PATHOPHYSIOLOGY AND NATURAL HISTORY
CARDIAC TRANSPLANTATION

Long-term hemodynamic follow-up of cardiac transplant patients treated with cyclosporine and prednisone

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ABSTRACT To evaluate the long-term hemodynamic results in cardiac transplant patients treated with cyclosporine and prednisone, 19 patients were studied by cardiac catheterization and endomyocardial biopsy 13 ± 3 months after transplantation. Immunosuppression consisted of 6 ± 4 mg/kg/day cyclosporine and 20 ± 8 mg/day prednisone. Eighteen patients were asymptomatic but had developed postoperative systemic hypertension (17 on antihypertensive therapy). These patients were compared with a normotensive control group of 18 patients without cardiovascular disease. Significant differences were found in heart rate; right atrial, pulmonary arterial, pulmonary arterial wedge, systemic arterial, and left ventricular end-diastolic pressures; cardiac index and stroke volume index; systemic and pulmonary vascular resistance; and end-diastolic volume index and left ventricular ejection fraction. The most frequent hemodynamic abnormalities included an elevated arterial pressure in 10 patients (56%), an elevated left ventricular end-diastolic pressure in six patients (33%), and a reduced ejection fraction in five patients (28%). Hemodynamic abnormalities tended to resolve or improve in the five patients restudied 2 years after transplantation. There was no significant relationship between fibrosis or inflammation on endomyocardial biopsy and hemodynamic abnormalities. We conclude that mild-to-moderate hemodynamic abnormalities are common in asymptomatic cardiac transplant patients receiving cyclosporine and prednisone.


CARDIAC TRANSPLANTATION has become an accepted therapy for selected patients with refractory heart failure.1,4 Renewed interest in this technique stems from improved survival.1 It has been suggested that treatment with the immunosuppressive agent cyclosporine has further improved survival over that observed with conventional immunosuppression with azathioprine and prednisone.5 The 1 year actuarial survival rate approximates 80% with cyclosporine vs 60% with conventional immunosuppression.5 Other benefits of cyclosporine over azathioprine may include a 40% reduction in the initial hospital stay,3,5 a 30% reduction in hospital costs,5 and a “steroid-sparing” effect.5

Despite these potentially important advantages over previous immunosuppression, cyclosporine is associated with several untoward effects that are of concern.5–9 Essentially all long-term survivors of cardiac transplantation on cyclosporine develop systemic arterial hypertension,5,10 usually within the first 2 months after surgery. In addition, a form of myocardial fibrosis not seen with conventional immunosuppression has been reported to occur in nearly all patients treated with cyclosporine.5,11 In view of the potential of these factors to negatively influence cardiac performance, we prospectively studied long-term survivors of cardiac transplantation by cardiac catheterization and endomyocardial biopsy.

Methods

Patients. All 19 patients in this study had New York Heart Association class IV disease before surgery and met the criteria for cardiac transplantation described by Baumgartner et al.12 The details of immunosuppression and operative technique have been described previously.13 The mean donor age was 22 ± 5 years (mean ± 1 SD). The mean ischemic time for the donor heart (defined as the time from the clamping of the donor aorta to the release of the recipient aorta) was 148 ± 51 min.

Because of the high reported prevalence of coronary atherosclerosis in the transplanted heart,14,15 yearly cardiac catheter-
izations after transplantation are routinely performed at the University of Pittsburgh. Nineteen of 21 (90%) patients who survived at least 10 months after transplant underwent cardiac catheterization. Catheterization was performed 13 ± 3 months post transplantation. Five of six eligible patients (83%) underwent a second catheterization (mean restudy time 24 ± 4 months).

There were 18 men and one woman (mean age 42 ± 9 years). Eighteen patients were asymptomatic. These 18 comprise the patient group in the results except where specifically noted. One patient, who is discussed separately, had New York Heart Association class III disease with moderately severe dyspnea on minimal exertion.

The mean cyclosporine dose at the time of catheterization was 6 ± 4 mg/kg/day; the mean prednisone dose was 20 ± 8 mg/day. All 19 patients had postoperative hypertension; 17 were on antihypertensive medications at the time of study. Diuretics, hydralazine, and β-blockers were prescribed for 15, 14, and 10 patients, respectively. Prazosin and clonidine were taken by two patients and captopril by one.

**Hemodynamic evaluation.** Right and left heart catheterizations were performed in all patients. No attempt was made to withhold antihypertensive drugs before the hemodynamic study. Hemodynamic measurements included right atrial, pulmonary arterial, pulmonary arterial wedge, aortic, and left ventricular end-diastolic pressures. Cardiac output was determined by the Fick method (12 patients), by indocyanine green dye dilution (six patients), or by thermodilution (10 patients). Nine patients had cardiac output determined by two methods, with a mean difference of 10 ± 10% between methods. In eight patients who had cardiac output determined with both the Fick and indicator dilution methods, the indicator dilution output was arbitrarily chosen for data analysis. Pulmonary and systemic arterial blood was obtained simultaneously at the time of cardiac output measurement in all patients for measurement of systemic arteriovenous oxygen difference. After hemodynamics were measured, biplane left ventricular angiography (30 degree right anterior oblique and 60 degree left anterior oblique projections) and selective coronary angiography were performed. Cardiac index, stroke volume index, systemic and pulmonary vascular resistance, and ejection fraction were calculated from standard formulas. Ventricular volumes were calculated with a modification of Simpson’s rule.

Median outpatient systolic and diastolic blood pressure for the first year after transplant was determined in 17 patients who had an average of 10 ± 4 outpatient blood pressure readings. In addition, the cardiothoracic ratio was measured in 15 patients who had precatherization posteroanterior chest roentgenograms of good inspiratory and technical quality.

**Right ventricular endomyocardial biopsy.** After hemodynamics and angiography were completed, right ventricular endomyocardial biopsy specimens (usually three samples) were obtained with either the internal jugular or femoral venous approach with a No. 8F or 9F Scholten bioponite. All specimens were fixed in 10% phosphate-buffered formalin and processed by routine paraffin embedding with an Autotechnicon tissue processor. They were sectioned at three levels and stained with hematoxylin and cosin. An additional section was stained with Masson’s trichrome.

The presence of rejection was assessed according to the grading system of Billingham. In addition, interstitial fibrosis was graded according to the following classification with the Trichrome stain: 0, none; 1, minimal; 2, mild; 3, moderate; 4, severe. For analytical purposes, a single episode of rejection was defined as one biopsy specimen with moderate-to-severe rejection (3 to 4+) inflammation, usually accompanied by necrosis) or as two or more specimens with moderate-to-severe rejection separated by no more than 1 week.

**Control group.** The 18 New York Heart Association class I transplant patients were compared with a control group of 18 patients (mean age 53 ± 8 years) who underwent right and left heart catheterization, biplane left ventricular angiography, and coronary arteriography for chest pain syndromes and/or an abnormal exercise treadmill test result. All patients had normal ventriculography and coronary arteriography. None of the patients had clinical evidence of cardiovascular disease, systemic hypertension, or any systemic disorder known to involve the heart. No patient in the control group was taking a cardioactive drug at the time of catheterization, with the exception of one patient on a long-acting theophylline preparation given 4 hr before hemodynamic measurement.

Cardiac output was determined by the Fick method (four patients), by indocyanine green dye dilution (10 patients), or by thermodilution (six patients). In two patients who had cardiac output determined with both the Fick and indicator dilution methods, the latter was arbitrarily chosen for data analysis.

**Data analysis.** Hemodynamic data in the transplant group were compared with the control group by Student’s t test for independent means. To determine the prevalence of hemodynamic abnormalities in the transplant group, arbitrary criteria for abnormality were chosen on the basis of generally accepted limits of normality. Linear regression analysis was used to study the relationship between various hemodynamic parameters to each other and to the cardiothoracic ratio in the transplant group. Statistical significance was defined as a p value less than .05, and data are expressed as mean ± 1 SD.

**Results.**

**Hemodynamics.** Table 1 lists mean values of several hemodynamic parameters for the 18 asymptomatic transplant patients and for the control group. There were significant differences between the two groups in most hemodynamic variables (heart rate; mean right atrial, mean pulmonary arterial, mean pulmonary arterial wedge, left ventricular end-diastolic, and mean systemic arterial pressures; cardiac index and stroke volume index; systemic and pulmonary vascular resistance; end-diastolic volume index and left ventricular ejection fraction). End-systolic volume index was not significantly different between the two groups. Systemic arteriovenous oxygen difference tended to be greater in the transplant group but did not reach statistical significance. Mean pulmonary arterial pressure was higher in the transplant group because of an increase in both pulmonary arterial systolic pressure (24 ± 8 vs 19 ± 4 mm Hg, transplant vs control group; p < .025) and pulmonary arterial diastolic pressure (14 ± 5 vs 8 ± 3 mm Hg, transplant vs control group; p < .001). Both systemic arterial systolic and diastolic pressures were higher in the transplant group (154 ± 22 vs 134 ± 17 mm Hg [p < .005] and 100 ± 11 vs 76 ± 7 mm Hg [p < .001], respectively).

The prevalence of hemodynamic abnormalities in the transplant group is demonstrated in Table 2. Sys-
Pressure end-diastolic fraction had a hemodynamic abnormality. Left ventricular correlation between left ventricular end-diastolic pressure and ejection fraction (figure 1); four of the six patients with an elevated left ventricular end-diastolic pressure had a normal ejection fraction, and three of the five patients with a decreased ejection fraction had a normal left ventricular end-diastolic pressure. All patients with reduced ejection fraction had global hypokinesis. There was no systemic relationship between β-blocker therapy and specific hemodynamic abnormalities (figure 2). Coronary arteriographic findings were normal in all patients.

Abnormal hemodynamics at 1 year after cardiac transplantation tended to ameliorate by 2 years after transplant in the five patients studied at both times (table 3). There were 12 hemodynamic abnormalities distributed among the five patients at the 1 year follow-up; these decreased to six abnormalities at the 2 year follow-up. There were 11 instances of improvement or resolution of an abnormality and only three instances of no change, worsening, or development of a new abnormality. Figure 3 shows the change in left ventricular end-diastolic pressure and ejection fraction from 1 to 2 years after transplant.

The relationship of the systemic arterial pressure to other hemodynamic parameters was studied. There was a modest \( r = -0.47, p < .01 \) inverse correlation between mean aortic pressure and ejection fraction. Mean arterial pressure was slightly, but not significantly, higher \((131 \pm 17 \text{ mm Hg})\) in the patients with abnormal ejection fraction compared with that in patients with normal ejection fraction \((120 \pm 16 \text{ mm Hg})\). There was also a modest but significant relationship \( r = .46, p < .01 \) between mean arterial pressure and left ventricular end-diastolic pressure. Mean arterial pressure was not, however, significantly different.

### Table 1: Hemodynamics 1 year after cardiac transplantation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Transplant (n = 18)</th>
<th>Control (n = 18)</th>
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<tr>
<td>HR (bpm)</td>
<td>85 ± 10</td>
<td>76 ± 10</td>
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<td>RA (mm Hg)</td>
<td>4 ± 3</td>
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<td>PA (mm Hg)</td>
<td>18 ± 5</td>
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<td>9 ± 4</td>
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<tr>
<td>LVEDP (mm Hg)</td>
<td>13 ± 6</td>
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<td>MAP (mm Hg)</td>
<td>121 ± 16</td>
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<td>SVI (ml/beat/m²)</td>
<td>28 ± 7</td>
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<td>SVR (dyne-sec-cm⁻¹)</td>
<td>2150 ± 580</td>
<td>1469 ± 454</td>
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<td>PVR (dyne-sec-cm⁻¹)</td>
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<td>EDVI (ml/m²)</td>
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<td>EF (%)</td>
<td>53 ± 10</td>
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AVo₂ diff = systemic arteriovenous oxygen difference; CI = cardiac index; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MAP = mean systemic arterial pressure; PA = mean pulmonary arterial pressure; PAW = mean pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; RA = mean right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance.

### Table 2: Prevalence of hemodynamic abnormalities 1 year after transplantation

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Data are derived from 18 asymptomatic patients. Abbreviations as in table 1.
(123 ± 14 vs 116 ± 15 mm Hg) between the patients with elevated and those with normal left ventricular end-diastolic pressure. The correlation of systolic aortic pressure with ejection fraction (r = −.48, p < .01) and left ventricular end-diastolic pressure (r = .42, p < .01) was similar to that of mean arterial pressure with these parameters. There was no significant correlation between outpatient median systolic and diastolic blood pressure and left ventricular end-diastolic pressure or ejection fraction. All five patients who were restudied 2 years after transplant had a median blood pressure determined for the 12 months before the 2 year catheterization. Three of these patients had a higher median blood pressure in the second year after transplant compared with the first year but still had improved left ventricular end-diastolic pressure and/or ejection fraction at the 2 year study (figure 3).

The patients with an abnormal ejection fraction had a shorter ischemic time (107 ± 29 min) than the group with a normal ejection fraction (164 ± 43 min), but this was not statistically significant. There was no significant correlation between ischemic time and left ventricular end-diastolic pressure or between donor age and either ejection fraction or left ventricular end-diastolic pressure.

One of 19 patients was dyspneic on mild exertion (New York Heart Association class III) at the 1 year catheterization. At the time of catheterization, he had been hospitalized for 7 months for respiratory failure secondary to Pneumocystis carinii and cytomegalovirus pneumonia. Two weeks before catheterization he had an episode of acute rejection (his sixth since transplantation). He had received dobutamine intravenously for 1½ months until 2 days before catheterization.
Hemodynamic studies revealed elevation and equilibration of the ventricular filling pressures at 18 mm Hg. The cardiac index was 2.0 liters/min/m², systemic arteriovenous oxygen difference was 6.1 vol%, end-diastolic volume index was 39 ml/m², and ejection fraction was 48%. Coronary angiographic results appeared normal. Endomyocardial biopsy showed 4+ fibrosis, 4+ inflammation, and 4+ necrosis. The patient died 6 weeks after catheterization. Postmortem examination revealed diffuse atherosclerotic narrowing (approximate 75% reduction of the luminal diameter) of the left anterior descending and circumflex coronary arteries. There was extensive fibrosis of the pericardium and epicardium. Sections of heart revealed only patchy myocardial fibrosis involving the left ventricle and no acute rejection. Marked interstitial pulmonary fibrosis was present as well as foci of bronchopneumonia.

**Results of biopsy.** Abnormal endomyocardial biopsy specimens were observed in 11 of the 18 asymptomatic patients (61%) at the time of the 1 year catheterization. There were both fibrosis and inflammation in five patients, fibrosis alone in three, and inflammation alone in three. The mean fibrosis score was 1.7 ± 0.6; the mean inflammation score was 1.6 ± 0.7. None of the patients had myocardial necrosis. In summary, the morphologic abnormalities were mild to moderate in nature. No patient was treated for rejection on the basis of these results. There was no significant difference in mean ejection fraction and left ventricular end-diastolic pressure between those patients with and without fibrosis on biopsy, or between those with and without inflammation.

There was an average of 2 ± 2 episodes of rejection from the time of transplant to the 1 year catheterization. Ten patients had 0 to 2 episodes of rejection (mean 1 ± 1) and eight patients had 3 to 6 episodes of rejection (4 ± 1). There was no significant difference in mean left ventricular end-diastolic pressure, ejection fraction, or cardiac index between the group with occasional (0 to 2) vs the group with more frequent (3 to 6) episodes of rejection.

One of the patients catheterized both at 1 and 2 years after transplant had one episode of rejection between catheterizations. The other four patients studied at both

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**TABLE 3**

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Abbreviations as in table 1.
intervals did not have any episodes of rejection during the second year after transplant. All five patients at the 2 year catheterization had normal biopsy results. The previously described pattern of fine, interstitial myocardial fibrosis was not noted in any biopsy specimen at any time.

**Cardiothoracic ratio.** The mean cardiothoracic ratio was 0.53 ± 0.05; 67% of the patients had a ratio greater than 0.50. There was a significant correlation between the cardiothoracic ratio and end-diastolic volume index (r = .60, p < .01) and end-systolic volume index (r = .64, p < .01) but not to left ventricular end-diastolic pressure or dose of prednisone.

**Discussion**

**Hemodynamic abnormalities.** This study demonstrates a relatively high prevalence of mild-to-moderate hemodynamic abnormalities in asymptomatic patients undergoing cardiac catheterization 1 year after transplantation compared with a control group. Significant differences were noted between the transplant and control patients in almost all hemodynamic parameters (table 1). The most striking and frequent abnormalities (excluding systemic hypertension, which was present in the majority of the transplant group and absent from the control group by design) were in the ejection fraction and left ventricular end-diastolic pressure (table 2). Over half the transplant patients were receiving β-blockers, drugs that may cause mild hemodynamic abnormalities in normal subjects. Our data demonstrate that there was no systematic bias relating hemodynamic abnormalities to β-blockade (figure 2). In fact, five of the six patients with an elevated left ventricular end-diastolic pressure and all three patients with an ejection fraction less than 40% were not receiving β-blockers. We emphasize, however, that the use of antihypertensive drugs may have modified the hemodynamic values in the transplant group. For example, withdrawal of diuretics, prazosin, hydralazine, or clonidine would probably have resulted in a higher systemic vascular resistance and systemic blood pressure, which in turn may have produced further rises in left ventricular end-diastolic, pulmonary arterial, and right atrial pressures. In the two patients on clonidine, withdrawal may have increased the cardiac index. On the other hand, the observed abnormalities compared with a normotensive group may have been the result of the hypertension for which the drugs were being used. Since a high percentage (90%) of eligible patients actually underwent catheterization at 1 year after surgery, we consider the observed hemodynamic abnormalities to be representative for asymptomatic heart transplant patients treated with cyclosporine and prednisone.

Long-term hemodynamic follow-up of cardiac transplant patients treated with azathioprine has been reported. Right heart pressures were within normal limits in eight asymptomatic patients studied 1 year after transplant. No control group data from the same hemodynamic laboratory were reported. Mean left ventricular end-diastolic pressure in this group was borderline elevated (12 mm Hg), while the mean cardiac output was considered to be “just within the normal range” (4.4 liters/min). In a later article from the same institution, ejection fraction in nine asymptomatic posttransplant patients calculated by fluoroscopic analysis of surgically implanted radiopaque left ventricular myocardial markers was slightly depressed; over half had an ejection fraction below 50% by this method. More recently, this same group reported an ejection fraction of 59% in 22 patients treated with azathioprine undergoing contrast left ventriculography 1 year after transplant. A relatively high prevalence of segmental wall motion abnormalities (32%) was noted in that study. Again, no data from a control group studied in the same hemodynamic laboratory were reported. Only patients preselected for survival 5 years or more after transplant (representing only 24% of the patients transplanted between 1968 and 1975) were included in that study.

The available data make comparison difficult between the spectrum of hemodynamic abnormalities with azathioprine and prednisone vs cyclosporine and prednisone, except that systemic hypertension appears more prevalent with cyclosporine and prednisone. Despite the presence of hemodynamic abnormalities reported in patients on conventional immunosuppression, mortality in this group does not appear to relate to progressive isolated myocardial dysfunction but rather to infection, acute rejection, and graft atherosclerosis. This observation, coupled with an improvement in hemodynamics in the five patients studied at 2 years in our study, suggests that hemodynamic abnormalities noted at 1 year follow-up may not portend an unfavorable outcome.

**Etiology of hemodynamic abnormalities.** Hemodynamic abnormalities must precede surgery, develop postoperatively, or both. The former category includes preexisting heart disease in the donor and abnormalities incurred during graft preservation. Preexisting heart disease in the donors appears very unlikely in view of their youth and negative history and lack of clinical evidence of heart disease. Likewise, the lack of correlation between ischemic time and hemodynamic ab-
normalities suggests that inadequate graft preservation is unlikely to account for these findings.

Postoperative factors that might cause left ventricular dysfunction include rejection, systemic arterial hypertension, or less well-defined factors. Acute rejection may result in myocardial fibrosis. Endomyocardial biopsy specimens obtained at the time of cardiac catheterization did not demonstrate a relationship between hemodynamic abnormalities and myocardial fibrosis or inflammation. A relatively large proportion of patients had totally normal biopsy results, with the remainder having only mild-to-moderate abnormalities. When patients with infrequent and those with frequent episodes of rejection were compared, there was still no significant difference in mean left ventricular end-diastolic pressure or ejection fraction. We and others were unable to confirm the finding of fine intercellular fibrosis associated with cyclosporine use after transplant. Thus it seems unlikely that either myocardial fibrosis or inflammation are responsible for the hemodynamic abnormalities noted in this study.

Accelerated coronary atherosclerosis and secondary left ventricular dysfunction may occur as a manifestation of chronic rejection. However, coronary arteriography was normal in all of the asymptomatic patients.

The almost universal development of hypertension in heart transplant patients receiving cyclosporine is in marked contrast to the infrequent occurrence of hypertension in patients treated with azathioprine and prednisone. By comparison, in a large randomized trial of cyclosporine vs azathioprine in renal transplant patients, approximately half of the patients in each group developed hypertension. Preliminary data from our institution indicate that this new-onset hypertension after cardiac transplantation is relatively resistant to treatment and is associated with modest renal insufficiency (mean creatinine 2.2 mg/dl) and normal values for peripheral plasma renin activity and urinary catecholamines. Unlike the patients with early essential hypertension who have been reported to have an elevated cardiac output and a normal calculated peripheral vascular resistance, the cardiac transplant patients demonstrated a mildly reduced cardiac output and an elevated peripheral vascular resistance (table 1) more typical of long-standing hypertension.

A significant correlation existed between systemic blood pressure at the time of cardiac catheterization and both left ventricular end-diastolic pressure and ejection fraction. Although the correlation was not particularly high, it is similar to the correlation between arterial pressure and echocardiographically determined left ventricular hypertrophy and may reflect the fact that systemic blood pressure is not linearly related to abnormal left ventricular function at all stages of hypertension. Another factor that may have reduced the closeness of fit between blood pressure and hemodynamic abnormalities is the antihypertensive therapy these patients were receiving, which can ameliorate cardiac abnormalities somewhat independently of the level of arterial pressure.

Another possibility is that hemodynamic abnormalities seen after transplant are independent of systemic hypertension. Evidence in favor of this hypothesis is the fact that azathioprine-treated patients seemed to demonstrate a similar depression in ejection fraction despite a low prevalence of hypertension.

One patient was symptomatic at the time of the 1 year hemodynamic study. On the basis of his catheterization and biopsy data, he was presumed to have constrictive pericarditis or restrictive cardiomyopathy secondary to chronic and/or acute rejection. At autopsy, marked pericardial and epicardial fibrosis were found. This case emphasizes that constrictive pericarditis may be the cause of cardiac symptoms and abnormal hemodynamics after transplantation.

Abnormal cardiothoracic ratio. The increased cardiothoracic ratio in the majority of asymptomatic patients demonstrates that `cardiomegaly' is not necessarily a sign of left ventricular volume overload, since the end-systolic volume and end-diastolic volume indexes in these patients were comparable to those in our control group. However, a significant correlation existed between ventricular volumes and cardiothoracic ratio, suggesting that left ventricular volume does represent a component, although perhaps not the major one, in the increased cariothoracic ratio. Potential causes for this increase not examined include subepicardial fat secondary to administration of steroids, left ventricular hypertrophy, and pericardial effusion.

In summary, asymptomatic heart transplant recipients treated with cyclosporine and prednisone have a relatively high prevalence of mild-to-moderate hemodynamic abnormalities. The etiology of these abnormalities remains to be determined but may be related to the universal development of hypertension after transplantation. Although the findings in patients studied at 2 years demonstrate that the frequency and severity of these abnormalities may ameliorate over time, continued follow-up will be required to clarify the long-range effect of cyclosporine in the cardiac transplant patient.

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