of them develop severe pulmonary hypertension and right ventricular failure in the subsequent years, and then endstage heart failure. Such patients at National Taiwan University Hospital (NTUH) undergo heart transplantation, but no long-term studies exist regarding this patient cohort.14-16 Therefore, this study assessed the long-term outcome and valve function after heart transplantation in this special cohort.

Methods

Patient Population

In total, 406 consecutive patients underwent heart transplantation from June 1987 through March 2012 at NTUH. Of them, 23 (5.67%) were diagnosed with endstage RHD. During the same period, 226 (55.6%) patients with dilated cardiomyopathy (DCM) who underwent heart transplantation were enrolled as a control group. Pretransplantation clinical and demographic information of these patients were collected and recorded. Echocardiography reports for the aortic, mitral and tricuspid valves were reviewed. Valve dysfunction was defined as more than mild regurgitation. Data for pre- and post-transplant liver function, renal function, cardiac output (CO), central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary
Immunosuppression and Rejection Surveys

All patients received triple-drug immunosuppressive therapy according to NTUH heart transplantation protocol as described previously. Since 1995, rabbit antithymocyte globulins has been used as induction therapy. Azathioprine (4 mg/kg) was given 1 h before the operation. Solumedrol (1,000 mg) was infused when the aortic cross-clamp was released. Rabbit anti-thymocyte globulin (1.5–2.5 mg · kg⁻¹ · day⁻¹) was administered fused when the aortic cross-clamp was released. Rabbit antithymocyte globulin was tapered and was discontinued after transplantation; the dosage was adjusted to maintain at the trough level of 300–500 ng/ml during the first 3 months and then 200–300 ng/ml at 1 year after transplantation.

Renal function and serum cyclosporine levels, which were maintained at the trough level of 250–350 ng/ml during the first 3 months after transplantation or after renal function recovery. The cyclosporine dosage was adjusted according to NTUH heart transplantation protocol as described previously. Since 1995, rabbit antithymocyte globulins has been used as induction therapy. Azathioprine (4 mg/kg) was given 1 h before the operation. Solumedrol (1,000 mg) was infused when the aortic cross-clamp was released. Rabbit anti-thymocyte globulin (1.5–2.5 mg · kg⁻¹ · day⁻¹) was administered for 5 days after transplantation. Oral cyclosporine was started within 5 days following transplantation or after renal function recovery. The cyclosporine dosage was adjusted according to renal function and serum cyclosporine levels, which were maintained at the trough level of 300–500 ng/ml during the first 3 post-transplantation months and then 200–300 ng/ml at 1 year after transplantation. Azathioprine 1–2 mg · kg⁻¹ · day⁻¹ was prescribed after transplantation; the dosage was adjusted to maintain a white blood cell count of 4,000–6,000/mm³. Prednisone (0.5 mg · kg⁻¹ · day⁻¹) was initiated on postoperative day 2 and gradually reduced to 0.2 mg · kg⁻¹ · day⁻¹ by the first month after transplantation. Tacrolimus (FK-506) and mycophenolate mofetil (Cellcept) were used for recurrent rejection or severe adverse reactions to cyclosporine and azathioprine. Since 2004, mycophenolate mofetil has been substituted for azathioprine for primary immunosuppression. To prevent nephrotoxicity, the cyclosporine dose was reduced to sustain a serum trough level of 250–350 ng/ml during the first 3 months after transplantation and 150–250 ng/ml at 1 year after transplantation.

All patients were followed monthly at a special cardiac transplantation clinic. Routine immune surveillance was performed at scheduled periodic endomyocardial biopsies, with rejection episodes treated with pulsed steroids. Rejection was defined as a biopsy-proven pathological finding and clinical event leading to specific immunosuppressive intervention. Standard chest roentgenogram, blood tests, electrocardiogram and physical examinations were routinely performed at regular intervals. Mean follow-up duration was 84.6±40.8 months. No patient was lost during follow-up.

**Results**

From 1987 to 2012, 406 consecutive patients underwent cardiac transplantation for endstage heart disease. The median age of the patients was 46.45 years (range, 0.1–70.8 years). Diagnosed underlying heart diseases were as follows: idiopathic DCM, 226 patients (55.6%); coronary artery disease, 98 (24.1%); valvular heart disease, 30 (7.3%); congenital heart disease, 28 (6.9%); postpartum cardiomyopathy, 5 (1.2%); transplant coronary artery disease, 5 (1.2%); restrictive cardiomyopathy, 2 (0.49%); primary amyloidosis, 1 (0.24%); and primary cardiac tumor, 1 (0.24%). Among the valvular heart disease patients, 23 were diagnosed with RHD. Diagnosis of RHD was confirmed by pathological findings for the valve closure or endocardial fibroelastosis. RHD was confirmed by pathological findings for the valve closure or endocardial fibroelastosis.
lesion. Fusion occurred at the level of the valve commissures, cusps, chordal attachments, or any combination of these resulting in stenosis or a combination of stenosis and insufficiency; these were findings were common to all RHD patients when they underwent valve surgery. During the same study period, 226 patients diagnosed with DCM who underwent cardiac transplantation were enrolled as the control group.

Baseline Patient Profiles
The mean age of the RHD patients was 48.1±15.4 years (range, 27–63 years; median age, 47 years). There were 13 males and 10 females. No statistical differences existed for age, height, weight, incidence of diabetes, hypertension or hyperlipidemia preoperatively between the RHD and DCM groups (Table 1). The DCM patients were predominantly male (81.0%). Prior to heart transplantation, all RHD patients had undergone at least 1 open-heart surgery for mitral valve stenosis or inefficiency (mean number of operations for RHD patients, 2±1.0, range, 1–3). The mean interval from first valve surgery to transplantation was 14.6±6.6 years (range, 8–30 years). Since 1997, bicaval anastomosis has been used in place of a standard midatrial anastomosis for orthotopic transplantation, particularly in patients with high PVR. Both groups of patients underwent the same anastomosis operation techniques.

Preoperative Condition
All the patients who underwent heart transplantation were preoperatively New York Heart Association functional class IV. Mean PAP was 38.7±7.7 mmHg and 32.6±7.2 mmHg in the RHD and DCM groups, respectively (P=0.085). The CO was 3.4±0.9 L/min and 2.6±0.8 L/min for the RHD and DCM groups, respectively (P=0.001). The PVR was 3.3±0.9 and 3.3±1.3 Wood units (P=0.992) for the RHD and DCM groups, respectively. The CVP level was significantly higher in the RHD group (18.6±6.5 mmHg) that in the DCM group (13.1±4.5 mmHg) (P=0.01). Serum creatinine level was 1.35±0.3 mg/dl for the RHD group and 1.02±0.4 mg/dl for the DCM group (P=0.14) and the bilirubin level was 1.9±1.0 mg/dl for the RHD group and 1.3±0.3 mg/dl for the DCM group (P=0.08) (Table 1). The hepatitis profile was similar in both groups. Taiwan has been an endemic area for hepatitis B infection in the past 15 years, and hepatitis B carrier status in the RHD and DCM group was 8.9% and 7.9%, respectively (Table 1).

Liver and Renal Function
The bilirubin level in the RHD group was higher than in the DCM group (1.9 vs. 1.3 mg/dl, P=0.008), which implied the higher CVP level in the RHD patients caused the long-term congestion of the liver. A similar result was noted for renal function (creatinine 1.35 vs. 1.02 mg/dl) in both groups.

Panel Reactive Antibody (PRA)
The PRA level in the RHD group was higher than in the DCM group (6% vs. 0%, P<0.01). RHD patients had more operations and more transfusions than the DCM group. To eliminate the incidence of acute rejection, T-cell and B-cell cross-matching was performed before transplantation and all cross-matches were negative in all patients.

Waiting Period
Based on their United Network for Organ Sharing (UNOS) status, both groups had a similar waiting time for a new heart. The mean waiting time for UNOS status I patients was 75 days and for status II patients was 250 days.

Long-Term Outcome
Mean survival rate after transplantation was 8.15 and 8.09 years for RHD and DCM patients, respectively (Figure 1). The 5-year survival rate was 54.4% and 72.2%, respectively (P=0.25), the 10-year survival rate was 45.3% and 56.8%, respectively, and the 15-year survival rate was 27.7% and 45.7% (P=0.038), respectively, for the RHD and DCM patients.
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Ventricular Function

The left ventricular ejection fraction (LVEF) at 5 years after transplantation was 59±17% in the RHD group and 62±15% in the DCM group (P=0.82). At 10 years after transplantation, it was 56±13% and 60±11% (P=0.73), respectively (Table 2).

Cause of Death in the RHD Group

Early death was defined as death with 1 year after transplantation and there were 4 cases in the RHD group, 2 from primary allograft dysfunction in the early era (1 from uncontrolled bacterial infection, 1 rejection related). Late death included infection (31%), rejection (26.3%), cardiac allograft vasculopathy (16%), hepatic failure (8%), and sudden death of unknown causes (16%).

Discussion

RHD is an autoimmune disease that attacks the cardiac valves and the myocardium. De Santo et al19 and Chauvand et al20...
each reported their long-term follow-up results for RHD patients who underwent mitral valve surgery. In the de Santo series, mean age at surgery was 31.4 years, and 25.8 years in the Chauvand series. The actuarial survival rate was 70.2% at 25 years and 82% at 20 years, respectively. Cause of death was reported as mainly of cardiac origin (85.7%). In our previous study between 1975 and 1999 at NTUH, a rheumatic etiology accounted for 95% of patients who underwent valvular replacement. Mean age at surgery was 40±14 years (mitral valve) and 43±19 years (aortic valve). Actuarial patient survival rates at 10 and 20 years were 83.8% and 35.8%, respectively. Our results implied that roughly 20–30% RHD patients suffered from progressively deteriorating myocardium function and death at 20–25 years after their first surgery. This is characteristic of RHD, which occurs at a very young age compared with the degenerative valve disease in the Western series. Consequently, RHD patients undergo surgery at a significantly younger age than those with degenerative disease; furthermore, some RHD patients face progressive deterioration of heart function even after valve surgery. In the study being reported here, the RHD patients underwent heart transplantation at a mean age of 48.1±15.4 years, and all RHD patients had previously undergone at least 1 valve operation. Mean interval from first valve surgery to transplantation was 14.62±6.69 years. Transplantations were not related to valve dysfunction but rather to biventricular failure in 10 RHD pa-
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Fusion occurred at the level of valve commissures, cusps, chordal attachments, or any combination of these, resulting in stenosis or a combination of stenosis and insufficiency.

The RHD patients had preoperative PAP values similar to those in the DCM group, and much higher CVP levels than the DCM group (18±6.5 mmHg vs. 13.1±4.5 mmHg, P=0.001) (Table 1). These findings reflected the more severe right ven-

No reliable serological markers exist for chronic RHD. In patients with chronic, inactive RHD, or in those with acute rheumatic fever without clinical signs of carditis, the characteristic myocardial and histological features of rheumatic inflammation, such as histiocytic aggregates, myocyte degeneration, and interstitial degeneration, are not identified on endomyocardial biopsy. Pathognomonic Aschoff nodules are more common in cases of severe rheumatic carditis than in less severe acute rheumatic episodes. Thus, Aschoff nodules are generally detected at necropsy after severe congestive failure because of acute rheumatic carditis. Consequently, Narula et al suggest that endomyocardial biopsy for rheumatic carditis should be limited primarily to clinical investigation.

In the present series, all RHD patients had typically pathological valve lesions identified during their first valve surgery.
tricular failure suffered by the RHD patients than by the DCM patients. Preoperative severe right ventricular failure caused venous congestion, and worse renal function and liver function in RHD patients. The preoperative bilirubin and creatine levels were also increased in the RHD patients, because of higher CVP (Figures 5, 6). In contrast, these patients cannot generate a high PAP, indicating worsened right ventricular function.

During the 10-year follow-up, the RHD group had more tricuspid regurgitation than those in the DCM group (free-from-regurgitation rate, 67.8% vs. 88.6%, P=0.06). Many tricuspid valve studies have identified a very high incidence of tricuspid regurgitation following transplantation. Some investigators identified a correlation between the number of endomyocardial biopsies performed and development of flail tricuspid leaflets or chordal rupture. They hypothesize that inadvertent tearing of these structures by the jaws of the cardiac biopomme is the cause of regurgitation. However, in the present series, no difference existed between the groups in the number endomyocardial biopsies performed. Some studies have suggested that tricuspid regurgitation in post-transplantation patients may be related to surgical method. A number of these studies indicated that bicaval anastomosis technique can maintain a lower incidence and severity of tricuspid valve dysfunction compared with the mid-atrial anastomosis technique. In this study, all RHD patients had undergone surgery prior to transplantation and both groups of patients underwent the same anastomosis technique. Risk factors for tricuspid regurgitation were analyzed by Cox regression (proportional hazard model) and only RHD was a risk factor. Notably, RHD had a hazard ratio of 4.17 (P=0.047) for tricuspid regurgitation relative to DCM; no other variables (CVP, PAP, CO, PVR, anastomosis technique, age, sex) in the database generated significant hazard ratios for tricuspid regurgitation.

We speculate that the reasons for tricuspid regurgitation may be a combination of a large right atrial cuff, surgical technique, and very high preoperative CVP in the RHD patients. All these factors contributed to a high incidence of regurgitation over the long term.

During the 10-year follow-up period, aortic valves functioned well in the RHD and DCM group (free-from-regurgitation or stenosis rate 100% vs. 93.33%, P=0.45). For the mitral valve, both groups had similar 10-year free-from-regurgitation rates (RHD 62.3% vs. DCM 70.6%, P=0.56). From this perspective, after transplantation, both the aortic and mitral valve functioned well. Risks for tricuspid regurgitation were significantly higher in RHD patients than DCM patients. In this study, tricuspid regurgitation relative to DCM; no other variables (CVP, PAP, CO, PVR, anastomosis technique, age, sex) in the database generated significant hazard ratios for tricuspid regurgitation. We speculate that the reasons for tricuspid regurgitation may be a combination of a large right atrial cuff, surgical technique, and very high preoperative CVP in the RHD patients. All these factors contributed to a high incidence of regurgitation over the long term.

References


