Increasing Pericardial Effusion in Cardiac Transplant Recipients

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Although pericardial effusion after cardiac surgery is frequent and usually benign, its etiology and prognosis after cardiac transplantation are unknown. During 1 year (1985–1986), 12 of our current transplant population (total, 189) developed moderate or large pericardial effusions confirmed by two-dimensional echocardiography. These effusions occurred within 1 month of transplantation in 10 patients and at 3 months and 4.5 years in the other two. Pericardiocentesis was performed because of clinical evidence of increasing effusions in eight patients, with demonstrable hemodynamic compromise secondary to tamponade in five. Pericardial fluid was sterile in all but one. Endomyocardial biopsy at the time of increasing effusion revealed moderate acute rejection in five patients, mild rejection in three, and no rejection in four. All three patients with mild rejection had moderate acute rejection on subsequent biopsy performed within 7 days. In two of the four with no rejection, repeat biopsy within 5 days showed moderate acute rejection; in a third, moderate rejection was present on biopsy performed 14 days later. *Legionella dumoffii* was isolated from the pericardial fluid of the fourth patient, whose subsequent biopsies never showed rejection. Three of the 12 patients developed progressive ventricular dysfunction sufficiently severe to require retransplantation. One patient died suddenly 12 months after transplantation, and autopsy examination revealed severe coronary artery disease. Two died of sepsis within 3 months of transplantation. Intense inflammatory infiltrates and thickening of the pericardium and epicardium were characteristically present in explanted and autopsy hearts. The remaining six patients were fully rehabilitated with normal ventricular function at 12–20 months after transplantation. These data suggest a temporal relation between development of moderate or large pericardial effusions and allograft rejection that may involve the pericardium. The clinical course and autopsy findings of these transplant recipients indicate an etiology and prognosis of pericardial effusions different from those associated with other forms of cardiac surgery. (*Circulation* 1989;79:603–609)

Pericardial effusions of moderate size occur in at least 56% of patients early after cardiac surgery. They are usually related to hemorrhage, rarely cause tamponade, and therefore are thought to be of little clinical significance. The etiology and prognosis of pericardial effusions after cardiac transplantation are unknown. Our index patient was known to have a small but stable pericardial effusion since transplantation. The patient had a large pericardial effusion associated with acute rejection 4.5 years after transplantation. During a concurrent study of echocardiographic changes associated with acute rejection, we noted small pericardial effusions in all patients during the first postoperative week. In some of them, pericardial effusions increased in size sufficiently to require pericardiocentesis. We, therefore, prospectively examined the clinical course of these patients with reference to the temporal relation between acute rejection episodes and increasing effusion and assessed their subsequent ventricular function. This report documents the findings from our index patient and 11 other patients after transplantation.

Methods

Patients

The study population was drawn from a total of 189 patients, of whom 85 were undergoing routine postcardiac transplantation surveillance at Stanford...
Medical Center. These 85 patients were seen at regular intervals in the early (1–6 weeks), intermediate (6–24 weeks), and late (>24 weeks) postoperative period. Time that elapsed between transplantation and entry to the study ranged from 5 days to 17 years: 17 patients, more than 1 year; 11 patients, 6–12 months; eight patients, 3–6 months; and 49 patients, 7 or fewer days. During the 1-year study period, none of the 104 patients receiving routine follow-up care outside of Stanford developed increasing pericardial effusion. Of the Stanford patients, 10 in the early and one in the intermediate postoperative period had enlarging pericardial effusions. Observations from these 11 patients and our index patient (10 men and two women; aged 20–50 years; mean, 41 years) form the basis of this report. All subjects gave informed consent to the protocol approved by the Committee for the Protection of Human Subjects at the Stanford University Medical Center.

Patient characteristics are summarized in Table 1. Indications for transplantation were dilated cardiomyopathy in eight patients, coronary artery disease in three, and retransplantation for graft atherosclerosis in one. Maintenance immunosuppression in all patients included cyclosporine (2–10 mg/kg/day), azathioprine (1.0–2.0 mg/kg/day), and prednisone (0.3–0.5 mg/kg/day).

Control Subjects

Echocardiography was performed in two control groups. The first consisted of 17 concurrent transplant recipients of age and gender distribution similar to those defined above. In these control transplant patients with little or no pericardial effusion and normal biopsy results, serial biopsy-correlated ultrasound studies were performed during the early and intermediate postoperative periods. Control transplant patients were matched to study patients with respect to donor and recipient age, and time elapsed from transplantation. Measurements made in the absence of acute rejection were used for comparison. The second control group consisted of 10 age- and gender-matched normal subjects.

Serial Assessment

In addition to daily physical examination to document clinical signs of hemodynamic compromise, the following serial investigations were performed.

Chest radiography and electrocardiography. Daily chest radiographs and electrocardiograms were performed during the initial 2 weeks after transplantation, and twice weekly thereafter. For the purpose of this study, chest radiographs were evaluated for evidence of enlarging cardiac silhouette. Electrocardiographic analysis included summation of voltages in leads I, II, III, V_{1}, and V_{6}.

Endomyocardial Biopsy

Patients in the early postoperative period had endomyocardial biopsies performed routinely at weekly intervals during the initial 4–6 weeks and at 2-week intervals thereafter. Additional biopsies were performed when either enlarging pericardial effusion or hemodynamic deterioration was noted and in all patients undergoing pericardiocentesis. In the late postoperative period, endomyocardial biopsies were obtained at 3-month intervals and when clinically indicated. Biopsies were performed from the right internal jugular vein with a Caves-Schultz biopsy technique previously described and analyzed by an experienced pathologist (M.E.B.) without prior knowledge of clinical status of the patients. Biopsies were graded according to the Billingham criteria: no rejection, mild or resolving rejection, moderate rejection, or severe rejection. For the purpose of quantitative analysis, a numerical score was assigned to each biopsy grade: no rejection, 1; mild or resolving rejection, 2; moderate rejection, 3; and severe rejection, 4.

For analysis of the temporal relation of acute rejection to increasing pericardial effusion, biopsy findings before and after development of clinical signs of increasing effusion were evaluated.

Echocardiography. Two-dimensional and M-mode echocardiographic studies were obtained in all patients to detect pericardial effusion and assess left ventricular systolic function. Serial studies were obtained biweekly during the initial 6 postoperative weeks and at weekly intervals thereafter. Two observers, by consensus, graded each pericardial effusion on serial two-dimensional echocardiographic views as small, moderate, or large. M-mode analysis included left ventricular end-diastolic and end-systolic dimensions and calculation of shortening fraction by standard methods. All patients were analyzed without previous knowledge of biopsy findings.

Pericardiocentesis. Pericardiocentesis was performed from the subxiphoid approach with sterile technique. The volume and gross appearance of the pericardial fluid were recorded. Microscopic examination for organisms, red blood cells, and differen-
tial white cell count was performed. Gram stain was performed routinely, and all samples were cultured for bacteria, viruses, and fungi. Protein analysis was not obtained.

Clinical outcome. The subsequent clinical courses of these 12 patients were evaluated with respect to development of ventricular dysfunction, coronary artery disease, sepsis, and survival.

Autopsy study. Sections of the right ventricle, left ventricle, and pericardium obtained from the explanted heart or at autopsy were reviewed.

Statistical Methods

Analysis of variance was used to compare the differences between group mean values for echocardiographic measurements and biopsy scores. The Scheffé F test for statistical significance was used.

Results

The clinical features documented when increasing pericardial effusions were initially recognized are summarized in Table 2.

Diagnosis of Increasing Pericardial Effusion

Our index patient (Patient 1) had a large pericardial effusion on day 1,354 after transplantation. Of the remaining 11 patients, enlarging effusion was recognized during the initial 10 postoperative days in four, between days 10 and 20 in five, and at days 22 and 83 in the others.

Our index patient had previous evidence of a small effusion that had been stable since the initial 6 months after transplantation. Hemodynamic compromise with a large effusion at presentation necessitated pericardiocentesis within 24 hours. One other patient (patient 10) had acute pulmonary edema, and a moderate-sized pericardial effusion was diagnosed incidentally on echocardiography performed to assess left ventricular function. Progressive enlargement of pericardial effusion was documented in 10 patients based on increasing cardiac silhouette. By echocardiography, moderate-sized effusions had become large in eight patients; in one, a small effusion had become moderate; and one appeared to have a stable moderate effusion on both studies.

Summated electrocardiographic voltage decreased in seven patients, remained unchanged in four, and increased in one.

Evidence of hemodynamic compromise was present in six patients: all had a decrease in blood pressure compared with previous serial measurements; pulsum paradoxus of more than 15 mm Hg was noted in four; and one developed acute pulmonary edema. Pericardiocentesis was performed in eight because of increasing effusion or the need to exclude an infectious etiology or both. Four patients with moderate-sized effusions did not undergo pericardiocentesis: all of them showed resolution of effusion after treatment for moderate acute rejection. Despite an initial decrease in effusion after treatment for acute rejection in one patient, subsequent recurrence of effusion, in association with further rejection, necessitated pericardiocentesis. Elapsed time between initial recognition of increasing effusion and pericardiocentesis ranged from 1 to 56 days. In four patients, intervention was decided on within 1 week.

Echocardiographic Features

Table 3 compares M-mode indexes of ventricular function in the 10 patients with moderate or large pericardial effusions with those in the two control groups. Pericardial effusion was typically located posteriorly and laterally, with little or no effusion being present anteriorly in most cases.

Abnormal septal motion was present in most transplant recipients. Mean values for cavity dimensions were similar in transplant recipients with effusion versus control transplant patients. How-
TABLE 3. Echocardiographic Indexes in Patients and Normal Subjects

<table>
<thead>
<tr>
<th>Patient</th>
<th>LVESD (cm)</th>
<th>LVEDD (cm)</th>
<th>FS (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>3.0</td>
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<td>2</td>
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</tr>
<tr>
<td>12</td>
<td>2.4</td>
<td>4.0</td>
<td>40</td>
</tr>
</tbody>
</table>

Mean values

PE patients: 2.8±0.7 4.3±0.35 36.4±14.0
Control patients: 2.6±0.4 4.3±0.6 38.0±2.1
Normal subjects: 3.5±0.4* 5.2±0.3* 32.0±1.0*

LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; FS, fractional shortening; PE, pericardial effusion.

Ever, three study patients with moderate acute rejection had increased left ventricular end-systolic dimension and decreased fractional shortening. Compared with normal subjects, cavity dimensions were lower and percent fractional shortening was higher in transplant recipients, with or without effusion.

Pericardial Effusions at Pericardiocentesis

The volume of pericardial fluid obtained ranged from 650 to 1,200 ml, and all were serosanguinous.

TABLE 4. Endomyocardial Biopsy Findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Bx before inc. PE</th>
<th>Bx on day of inc. PE</th>
<th>No. of days to next Bx</th>
<th>Bx post inc. PE</th>
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<tbody>
<tr>
<td></td>
<td>Grade</td>
<td>Score</td>
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<tr>
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<td>NR</td>
<td>1</td>
<td>MAR</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>2</td>
<td>MAR</td>
<td>3</td>
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<td>3</td>
<td>Mild</td>
<td>2</td>
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<td>4</td>
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<td>1</td>
<td>NR</td>
<td>1</td>
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<tr>
<td>5</td>
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<td>1</td>
<td>Mild</td>
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<tr>
<td>6</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
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<td>NR</td>
<td>1</td>
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<td>1</td>
<td>Mild</td>
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<tr>
<td>9</td>
<td>NR</td>
<td>1</td>
<td>MAR</td>
<td>3</td>
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<td>MAR</td>
<td>3</td>
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<tr>
<td>11</td>
<td>NR</td>
<td>1</td>
<td>Mild</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
<td>1</td>
</tr>
</tbody>
</table>

Mean biopsy score: 1.17±0.39 2.08±0.9* 2.42±0.79* 2.25±0.75*

Bx, biopsy; inc. PE, increasing pericardial effusion; NR, no rejection; Mild, mild rejection; MAR, moderate acute rejection; Res, resolving rejection.

*p<0.05 vs. biopsy score before increasing pericardial effusion.

Nine effusions were sterile, and Legionella dumoffii was cultured from the tenth. The sterile effusions generally had a low white cell count that included polymorphonuclear leucocytes and mononuclear cells.

Endomyocardial Biopsy

During the entire study period, 115 endomyocardial biopsies were obtained in the 12 patients who developed increasing pericardial effusion. Of these, 24 revealed moderate acute rejection; six, mild rejection; and 18, resolving rejection. The remainder showed no evidence of acute rejection. Moderate acute rejection was diagnosed in 16% of biopsies performed during the 1-year study period; 70% of positive biopsies in the 12 patients reported were associated with increasing effusion. None of the remaining 177 patients developed increasing pericardial effusion during the study period, despite an average of 0.5 rejection episodes/patient.

Results of serial endomyocardial biopsies and their temporal relation to clinical evidence of increasing pericardial effusion are summarized in Table 4. Biopsies performed 7 days before increase in effusion in patients 2–12 showed mild rejection in two patients and no evidence of rejection in all others. In our index patient, the endomyocardial biopsy 6 weeks preceding her presentation, as well as four others during the preceding 12 months, showed no rejection.

Endomyocardial biopsy performed within 24 hours of diagnosis of increasing effusion revealed moderate acute rejection in five patients, mild rejection in three, and no evidence of rejection in four. The mean rejection score was significantly higher at the time of increasing pericardial effusion compared with the previous biopsy. Despite the administra-
tion of acute rejection therapy to patients showing moderate rejection, the mean rejection scores in the two subsequent biopsies remained higher compared with pre-effusion scores.

All five patients with biopsy evidence of moderate acute rejection were treated with intravenous methylprednisolone (3 g). Follow-up biopsy performed 7–14 days after the one performed at the time of detection of effusion showed absence of rejection in one patient, reversal of rejection in three, and continued moderate rejection in two. In one of these two, resolution of moderate rejection was achieved after a further course of methylprednisolone. In the other, a third course of methylprednisolone in addition to rabbit antithymocyte globulin was required for adequate treatment of the rejection episode.

The three patients with mild rejection on the initial biopsy had all progressed to moderate acute rejection on subsequent biopsy performed 7–14 days later. Resolution of rejection in two of them required two courses of methylprednisolone as well as rabbit antithymocyte globulin in one. In the third patient, rejection was adequately treated by one course of methylprednisolone.

Of the four patients showing no evidence of rejection at the time of increasing pericardial effusion, two had moderate acute rejection on biopsy performed within 5 days subsequently. Both required three courses of methylprednisolone for treatment of persistent rejection on the two subsequent biopsies. The third patient had mild rejection on the next biopsy, but moderate rejection on the subsequent biopsy 14 days later. The fourth patient (patient 4) was found to have pericarditis with *Legionella*, and all four subsequent endomyocardial biopsies showed no evidence of rejection.

**Clinical Course and Autopsy Results of Patients**

Three patients developed progressive decline in left ventricular function consistent with nondilated, restrictive cardiomyopathy and had symptoms sufficiently severe for retransplantation. One died of intractable heart failure before a donor heart could be found; autopsy examination revealed a thickened epicardium with a pronounced perivascular infiltrate. Examination of the endomyocardium from the right ventricle showed focal areas of mild inflammatory infiltrate. The second is currently stable in New York Heart Association functional Class III. Our index patient underwent retransplantation but died of sepsis in the early postoperative period. The explanted heart weighed 360 g without atria. The pericardium was thickened, and histologic sections contained extensive lymphocytic infiltrates. The subendocardium of the left ventricle demonstrated severe myocyteolysis. Within the left ventricle and ventricular septum were multiple foci of organizing infarcts. A small focus of recent infarction was present in the posterior papillary muscle. There were focal areas consisting of spindle-shaped fibroblasts, hemosiderin-laden macrophages, and small aggregates of lymphocytes and plasma cells, suggesting healed or resolving rejection. In the right ventricle, there were also extensive interstitial collections of lymphocytes and plasma cells, consistent with previous rejection.

Three other patients have died since their initial evaluation. In one, sudden death occurred 12 months after transplantation and, despite a normal endomyocardial biopsy and coronary angiographic appearance 1 week before death, autopsy examination revealed a vasculitis affecting the large coronary arteries. The pericardium was thickened and contained a marked inflammatory infiltrate. The two remaining patients died of sepsis within 3 months of transplantation. Autopsies were performed, and in one confirmed pericarditis with *Legionella*. Six patients have clinical and echocardiographic evidence of normal ventricular function 6–20 months after transplantation.

**Discussion**

Although pericardial effusions have been reported after experimental and clinical cardiac transplantation,5–7 their etiology and prognostic implications are unknown. In early experimental studies to evaluate change in electrocardiographic voltage associated with acute rejection, pericardial effusion was postulated as a cause of decreased voltage.6 Direct measurement of myocardial voltage, however, demonstrated that the changes may be independent of pericardial effusion.6 In the present study, decrease in electrocardiographic voltage was documented in seven patients, including two whose biopsies did not show evidence of myocyte necrosis or myocardial edema at that time. One of the five patients with moderate rejection had no demonstrable change in electrocardiographic voltage. These findings indicate that observations of ECG changes in the present series were primarily related to development of moderate or large pericardial effusions. Since increase in cardiac silhouette occurred in 10 patients, simple radiographic changes may identify most patients who develop moderate or large effusions after cardiac transplantation.

Previous studies have used echocardiography to characterize changes in left ventricular function of the human allograft during rejection.4,8 In patients treated with cyclosporine, echocardiographic indexes of systolic function have been shown to be poor predictors of acute rejection. In this study, transplant recipients (with or without effusion) had lower mean left ventricular end-systolic dimension and higher fractional shortening compared with normal subjects. This may be explained by the more rapid heart rate and increased sensitivity to circulating catecholamines characteristic of these patients.9 In three patients with effusion and acute rejection, left ventricular end-systolic dimension was increased and shortening fraction reduced. This evidence of systolic dysfunction cannot be
explained by pericardial effusion and suggests that concomitant myocardial dysfunction occurs in some patients with acute rejection.

Pericardial effusions in these patients were not typically circumferential but more localized laterally and posteriorly, with little or none anteriorly. The explanation for this asymmetric distribution is uncertain but may be related to fusion of tissues anteriorly where the pericardium is left open.

The natural history of pericardial effusion in transplant recipients is unknown. In patients undergoing other forms of cardiac surgery, pericardial effusions were noted to increase during the initial week, becoming maximal by the 10th postoperative day, and most commonly subsequently resolving without complications. The transplant recipients we report behaved differently in that pericardial effusions increased after the 1st postoperative week, often having been present but stable for a long period after the initial diagnosis.

Late pericardial effusions after cardiac surgery have most frequently been associated with the postpericardiotomy syndrome. This condition is usually accompanied by constitutional symptoms, and an immune etiology has been postulated. The late presentation of our patients and subsequent benign course in half of them is thus at least consistent with a postpericardiotomy syndrome. Against this, however, was the accompanying impairment of systolic function in three patients. This clinical course is seldom associated with the postpericardiotomy syndrome. Moreover, maintenance prednisone administration would be expected to minimize the influence of the usual postpericardiotomy syndrome.

Previous reports have failed to document a strong relation between pericardial effusion and acute allograft rejection. Vandenberg et al reported on 52 patients who underwent regular echocardiographic examination. These authors did not identify any single clinical variable, including acute rejection, associated with effusion. They suggest that the combination of cyclosporine therapy, preoperative diagnosis of idiopathic dilated cardiomyopathy, and acute rejection yielded a probability of 86% of having pericardial effusion after transplantation. The results of the present study therefore contrast with those of Vandenberg et al and may be explained by the different methodology used. Because the present study was prospective, we were better able to assess the temporal relation of biopsy findings to development of increasing effusion. As in the Vandenberg study, stable pericardial effusions were frequently noted in the early postoperative period, and showed little correlation with acute rejection. Increasing pericardial effusion, however, was associated with, and often preceded, acute rejection.

In the present study, one third of the patients were studied during the initial 6 weeks after transplantation, when acute rejection is common. The high frequency of biopsies needed in the 12 patients reported and the temporal relation we observed may, therefore, be coincidental. Because increasing pericardial effusion associated with acute rejection occurred in only one (index) patient during the late postoperative period, the data indicate that increasing pericardial effusion is a rare manifestation of late acute rejection. Nevertheless, our index patient presented 4 years after transplantation, with a large pericardial effusion associated with acute rejection. Even though subsequent reaccumulation of effusion was unassociated with biopsy evidence of acute rejection, histologic findings of the explanted heart suggest that an immune process unrecognized on the many previous endomyocardial biopsies examined may have accounted for the progressive decline in ventricular function during this interval. In addition to a heavy lymphocytic infiltrate, considerable plasmacytosis was noted in the right ventricle of the explanted heart. In this patient and the two others who had autopsy examinations, the pericardium was thickened and contained a lymphocytic infiltrate.

These results provide evidence, previously unreported, in support of a noninfectious inflammatory reaction involving the pericardium that is associated with acute rejection. The absence of histologic evidence of acute rejection at the time of increasing effusion in three patients and their subsequent rapid progression to acute rejection (within 2, 5, and 7 days) may be partly related to biopsy sampling error. Experimental studies have shown that acute rejection may preferentially affect either ventricle, but none have indicated that the pericardium may similarly be involved. Results of the present study suggest that during acute rejection an inflammatory reaction may also occur in the epicardium and the pericardium, with rapid increase in pericardial effusion.

A recent study examined the influence of different maintenance immunosuppressive regimens on the frequency of pericardial effusion in cardiac transplant recipients. The highest frequency of effusion occurred in patients maintained on cyclosporine without steroids. Although the relation of acute rejection to pericardial effusion was not examined, the increased prevalence of effusion in patients not maintained on steroids indicates an immune etiology. Therefore, we believe that an increasing, as opposed to stable, pericardial effusion in transplant recipients should alert physicians to the possibility of rejection or of an immune-mediated process that may become severe enough to adversely affect ventricular function.

References

**KEY WORDS** • pericardial effusion • transplantation
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