Effect of Acute Allograft Rejection on Exercise Hemodynamics in Patients Who Have Undergone Cardiac Transplantation*

John N. Nanas, MD; Maria I. Anastasiou-Nana, MD; Richard B. Sutton, MD; and Theofilos J. Tsagaris, MD

The effect of acute allograft rejection on exercise hemodynamics was evaluated in 8 consecutive cardiac allograft recipients (group 1) when the right ventricular endomyocardial biopsy showed evidence of allograft rejection (R), and when no evidence of rejection (NR) was present. A separate group of 10 cardiac transplant recipients (group 2) with no evidence of rejection on biopsy done at the end of the first and second year post-transplantation served as controls. The exercise hemodynamics were abnormal in both groups in both studies with a moderate increase of the pulmonary artery wedge pressure to a mean of 17.2 (NR) and 19.4 mm Hg (R) in group 1 (p=not significant [NS]) and 20.1 and 21.2 mm Hg in group 2 (p=NS), a mild increase of the mean right atrial pressure to a mean of 10 mm Hg (NR) and 10 mm Hg (R) in group 1 (p=NS), 11.9 mm Hg and 12.5 mm Hg in group 2 (p=NS), and a moderate increase of the arteriovenous oxygen content difference to a mean of 8.5 (NR) and 8.4 vol percent (R) in group 1 and 8.3 and 8.0 vol percent in group 2. No significant difference was observed between the two studies of the same group in any of the hemodynamic parameters except for the heart rate in group 1 (from 91 ± 16 to 97 ± 16 beats/min [p<0.05] with and without evidence of allograft rejection, respectively). In conclusion, heart transplant recipients do not usually manifest further exercise hemodynamic deterioration during mild to moderate rejection.

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NR=without rejection or no rejection; R=rejection

Key words: allograft rejection; cardiac transplantation; cyclosporine; exercise hemodynamics

It has been postulated that there is a significant relationship between rejection history and exercise performance in patients who have undergone cardiac transplantation. It has also been found that acute cardiac rejection is accompanied by alteration in left ventricular filling dynamics detectable by Doppler echocardiography without measurable changes in systolic function.

In the pre-cyclosporine era, allograft rejection was uniformly associated with myocardial edema, lymphocytic infiltration, and a decrease in diastolic compliance with the appearance of S3 or S4 gallops. Reduction in ECG voltage, atrial arrhythmias, and variable degrees of atrioventricular block completed the clinical picture of acute rejection. However, allograft rejection in patients treated with cyclosporine is not associated with myocardial edema and occurs most of the time without hemodynamic compromise arrhythmias, echocardiographic findings, or ECG findings. To our knowledge, the response of these patients to exercise has not been studied.

The present study was undertaken therefore to evaluate the exercise hemodynamics during acute allograft rejection in heart transplant recipients.

METHODS

This retrospective study consisted of two groups of patients: the first group (group 1) included 8 consecutive cardiac allograft recipients (men) aged 33 to 61 years, without complaints of fatigue, dyspnea, or findings of more than 20 mm Hg decrease in systolic blood pressure from the baseline, elevated jugular venous pressure, or an S3 gallop, who had undergone rest and supine bicycle exercise hemodynamic studies when their right ventricular endomyocardial biopsy specimen had shown acute mild rejection (R) in seven patients and moderate rejection in two patients (one patient had undergone hemodynamic studies during two different allograft rejections). These patients had also undergone a hemodynamic study at rest and during exercise when right ventricular biopsy specimen showed no evidence of acute allograft rejection.

The allograft rejection study was performed 15.6 ± 11 months (range, 4 to 27 months) posttransplantation and the study with no evidence of rejection 8 to 11 months from the previous one. All patients were receiving cyclosporine and azathioprine and three patients were additionally receiving prednisone, 10 mg/d, in both studies.

The second group of patients (group 2) consisted of 10 consecutive cardiac transplant recipients (men) aged 33 to 62 years, who...
had undergone hemodynamic studies at rest and during supine bicycle exercise at the end of the first and second posttransplantation years, when there was no evidence of allograft rejection in the right ventricular endomyocardial biopsy specimen in either study and served as controls. All patients of group 2 were also receiving cyclosporine and azathioprine and only 1 patient was additionally receiving prednisone, 10 mg/d, at the end of the first and second posttransplantation year.

The patients of the control group (group 2) were randomly chosen and the only inclusion criterion was to have undergone right ventricular biopsy without evidence of allograft rejection, and rest and exercise hemodynamic study at the end of the first and second posttransplantation years. The patients who had undergone retransplantation were excluded. However, all patients in both groups were men and there was no difference in their age: 50.8 ± 10 years in group 1 and 50.9 ± 9.3 years in group 2; rest ejection fraction of 49.9 ± 7% in group 1 on the evaluation without evidence of allograft rejection and 49.5 ± 10% at the end of the first posttransplantation year in group 2; immunosuppressive therapy was similar and the frequency of rejection, 3.4 ± 1.4 episodes of rejection per patient in group 1 and 2.0 ± 1.9 in group 2 (p = not significant [NS]), were not significantly different.

Hemodynamic Studies

The cardiac transplant recipients included in group 1 had undergone a right ventricular endomyocardial biopsy and subsequently right and left heart catheterization at rest, during supine bicycle exercise with evidence of rejection and without rejection in the endomyocardial biopsy specimen. Measurements and calculations included right atrial, pulmonary artery wedge, and brachial artery pressures, oxygen consumption, arterial and mixed venous oxygen content difference, and cardiac output using the Fick method. The systemic vascular resistance, pulmonary vascular resistance, cardiac index, stroke volume index, and exercise factor (cardiac output increase in mL/min per 100 mL increase of the oxygen consumption) were also calculated. The cardiac transplant recipients included in group 2 had undergone similar hemodynamic studies at the end of the first and second posttransplantation years.

Statistical Analysis

The data are expressed as mean ± SD. Differences between rest and exercise data were determined with the Student’s t test for paired data since all patients included in this study had undergone two similar studies. The Student’s t test for unpaired observations was used to determine differences between groups.

RESULTS

The hemodynamics were normal at rest with

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<th>Table 1—Rest Hemodynamics Obtained at Two Different Periods for Each of the Groups 1 and 2*</th>
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<td>PAWP, mm Hg</td>
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*RV = right ventricular; R = rejection; TX = transplantation; PAWP = mean pulmonary artery wedge pressure; PAP = mean pulmonary artery pressure; RAP = mean right atrial pressure; BAP = mean brachial artery pressure; VO2 = oxygen consumption; Ca-VO2 = arteriovenous oxygen content difference; HR = heart rate; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

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<th>Table 2—Exercise Hemodynamics Obtained at Two Different Periods for Each of the Groups 1 and 2*</th>
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rejection and without rejection in group 1 and at the end of the first and second post transplantation year in group 2 (Table 1). However, in group 2, the pulmonary artery wedge pressure increased slightly from 9.6 ± 1.0 mm Hg at the end of the first year to 11.4 ± 2.2 mm Hg at the end of the second year (p<0.05) and the right atrial pressure increased from 6.1 ± 2 mm Hg to 7.5 ± 3.1 mm Hg (p<0.05).

The exercise hemodynamics are summarized in Table 2 for group 1 (with and without evidence of acute cardiac allograft rejection in the right ventricular endomyocardial biopsy specimen) and for group 2 (at the end of the first and second posttransplantation years without evidence of rejection in the right ventricular endomyocardial biopsy specimen). In both groups during exercise, the pulmonary artery wedge pressure increased a moderate level (Figs 1 and 2), the right atrial pressure to a mild level (Table 2), and the cardiac index increased from the baseline level to 3.6 to 4.2 L/min/m². The oxygen consumption was almost identical at rest in both studies and was triple during exercise, indicating that patients most likely had undergone a similar level of mild exercise for their hemodynamic evaluation at two different times in both groups. The arteriovenous oxygen difference increased moderately. The heart rate increased to a level of 104 beats/min. The pulmonary vascular resistance did not change while the systemic vascular resistance decreased and the mean arterial pressure increased slightly.

**Discussion**

The introduction of cyclosporine in heart transplant recipients in 1980 started a new era in heart transplantation. Cyclosporine has improved survival, increased the number of procedures, and changed the clinical picture and hemodynamics in acute cardiac rejection. Nevertheless, acute cardiac rejection remains responsible for 25% of deaths in patients undergoing heart or heart-lung transplantation.

Previous studies in heart transplant recipients have documented an increase in left ventricular filling pressure during exercise and an abnormal response to volume loading, suggesting impairment of left ventricular compliance. Echocardiographic studies have shown changes in Doppler features of left ventricular filling and increased left ventricular mass.

**Figures**

1. Exercise pulmonary artery wedge pressure (PAWP) in group 1 without evidence of acute cardiac allograft rejection in the right ventricular endomyocardial biopsy specimen and during mild (continuous line) to moderate (dotted line) acute cardiac allograft rejection.

2. Exercise pulmonary artery wedge pressure (PAWP) of group 2 at the end of the first and second posttransplantation year without evidence of acute cardiac allograft rejection in the right ventricular endomyocardial biopsy specimen in either study.
and wall thickness and decreased rate of posterior wall thinning during acute allograft rejection, also suggesting impairment of left ventricular compliance. Reduction of the left ventricular compliance during acute allograft rejection is expected to impair the abnormal exercise hemodynamics of the heart transplant recipients.

In our study, the rest and exercise hemodynamics were similar at the first and second posttransplantation years in control group 2. Surprisingly enough, neither the rest nor the exercise hemodynamics during acute allograft rejection were different from those obtained in the same patients (group 1) during the period of no rejection. It should be emphasized that with and without evidence of cardiac allograft rejection in group 1, the exercise hemodynamics were abnormal, showing an elevation of right and left ventricular filling pressures (Fig 1 and Table 2), an increase of the arteriovenous oxygen (A\textsuperscript{v}O\textsubscript{2}) content difference, and an inadequate increase of the cardiac index manifested by a low exercise factor. However, these findings are consistent with the exercise hemodynamics in group 2 (Fig 2 and Table 2) that showed similar results without evidence of allograft rejection in either evaluation. The reduced exercise factor in both groups may be related to a combination of factors: denervation resulting in a loss of adrenergically mediated inotropic and chronotropic support, the cumulative effects of repeated bouts of rejection, prolonged ischemic time during transplantation, and an increased afterload. The absence of further deterioration of the exercise hemodynamics during acute rejection cannot be easily explained.

These findings lead to two different explanations: according to the first explanation, the impairment of heart function during acute mild (7/9) and moderate allograft rejection (2/9), without clinical evidence of allograft rejection, is so minor that maximum exercise would probably be required to bring out a further hemodynamic deterioration. The second one concerns the histologic diagnosis of the rejection itself. Morphologic features and grading of rejection by endomyocardial biopsy specimen are based on those described by Billingham for patients in the precyclosporine era. Acute rejection prior to the routine use of cyclosporine was usually associated with hemodynamic deterioration. The introduction of cyclosporine appears to have reduced the magnitude of myocardial edema during acute rejection without gross impairment of heart function during mild exercise as reflected in this study.

Limitations

This is a retrospective study in which the cardiac transplant recipients with mild to moderate allograft rejection underwent a hemodynamic evaluation at a mild level of exercise. It is possible that the results would be different if the level of exercise was higher. In our study, the use of a control group showed similar hemodynamic changes for a similar level of exercise at the end of the first and second posttransplantation years, suggesting that a higher level of exercise would result in no different changes. The nonuse of radionuclide and echocardiographic evaluation of the left ventricular performance during exercise does not permit this study to conclude on the left ventricular systolic and diastolic performance on exercise during mild to moderate rejection.

CONCLUSION

This study has shown that heart transplant recipients treated with cyclosporine without clinical evidence of allograft rejection manifest no further exercise hemodynamic deterioration during mild to moderate acute rejection, constituting the diagnosis of acute rejection almost impossible without myocardial biopsy specimens.

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