Acute Rejection
Following Cardiac Transplantation
Phonocardiographic and Ultrasound Observations

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SUMMARY
Nine patients have undergone cardiac transplantation at Stanford University Hospital. Three of these showed no clinical evidence of rejection and had essentially normal physical and phonocardiographic findings. There were eight distinct early rejection episodes in the other six patients. Early rejection was accompanied by decreasing QRS voltage, an early diastolic gallop, and frequently a rightward shift of the mean electrical axis of the heart. If not treated, this progressed to severe heart failure with a right ventricular heave, biventricular gallop, marked elevation of venous pressure with rapid y descent and severe dyspnea without orthopnea. Ultrasound measurements show increasing posterior wall thickness and overall heart diameter during the rejection episode. With aggressive therapy, all of these signs usually resolve rapidly, suggesting that dysfunction of the rejecting heart is secondary to the interstitial edema, vascular engorgement, and cellular infiltration, causing restriction of diastolic filling. These cardiovascular signs appear to aid detection of early cardiac rejection and allow treatment at an earlier stage of the rejection process.

Additional Indexing Words:
Heart sounds  Posterior wall thickness  Immunosuppressive agents
Prednisone  Azathioprine  Antilymphocytic globulin

OVer 100 cardiac transplantations have been accomplished in the world over the past year, with approximately 20 to 30% survival for 3 months or longer. After initial recovery from surgery, acute rejection and infection secondary to high doses of immunosuppressive agents have been major causes of the high mortality. Efforts to detect earlier signs of rejection continue, so that maintenance immunosuppression can be at lower doses, and yet aggressive therapy may be begun at an earlier stage of the rejection before irreversible damage to the heart has occurred. Presently, a decrease in electrocardiographic voltage appears to correlate most closely with beginning cardiac rejection. Of the nine patients undergoing cardiac transplantation at Stanford University Hospital, six have had eight distinct rejection episodes. This report presents the physical, phonocardiographic, and ultrasound cardiac findings during acute rejection in four of these patients. Experimental histopathologic data can be correlated with the clinical findings and may explain the nature of cardiac dysfunction during acute rejection and, therefore, may explain other early physiologic signs of the rejection process.

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Methods

Standard electrocardiograms were taken daily on a Sanborn model 500 with the patient's head elevated at 15°. To assure constant position, precordial placement for the exploring electrode was marked with ink. All illustrated graphs represent the sums of voltages for leads I, II, III, V1, and V6. Phonocardiograms were taken with a Sanborn Twin-Beam portable model 62. Carotid artery, external jugular venous and apex cardiograms, in addition to the ECG, were recorded when possible. Corrected ejection times were calculated according to the method of Weissler, and associates.3

Ultrasound cardiac examinations were made every other day using a commercially available ultrasonoscope* utilizing 1,000 impulses/sec repetition with an 0.75-inch diameter, 2.25-mega-Hertz transducer. The transducer was placed at the left sternal border in the fourth intercostal space and directed posterolaterally to record the posterior left ventricular wall echoes as previously described.4 5 The instrument was adjusted to display the echoes from the interventricular septum as well as the posterior wall echoes. The M or motion display was used. The records were measured at a point in the cardiac cycle which corresponded to end-diastole, as judged from the electrocardiogram simultaneously recorded. Overall heart size from the anterior wall to the posterior wall was the total distance from the first myocardial echoes, just behind the chest wall echoes, to the posterior pericardial echo. Right ventricular dimension was the distance from the anterior heart wall to the most anterior of the interventricular septum echoes. Posterior wall thickness was the distance from the endocardial surface of the posterior left ventricular wall to the pericardium. Measurements were facilitated by distance markers which correspond to 1 cm of tissue and are part of the ultrasound record. Measurements were performed by a single observer (R.L.P.) with repeated measurements of the same records after randomization of the sequence of the records on at least three occasions. If variation of measurement was found, an average figure was used for each record. When measurements of wall thickness determined in this manner were compared with data from necropsy in four patients, an average error of ±1 mm was observed.

Report of Cases

Detailed case histories have been reported elsewhere, and will not be repeated in this article.6

Case L.D.

A 42-year-old man had a cardiac transplant on August 22, 1968, for severe coronary artery disease. Immediately after operation he was digitalized because of an elevated venous pressure. His course was otherwise uncomplicated and he was ambulating fully by postoperative day 9. The heart sounds were normal (fig. 1) and the cardiac silhouette was normal by x-rays. On postoperative day 15, treatment with antilymphocytic globulin was stopped because of severe allergic reaction to this material. Two days later, on days 17 to 19, the QRS voltage began to decline (fig. 2). On day 19, an early diastolic gallop 0.10 sec after A2 was first heard and continued to increase in intensity, but remained early in diastole. On day 23, right atrial biopsy was done during repair of sternal dehiscence. The histologic findings showed round cell infiltration, vascular engorgement, and interstitial edema, consistent with early rejection; immunosuppressive drugs were increased. On postoperative day 25, ultrasound measurements of the overall heart diameter (AW-PW) and right ventricular diameter (RVD) increased with subsequent increase in posterior wall thickness (PWT) by days 27 to 29 (fig. 2). By day 30 the patient complained of severe lethargy, and a further decline in the QRS voltage accompanied by a shift of the mean frontal electrical axis of the heart to the right had occurred. There was marked venous distention with rapid y descent and clinical signs of low cardiac output. A parasternal heave and a loud,

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*An Ekoline 20 instrument was kindly loaned to us for this study by the Smith Kline Instrument Company, Palo Alto, California.
Figure 2

Outline of postoperative course in case L.D. From the top down are shown: Posterior wall thickness (PWT) in mm; right ventricular diameter (RVD) in mm, represented by solid triangles; overall heart dimensions from anterior to posterior wall (AW-FW) in mm, represented by the open triangles (note inverted scale for RVD and AW-FW); mean frontal electrical axis in degrees represented by solid circles; total QRS voltage (sum of leads I, II, III, V_{1}, and V_{6}) represented by open circles; prednisone dosage (PRED) in mg/day; antilymphocyte globulin (ALG); azathioprine (AZA) in mg/day; postoperative day (POD); phonocardiogram (Phono ↑) showing dates of recordings illustrated in figure 1.
early diastolic gallop were present. The patient was able to lie flat in bed comfortably but complained of dyspnea on the slightest exertion. Treatment for rejection was increased with only slight clinical improvement from days 30 to 36. QRS voltage remained low, and there continued to be an early diastolic $S_8$ and occasionally $S_4$. Retreatment with high doses of steroids on day 40 could not be continued because of intercurrent pulmonary infection by Pneumocystis carinii, and the patient expired on postoperative day 46, despite treatment with pentamidine. At postmortem examination, moderate rejection was manifested by mild mononuclear infiltration, interstitial edema, areas of myocardial degeneration, and proliferative arterial lesions. The posterior left ventricular wall thickness measured 17 mm and correlated well with the ultrasound measurement of 18 mm on the day of death.

The decline in QRS voltage and appearance of the early diastolic gallop 17 to 19 days after operation coincide with the increase in right ventricular and overall heart dimensions, and posterior wall thickness. Since this was the first transplant patient to have ultrasound measurements, there was more day-to-day variation on these records; however, the general changes are consistent with those in subsequently described cases. There was further decline in QRS voltage over days 19 to 29. By postoperative day 29 to 30, definite signs of cardiac failure were evident. Despite treatment, the abnormalities continued, and at postmortem examination, there was gross and microscopic evidence of cardiac rejection.

**Case R.M.**

This 51-year-old man had been followed at Stanford Medical Center for 1½ years for progressive disability secondary to atherosclerotic coronary heart disease. He underwent cardiac transplantation on August 31, 1968. Immediate postoperative recovery was satisfactory; however, an early $S_8$ was first noted on postoperative day 3 (fig. 3). By day 7, QRS voltage was declining, and ultrasound studies showed increased right ventricular diameter (RVD), overall heart dimensions (AW-PW), and posterior wall thickness (PWT) (fig. 4). By days 9 and 10, the patient was complaining of marked fatigue, anorexia, and weakness. Venous distention with prominent $a$ and $v$ waves, hepatomegaly, peripheral edema, and cool extremities developed. QRS voltage remained low, and the right axis shift was marked. There was a marked right ventricular heave and the $S_3$ corresponded in timing with the rapid filling wave in the right ventricular apexcardiogram. Treatment for rejection was initiated on day 8, and by day 15 the axis had returned to normal, QRS voltage had risen, and ultrasound measurements returned toward normal range. The patient resumed normal hospital activity. The $S_8$ diminished markedly in magnitude but remained audible and increased in intensity on exercise or inspiration. By day 24, the $S_3$ had become pronounced, coincident with an increase in posterior wall thickness and decline in QRS voltage. By day 29, the patient again had clinical signs of rejection with heart failure. He received massive doses of methylprednisolone sodium

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**Figure 3**

Phonocardiograms recorded after cardiac transplantation in case R.M.: Abbreviations same as in figure 1.
sucinate, and over the next 2 weeks there was gradual improvement in his QRS voltage and ultrasound measurements. The early diastolic gallop diminished but remained present through day 46; it was particularly noticeable on inspiration or exertion and did not disappear completely until day 56. At day 150 he had no cardiovascular symptoms on moderate exertion, including bicycle riding, and there are no abnormal heart sounds on examination. Ultrasound measurements and QRS voltage remain stable.

It is possible that the early diastolic gallop heard on postoperative days 2 and 3 may have been the first sign of early rejection. The rejection process became clinically evident on days 8 through 10. With treatment there was clinical improvement but only temporary reversion in the ultrasound measurements and QRS voltage. Although the S₃ also diminished in intensity, it

Outline of postoperative course in R.M. See figure 2 for explanation. Actinomycin D (ACT-D) was given on days 10 and 11.

Figure 4
remained present and gradually became louder on days 20 to 30, with clinically obvious recurrent rejection present on days 29 to 30. The slow improvement in QRS voltage and ultrasound measurements after this may represent slower resolution of the rejection process. The presence of an S₃ until day 56 raises the question of residual damage from the two episodes of acute rejection. These two episodes could represent inadequate treatment of the first rejection episode, as suggested by the abnormal ultrasound measurements and continuing S₃, or a second separate rejection soon after the first.

**Case V.A.**

This 54-year-old housewife underwent cardiac transplantation on September 9, 1968, because of coronary heart disease with a huge aneurysm involving the entire apex of her left ventricle. Postoperatively she did extremely well, and was ambulatory by the second postoperative day. There were no clinical episodes of rejection. QRS voltage, although varying, showed no definite trend and the QRS axis remained stable (fig. 5). Her ultrasound measurements also remained stable. Except for a systolic ejection flow murmur and split S₃ (fig. 6), her heart sounds remained normal. She was discharged from the hospital on day 30, and continued to have clinically normal cardiovascular function as well as stable ECG and ultrasound measurements until her death from serum hepatitis at 135 days after operation. At postmortem examination the heart was grossly normal. The ultrasound measurement of the posterior left ventricular wall of 18 mm on the day of death was the same as the direct measurement at necropsy.

Although there were mild variations in daily QRS voltage, there was no confirming evidence of rejection by ultrasound or phonocardiographic measurements, and clinical evidence of rejection never appeared. A soft S₄ was recorded on postoperative day 125, but there were no changes in other parameters. The significance of this is not known at present.

**Case G.L.**

This 54-year-old woman had severe atherosclerotic coronary artery disease with diffuse ventricular fibrosis. Cardiac transplantation was performed on October 5, 1968. Her immediate postoperative course was uncomplicated. On day 3, there was a precipitous fall in QRS voltage (fig. 7) and onset of an early S₃ gallop (fig. 8). Treatment for 2 days with increased steroids resulted in an increase in the voltage, disappearance of the S₃, and decrease in the posterior wall thickness. The QRS axis was not helpful because of a right bundle-branch block pattern present preoperatively in the donor heart. By day 7, the S₃ reappeared with subsequent fall in voltage, increasing right ventricular dimension, overall heart dimension, and posterior wall thickness. On day 8 to 9, the patient was severely limited by exertional dyspnea and fatigue. Examination revealed marked substernal heave, biventricular...
gallop, marked venous distention with a and v waves and rapid y descent (fig. 7). Massive amounts of methylprednisolone and actinomycin D were given. By day 13 signs of cardiac failure receded, and the patient resumed normal activity. By day 18, the S3 had disappeared completely.

Figure 7
Outline of postoperative course in patient G.L.: See figure 2 for explanation. Omission of electrical axis because of a right bundle-branch block pattern in the donor heart.
There was gradual improvement in ultrasound measurements over this period with stable measurements by day 25.

Again there was marked consistency between the appearance of an early diastolic gallop and decreasing QRS voltage heralding rejection. The changes in ultrasound measurements appeared to confirm the onset of a rejection process.

Comment

The onset of progressive heart failure and its reversal with increased administration of immunosuppressive agents remain the most objective evidence of acute rejection of the transplanted heart against which all other predictive criteria must be compared. During our early experience these data were not defined always clearly enough to allow prediction of early rejection; treatment, therefore, was initiated at a later stage than we would prefer. In subsequent cases rejection has been treated earlier, before the appearance of flagrant cardiac failure, as determined by changes in voltage, axis, ultrasound measurements, and extra diastolic sounds.

Other phonocardiographic measurements have been analyzed. Actual and corrected ejection times remain essentially unchanged until obvious heart failure is present, at which time they do decrease, as would be expected from the work of Weissler and associates. The maximal rate of rise of the externally recorded carotid pulse roughly corresponds to changes in pulse pressure and because of the wide daily variation has not been useful in predicting rejection. It has been suggested by Cooley and his associates that the earliest clinical sign of rejection is pericardial friction. In objective analysis of daily phonocardiograms on our nine patients, pericardial rubs were invariably present during the first postoperative week. Subsequently they would come and go, occasionally accompanying early rejection, but just as frequently disappearing without a change in medication or clinical course. We have, therefore, been unable to rely upon this clinical sign.

The ultrasonic technics used on these patients are quite new. Ultrasound has been validated only recently as a quantitative as well as a qualitative tool for cardiac measurement. In these studies measurements on a single patient are reproducible in a stable clinical state, as illustrated by case V.A. The measurements of overall heart size correspond to the changes seen on chest x-rays. The posterior wall thickness measured just prior to death is in excellent agreement with the measurements made at necropsy for the four patients in whom the comparison was possible. The changes in right ventricular dimension are consistent with those seen in animal studies and the clinical findings mentioned previously. Good quality records could be obtained on all patients with the exception of the first case studied (case L.D.). The ultrasound changes seen from day to day and the trends seen over many days appear to be of value when compared with the electrocardiographic and clinical data.

Discussion

The remarkable physical findings in all of these patients during acute, severe rejection were progressive signs of low cardiac output with decreased pulse pressure, cool extremities, and marked elevation of venous pressure. Certain signs appear before these obvious signs of heart failure. These include decreasing QRS voltage and usually a shift of the electrical axis to the right. A diastolic gallop appears and remains early in timing. Ultrasound measurements show an increasing posterior wall thickness, right ventricular and overall heart dimensions (AW-PW) early in the rejection process.

Figure 8

Phonocardiograms recorded after cardiac transplantation in patient G.L.: Abbreviations same as in figure 1.
The a and v waves in the venous pulse were prominent with a rapid y descent. This, in addition to the early timing of the diastolic gallop, usually 0.10 to 0.14 sec after A\textsubscript{2}, was consistent with restriction of diastolic filling as seen in pericardial constriction, restrictive endocardial fibrosis, and infiltrative myocardial disease.\textsuperscript{9-11} Despite the marked heart failure, fatigue, and dyspnea on exertion, orthopnea was strikingly absent in all patients.

Kosek and associates\textsuperscript{12} have reported the histologic findings during rejection in the dog. The typical picture is vascular engorgement, capillary thrombosis, infiltration by large monocytes, and widespread interstitial edema. These changes occur at a time when the QRS voltage is declining; yet there is little histologic evidence of injury to the myocytes. They reported that with treatment for acute rejection, the changes are rapidly and completely reversed.

These data parallel the clinical experience in the patients described. The decrease in QRS voltage during rejection could be explained by interstitial edema as suggested by Lower and his associates.\textsuperscript{13} The ultrasound measurements showing increasing posterior wall thickness during rejection would confirm an infiltrative process in the myocardium. The clinical picture of restrictive heart disease with an early S\textsubscript{3} gallop and marked venous distention with prominent a and v waves again suggests progressive interstitial edema with gradual decrease in myocardial compliance and impaired diastolic filling as the pathophysiologic cause of heart failure during rejection. During severe rejection, a biventricular gallop can frequently be heard (figs. 1 and 8); however, the right ventricular S\textsubscript{3} appears first and can usually be detected earlier in the rejection process by auscultation at the lower left sternal border during inspiration. During this period of early rejection, no consistent changes in SGOT, CPK, LDH\textsubscript{1}, or LDH\textsubscript{2}, which might reflect myocardial injury or death of cells, have been noticed.\textsuperscript{6} If the rejection episode is treated early, there is rapid reversal of decreased QRS voltage, thickened posterior wall, and S\textsubscript{3}, suggestive of resolution of the rejection process and interstitial edema with improvement in myocardial compliance.

It should be noted that the increase in overall heart dimensions as measured by ultrasound and confirmed by x-rays is almost entirely due to increase in right ventricular diameter. An explanation for the rightward shift in the mean electrical axis of the electrocardiogram is not apparent. Perhaps it is related to acute right ventricular dilatation. This may be due to right ventricular cardiac failure occurring before left ventricular failure, since the thin wall of the right ventricle would have less reserve when edema and cellular infiltration occur. Although pulmonary hypertension may also account for a shift in electrical axis, no other clinical signs of acute pulmonary hypertension are present during rejection. Further studies are necessary to define the etiology of this electrical finding. We are also unable to explain adequately why the increase in right ventricular diameter and right ventricular gallop appear first, although this, too, may be related to the relative thinness of the right ventricle.

From the present evidence, we propose that the earliest cardiovascular signs of acute rejection include decrease in QRS voltage, appearance of an early right ventricular diastolic gallop and an increase in posterior wall thickness, overall heart dimensions, and right ventricular diameter as measured by ultrasound. These findings can all be explained by the experimental evidence in dogs showing vascular engorgement and interstitial edema as an early finding in the rejection process. The heart failure in acute rejection may result from restriction of diastolic filling due to decreased compliance of the ventricular wall. Our experience to date suggests that this is rapidly reversible with early treatment.

The phonocardiographic and ultrasound observations which have been described lend insight to the pathophysiology of circulatory failure during cardiac rejection. Changes seen in these measurements have been of most value in predicting and confirming the onset of cardiac rejection.
References

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