Effect of acute human cardiac allograft rejection on left ventricular systolic torsion and diastolic recoil measured by intramyocardial markers

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ABSTRACT Left ventricular systolic torsion and diastolic recoil were quantified in 12 human cardiac transplant recipients with surgically implanted intramyocardial markers with the use of computer-aided analysis of biplane cineradiographic images. Measurements were performed between 6 and 16 weeks after surgery and related to the presence or absence of rejection as determined by cardiac biopsy. Torsional deformation, defined as twisting about the left ventricular long axis of the apical region with respect to the base, was characterized in terms of the rate and amplitude of systolic torsion and the rate of diastolic recoil by means of an internal reference system. Comparison of measurements before, during, and after recovery from 14 rejection episodes allowed assessment of the effects of acute reversible cardiomyopathy on left ventricular torsion and recoil. Compared with prerejection values, the amplitude of torsional deformation in the maximally deforming segment (θmax) decreased by 25% from 21.1 ± 15.2 to 16.0 ± 5.7 degrees (p < .005) during acute rejection with myocyte necrosis; this was associated with significant (p < .05) decreases in the peak systolic torsion rate (+dθ/dtmax), whereas the peak diastolic recoil rate (−dθ/dtmax) was unchanged. This suggests that the stiffness of elastic components of the myocardium may have increased, maintaining the rate of diastolic recoil when these elements are stretched less. With successful treatment of rejection episodes, the torsional deformation characteristics normalized. Heart rate, mean arterial pressure, left ventricular end-diastolic volume, stroke volume, ejection fraction, and peak left ventricular filling rate were unchanged with rejection episodes, whereas left ventricular end-systolic volume increased (p < .05) during acute rejection and returned to normal with resolution of the rejection process. These data suggest that left ventricular torsional deformation amplitude and rate are sensitive to episodes of subclinical left ventricular dysfunction and that such intramyocardial marker techniques may provide new insights regarding the elastic properties of the ventricular myocardium and their impact on left ventricular mechanics.


LEFT VENTRICULAR fiber angles vary greatly from epicardial to endocardial surface. Fibers in the left ventricular midwall are predominantly oriented circumferentially, whereas the fibers in the subendocardial and subepicardial layers are oriented obliquely.1–3 The functional significance of this fiber orientation has been a subject of speculation for anatomists and physiologists alike. One might expect that contraction of the obliquely oriented fibers would cause a twisting about the ventricular long axis, or torsional deformation. This was originally suggested by Giovanni Alphonso Borelli, a student of Galileo, who proposed that contraction of these fibers contributed to left ventricular ejection in a manner analogous to wringing out a wet towel.4

Torsional deformation of the human left ventricle has been demonstrated recently in our laboratory by means of myocardial marker techniques.5 The apical regions twist clockwise (as viewed from base to apex) about the left ventricular long axis with respect to fixed sites near the base. This is followed by rapid unwinding of the left ventricular chamber during early diastole. Our earlier study suggested that the amplitude of this torsional...
deformation is sensitive to the contractile state of the ventricular myocardium. The objective of the present study was therefore to determine the effect of diffuse reversible myocardial injury on left ventricular torsional deformation, using myocardial marker techniques and acute human cardiac allograft rejection as a model of such injury.

Methods

The study group comprised 12 patients undergoing orthotopic human cardiac allograft transplantation at Stanford University Medical Center between December 20, 1984, and November 15, 1985. Informed consent for implantation of intramyocardial markers at the time of cardiac transplantation and for the studies described were obtained from all patients, in accordance with the requirements of the Stanford University Medical Committee on the Use of Human Subjects in Research. All patients who received intramyocardial markers at our institution during this 11 month period were enrolled in the study. No complications resulted from these investigations.

Intraoperative management. The method for surgical implantation of intramyocardial markers has been described previously. In brief, 12 helices (0.8 × 2.2 mm) of pure tantalum wire were implanted at an approximate depth of 5 mm below the epicardial surface of the donor hearts with a specially designed inserter tool. Septal markers were implanted into the interventricular septum through the right atrium before performing the right atrial anastomosis. Figure 1 illustrates the positions of these markers. Markers were implanted at approximately 90 degree intervals around the circumference at basal, midventricular, and apical levels, maintaining roughly even spacing from base to apex. This was accomplished by epicardial landmarks. An array of three inferior wall markers were implanted in the basal, middle, and apical third of the inferior left ventricular wall along the posterior descending artery. The three markers comprising the anterior wall array were inserted into the basal, middle, and apical third of the anterior wall paralleling the left anterior descending artery on the left ventricular side. The three lateral wall markers were positioned at equidistant points in the basal, middle, and apical third of the lateral wall along the lateral margin. Only two septal markers were placed—one near the base, the other at the midventricular level; the apical portion of the interventricular septum was not accessible from the right atrial approach. A single marker was implanted at the apical dimple to mark the left ventricular apex.

Two stainless-steel clips (1 × 5 mm) were attached to the adventitia of the aorta just above the valve commissures to mark the approximate position of the aortic valve. In this manner, the left ventricular cavity was silhouetted in the 30 degree right (RAO) and 60 degree left anterior oblique (LAO) projections by these markers.

Postoperative management. The patients received standard postoperative transplant care. All received immunosuppressive therapy with cyclosporine, azathioprine, and prednisone. The dose of cyclosporine was adjusted to maintain trough serum cyclosporine levels between 100 and 200 ng/ml as measured by radioimmunoassay. Right ventricular endomyocardial biopsies were performed for surveillance of rejection. In general, biopsies were performed on a weekly basis for the first month, starting on the sixth or seventh postoperative day. Thereafter, biopsies were performed on alternate weeks for the next 4 to 6 weeks, followed by monthly biopsies for the next 2 to 3 months. A minimum of four tissue samples per study were obtained to provide histologic confirmation of the presence or absence of myocardial injury. The biopsies were graded according to previously published criteria. No evidence of rejection reflected absence of cellular infiltration or myocyte necrosis; "mild rejection" implied cellular infiltration without myocyte necrosis; "moderate rejection" was defined as cellular infiltration with myocyte necrosis; and "severe rejection" required the presence of myocardial hemorrhage. During this period, episodes of moderate or severe rejection were treated with 1000 mg iv methylprednisolone for 3 days, and biopsies were performed weekly until complete resolution of the rejection episode was achieved. In cases of severe or persistent rejection, rabbit or equine antithymocyte globulin was added.

For the purposes of the present study, three experimental stages were defined based on histopathologic findings. First, at least one biopsy (range one to three) was obtained that revealed no evidence of rejection before the first rejection episode (pre-rejection); second, an acute rejection episode with myocyte necrosis (rejection) followed during the second to fourth postoperative week; third, after complete resolution of the rejection episode, one to three additional studies were obtained (postrejection). In two patients, studies were performed before, during, and after a second episode of rejection; thus a total of 14 rejection episodes were studied.

Data acquisition. Immediately after each cardiac biopsy, biplane (30 degree RAO and 60 degree LAO projections) cinefluoroscopic images (60 frames/sec) of a 5 beat sequence were recorded at end-inspiration with a General-Electric MLX biplane L-U arm system with intensifiers in the 9 inch mode isocentered on the left ventricle. The 30 degree RAO and 60 degree LAO projections were selected so as to maximize the spatial area encompassed by the anterior and inferior wall markers for the RAO projection and the septal and obtuse marginal markers for the LAO projection. An electronic circuit was used to detect the peak R wave signal from a surface electrocardiogram and indicate this event on the cinefluoroscopic recordings by means of a triggered light-emitting diode to define precisely end-diastolic frames. To optimize image quality, the two x-ray tubes fired in alternating fashion with an offset of 8.3 msec. A lead grid with 1 cm squares was recorded at the position of the left ventricle with each imaging system to determine magnification and distortion factors. Images of a three-dimensional radiographic phantom of known dimensions were obtained and demonstrated that distance could be measured to within 0.4 mm and angles could be measured to within 1.0 degree. At the time of each study, measurements of systolic and diastolic blood pressure were obtained with a sphygmomanometer.

Data reduction and analysis

Image processing. For each study, a 3 to 4 beat sequence was

FIGURE 1. Biplane left ventricular midwall marker positions. Markers (depicted as closed circles) were positioned in the basal, midventricular, and apical portions of the inferior, anterior, and lateral walls of the left ventricle. Two additional markers were implanted in the basal and midinterventricular septum, and one marker was inserted at the apical dimple.
analyzed. With a specially modified Vanguard projector linked via a Vidicon camera to a Hewlett-Packard-1000 minicomputer and Tektronix light pen, the two-dimensional coordinates (x, y for the 30 degree RAO camera and y, z for the 60 degree L AO camera) of each marker image were manually digitized frame-by-frame as previously described. Special care was taken to use consistently the center of the projected marker images while digitizing. Correction for magnification and distortion of the imaging system was performed by the minicomputer. Data from the two corresponding biplane views were transferred to an IBM System/36 minicomputer for computation of three-dimensional coordinates at 16.7 msec intervals with a parallel-ray approximation. The y, z data from the 60 degree L AO projection were shifted by 8.3 msec, and the y-coordinates from the two projections were averaged.

Hemodynamic computations. Mean arterial pressure was estimated from the systolic (SBP) and diastolic (DBP) blood pressure as DBP + [1/3 × (SBP - DBP)]. Left ventricular volume was computed for each frame by a modification of the single-plane, area-length method of Sandler and Dodge. This method has been previously validated in our laboratory with, as volumetric standards, values computed from simultaneously obtained left ventricular contrast angiograms. The left ventricular volume data were smoothed by a Fourier filter at 8 Hz, the first time derivative \( [dV(t)/dt] \) of the resulting instantaneous left ventricular volume curve was computed throughout the cardiac cycle, and the peak left ventricular filling rate \( (+dV/dt)_{max} \) was determined. The volume at end-diastole (EDV) and end-systole (ESV) were calculated for each beat as the maximum and minimum left ventricular volume, respectively. Stroke volume (SV) was calculated as EDV - ESV. The left ventricular ejection fraction was calculated as SV/EDV. For each study, the reported values represent the mean value of 3 to 4 consecutive beats.

Computation of torsional deformation characteristics. An internal reference system (figure 2), defined by two basal markers and the marker at the left ventricular apex, was used to compute instantaneous torsional angles \( \{\theta(t)\} \) for each marker at 16.7 msec intervals. The line from the left ventricular apex marker to the midpoint of the transverse segment defined by the inferobasal and anterobasal markers defined the left ventricular long axis. The reference minor axis was defined as the line passing through the inferobasal and anterobasal marker sites. The perpendicular from the ventricular long axis to each marker in the middle and apical third of the ventricle was also determined. Torsional deformation about the left ventricular long axis was defined as the difference in the angle of rotation for each of the four midventricular and three apical markers relative to that of the basal reference axis. This is illustrated in figure 2, which shows the angle of rotation about the left ventricular long axis for the midventricular \( (\gamma_m) \) and apical \( (\gamma_a) \) markers of the anterior wall, along with that of the basal reference axis \( (\gamma_b) \). The clockwise direction (as viewed from base to apex) was defined as the positive direction for these angles. The time-varying torsional deformation angles \( \theta(t) \) for each of the midventricular and apical marker sites were computed at 16.7 msec intervals as \( \gamma_m - \gamma_b \) and \( \gamma_a - \gamma_b \), respectively. The peak-to-trough amplitude of \( \theta(t) \) was then calculated (in degrees) for each marker site as the mean value of 3 to 4 beats. The torsional angle of the marker site with the greatest torsional deformation (referred to as \( \theta_{max} \)) was selected at the time of the first prerejection study of a given patient for measurements of \( \theta_{max} \) in all subsequent studies of that patient.

Computed values of \( \theta(t) \) for the maximally deforming marker site were plotted as a function of time at 16.7 msec intervals and the raw data were smoothed by a Fourier filter at 8 Hz to interpolate the time-varying torsional deformation curve. Previous studies have shown that 95% or more of the information is contained below 8 Hz. The first time derivative of this curve \( [d\theta(t)/dt] \) was computed from the Fourier reconstruction and plotted. The peak rate of left ventricular systolic torsion \( (+d\theta/dt)_{max} \) and peak diastolic recoil rate \( (-d\theta/dt)_{max} \) were then computed as the mean of 3 to 4 beats.

Statistics. Group data are summarized as the mean ± SD. Based on the histologic appearance of the biopsy specimen, the cinefluoroscopic data were assigned to three distinct categories: prerejection, rejection, and postrejection, as defined above. For each patient, pre- and postrejection values represent the mean of 3 to 12 beats obtained during one to three studies. The coefficient of variation for grouped interstudy data was 10.5%. The rejection values are based on 3 to 4 beats from a single study, obtained before intensified immunosuppression. Data obtained during rejection that did not require specific treatment (i.e., cellular infiltration without myocyte necrosis) or while patients were receiving intensified immunosuppressive therapy were excluded. Prerejection, rejection, and postrejection data were compared by analysis of variance for a repeated-measures design. When indicated by a significant F statistic, Tukey’s multiple comparison test was used to determine which of the means differed. Sensitivity, specificity, and accuracy rates were determined as follows:

\[
\text{Sensitivity} = TP/(TP + FN) \\
\text{Specificity} = TN/(FP + TN) \\
\text{Accuracy} = (TP + TN)/(TP + FN + FP + TN)
\]

where \( TP = \) true positive, \( FN = \) false negative, \( TN = \) true negative, and \( FP = \) false positive. These ratios were expressed along with the corresponding 95% confidence limits.

Results
Prerejection and rejection studies selected from a representative patient (patient 1 of table 2) are illus-
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trated in figures 3 to 5. In this example, acute rejection with myocyte necrosis resulted in substantial injury to the ventricular myocardium (figure 3). This is apparent when the prerejection biopsy specimen (panel A) obtained on postoperative day 6, which shows normal-appearing myocardium, is compared histologically with the specimen obtained on postoperative day 26 (panel B). The latter shows extensive cellular infiltration and myocyte necrosis consistent with moderate rejection. Two intervening biopsies on postoperative days 10 and 16 (not shown) showed no evidence of rejection.

The corresponding left ventricular volume curves, derived from cineradiographic recordings obtained immediately after the biopsies described above, are shown in figure 4, top. During this rejection episode, end-systolic volume increased by 14 ml from its prerejection value of 123 ml, whereas end-diastolic volume decreased from 192 to 181 ml. As a result, left ventricular stroke volume decreased by 25 ml and left ventricular ejection fraction declined from 35.9% to 24.3%. In this example the peak rate of left ventricular ejection (−dV/dt\(_{\text{max}}\)) and filling (+dV/dt\(_{\text{max}}\)) also decreased markedly with rejection (figure 4, bottom).

The rate and extent of torsional deformation about the left ventricular long axis were quantified by the cineradiographic recordings described above and revealed that such injury also had pronounced effects on left ventricular torsion (figure 5). The contour of the time-varying torsional deformation curves obtained during prerejection (top left) and rejection (top right) are generally similar. Torsional deformation of the left ventricular chamber [θ(t)] increases rapidly during the ejection phase. At end-ejection (i.e., time of minimum volume in figure 4), θ(t) is near the maximum. Rapid uncoupling of the ventricle then follows so that the peak diastolic recoil rate (−dθ/dt\(_{\text{max}}\)) precedes dV/dt\(_{\text{max}}\) (see figure 4). Comparison of the multiple beat sequences obtained during prerejection and rejection reveals a substantial reduction in the amplitude of torsional deformation about the left ventricular long axis during this episode of acute rejection with the mean value of θ\(_{\text{max}}\) decreasing from 21.2 to 7.9 degrees. This was associated with substantial reduction in the peak rate of left ventricular systolic torsion (+dθ/dt\(_{\text{max}}\)). The peak rate of diastolic recoil (−dθ/dt\(_{\text{max}}\)) decreased much less.

Table 1 summarizes the effect of 14 episodes of acute cardiac allograft rejection with myocyte necrosis on selected hemodynamic variables in 12 patients. Rejection had no effect (p > .05) on heart rate, mean arterial pressure, end-diastolic volume, peak left ventricular filling rate, stroke volume, or ejection fraction. In contrast, end-systolic volume was greater than the prerejection value in 12 of 14 episodes of acute rejection with myocyte necrosis, with an average increase of 20% (p = .02). End-systolic volume subsequently decreased (p < .05) in 11 of 12 patients with resolution of rejection. Thus myocyte necrosis reduced the systolic performance of the ventricle, as reflected by the increase in left ventricular end-systolic volume at a similar level of arterial pressure.

Overall, θ\(_{\text{max}}\) decreased from the prerejection value in 13 of 14 episodes of acute rejection with myocyte necrosis, with a 25% reduction in the mean value of θ\(_{\text{max}}\) (table 2). With resolution of rejection, θ\(_{\text{max}}\) thereafter increased in nine of 12 cases. Thus θ\(_{\text{max}}\) fell with rejection and then normalized in most (but not all) patients with successfully treated transplant rejection. In patients 5 and 7, postrejection studies were not obtained because of refractory rejection requiring repeat cardiac transplantation; in these two patients, ongoing rejection was associated with a progressive fall in θ\(_{\text{max}}\). The decrease in θ\(_{\text{max}}\) that occurred with rejection was associated with a decline (p < .05) in +dθ/dt\(_{\text{max}}\), but the decrease in +dθ/dt\(_{\text{max}}\) was not as consistent, occurring in only 10 of 14 cases. Resolution of rejection was associated with subsequent increases (p < .05) in +dθ/dt\(_{\text{max}}\) in nine of 12 cases. Consistent changes in the peak rate of diastolic recoil (−dθ/dt\(_{\text{max}}\)) did not occur.

The effect of acute rejection with myocyte necrosis on the torsional angles of each marker site is summarized in table 3. There is considerable regional variability in torsional deformation. The greatest deformation (θ\(_{\text{max}}\)) occurred in the inferoapical marker site in six patients, the apical marker of the lateral wall in five patients, and the anteroapical marker in one patient. As expected, the amplitude of torsional deformation was nearly twice as large in the apical sites, compared with counterparts at the midventricular level. Acute rejection with myocyte necrosis was associated with significant changes in the torsional deformation amplitude measured in the apical portions of the inferior and lateral wall, whereas the changes in torsional deformation amplitude of the anteroapical and all midventricular sites were not significant. The greatest changes in torsional deformation amplitude were consistently measured in the maximally deforming marker site (i.e., θ\(_{\text{max}}\)), which had been selected on the basis of the initial prerejection results and used consistently thereafter.

Figure 6 relates the changes in θ\(_{\text{max}}\) in a representative patient (patient 2 of table 2) to myocardial his-
FIGURE 3. Photomicrographs of cardiac biopsy specimens obtained from patient 1 of table 2. The prerejection biopsy specimen at low magnification from postoperative day 6 (A) shows relatively normal myocardium. In contrast, the specimen at higher magnification from postoperative day 26 (B) shows extensive cellular infiltration and myocyte necrosis consistent with moderate rejection.
FIGURE 4. Effect of acute cardiac allograft rejection with myocyte necrosis on left ventricular volume, peak rate of filling, and ejection velocities. Determinations of left ventricular volume (ordinate) derived from cinefluoroscopy of the marker positions are plotted at 16.7 msec intervals as a function of time (abscissa), along with interpolated instantaneous left ventricular volume curves (top) and the first time derivative \([dV(t)/dt]\) of this curve (bottom). The vertical lines indicate the timing of the peak R wave from the lead II surface ECG. The 4 beat sequences shown were obtained from patient 1 on postoperative days 6 (left) and 26 (right), immediately after cardiac biopsy (shown in figure 3). Compared with the prerejection data (left), end-systolic volume (ESV) increased with acute rejection (right), whereas the end-diastolic volume (EDV) and peak rate of left ventricular ejection \([dV/dt_{max}]\) and filling \([+dV/dt_{max}]\) decreased in this patient.

In this patient, an episode of acute rejection with myocyte necrosis was detected by biopsy on postoperative day 15. This was associated with a 3.0 degree decrease in \(\theta_{max}\) from the prerejection value of 24.9 degrees. This rejection episode was treated with 1000 mg iv methylprednisolone daily for 3 days. Within 1 week (day 22), \(\theta_{max}\) increased from 21.9 to 30.9 degrees; the biopsy was interpreted to show early rejection with focal myocyte necrosis. Two weeks later (day 34), the biopsy showed complete resolution of the rejection episode; over the same interval, \(\theta_{max}\) was unchanged. One month later (day 72), without any intervening rejection episodes, \(\theta_{max}\) decreased to 22.3 degrees; the biopsy showed no evidence of rejection at this time. Azathioprine was then discontinued because of severe infection. Five days later (day 77), histologic evidence of moderate rejection with myocyte necrosis was found, and \(\theta_{max}\) had decreased further to 13.0 degrees. This prompted another course of methylprednisolone supplemented by antithymocyte globulin; azathioprine was also restarted on day 80. The next biopsy (day 85) showed evidence of continuing myocyte necrosis, and the possibility of repeat cardiac transplantation was considered; however, biopsy on day 107 revealed no evidence of rejection, and \(\theta_{max}\) had increased to 23.7 degrees.

The sensitivity, specificity, and accuracy of \(\theta_{max}\) as...
FIGURE 5. Effect of acute cardiac allograft rejection with myocyte necrosis on the amplitude and rate of torsional deformation about the left ventricular long axis. Time-varying torsional deformation angles $\theta(t)$ of the apical marker site in the lateral midwall were derived from the same 4 beat sequences shown in figure 4. The raw data points (closed circles) are shown along with the curve obtained by Fourier filtering of the data at 8 Hz (top) and the first time derivative of this curve (bottom). The vertical lines indicate the timing of the peak R wave from the lead II surface ECG. Compared to the prerejection study (left), torsional deformation amplitude ($\theta_{max}$) decreased during acute rejection with myocyte necrosis (right). The reduction in $\theta_{max}$ was associated with decreases in both the peak rate of left ventricular systolic torsion ($+d\theta/dt_{max}$) and, to a lesser extent, diastolic recoil ($-d\theta/dt_{max}$) in this patient.

Discussion

In a previous study of torsional deformation from our laboratory, inotropic state was altered by abruptly varying the rate of left ventricular contraction with an atrial stimulation protocol that permitted comparison of beats differing in contractile strength but similar in load. We found that torsional deformation was quite sensitive to such alterations in left ventricular contraction. This suggested that $\theta_{max}$ might be a clinically useful index of cardiac muscle performance. The present study provides further evidence for the potential clinical utility of $\theta_{max}$ in serial patient evaluations.

With diffuse myocardial injury, $\theta_{max}$ decreased by at least 4% in 13 of 14 episodes of acute rejection. Most of the rejection episodes took place during the first several weeks after surgery. In the absence of myocardial injury, one would expect left ventricular function to improve gradually over this phase of early

an indicator of acute rejection with myocyte necrosis in the early postoperative setting are shown in table 4. With a 4% decrease in $\theta_{max}$ as a threshold defining "rejection," 13 of 14 rejection episodes were detected, yielding a sensitivity of 93%, a true negative rate (specificity) of 65%, and a false-positive rate of 35%. The overall accuracy of this test was 73%. Increasing the threshold decrease in $\theta_{max}$ to 10% improved the specificity to 71%, but only 10 of 14 (71%) rejection episodes were detected and the overall accuracy fell to 71%.
TABLE 1
Effect of acute cardiac allograft rejection with myocyte necrosis on hemodynamic variables in 12 transplant recipients

<table>
<thead>
<tr>
<th></th>
<th>Prejection (n = 14)</th>
<th>Rejection with myocyte necrosis (n = 14)</th>
<th>Postrejection (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>100 ± 13</td>
<td>95 ± 15</td>
<td>94 ± 15</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>96 ± 14</td>
<td>92 ± 16</td>
<td>95 ± 10</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>176 ± 43</td>
<td>194 ± 48</td>
<td>176 ± 55</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>114 ± 34</td>
<td>137 ± 53&lt;sup&gt;a&lt;/sup&gt;</td>
<td>108 ± 41</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>62 ± 18</td>
<td>57 ± 20</td>
<td>68 ± 23</td>
</tr>
<tr>
<td>EF (%)</td>
<td>36 ± 8</td>
<td>33 ± 10</td>
<td>39 ± 9</td>
</tr>
<tr>
<td>+dV/dt&lt;sub&gt;max&lt;/sub&gt;</td>
<td>388 ± 144</td>
<td>394 ± 128</td>
<td>449 ± 138</td>
</tr>
</tbody>
</table>

Results expressed as mean ± SD.

n = number of episodes; HR = heart rate; MAP = mean arterial pressure; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction; +dV/dt<sub>max</sub> = peak left ventricular filling rate.

<sup>a</sup>p < .05 compared with pre- and postrejection values by Tukey’s multiple comparison test.

postoperative recovery. Thus the rejection episodes detected by this method were superimposed on this trend of improving left ventricular function (see figure 6), and it is likely that the “prerejection” values reported in this study may actually underestimate the value of θ<sub>max</sub> immediately before the onset of rejection. Nevertheless, reduction in θ<sub>max</sub> was an accurate indicator of acute rejection with myocyte necrosis, even when determinations were obtained only once a week (at the time of biopsy) during the early postoperative period. If we had reserved cardiac biopsy until a 4% decrease in θ<sub>max</sub> occurred, 65% of the negative biopsies would have been avoided in this group of patients, with only a 1 in 14 risk of delaying the diagnosis of treatable rejection episodes.

Acute cardiac allograft rejection with myocyte necrosis reduces the number of contractile units comprising the ventricular myocardium and may lead to deterioration of contractile performance of remaining units. Such a process would be expected to cause a significant deterioration in left ventricular pump function. Left ventricular stroke volume and ejection fraction, however, were relatively insensitive to acute rejection because left ventricular end-diastolic volume generally increased during rejection episodes and this would tend to maintain stroke volume by the Starling mechanism, as left ventricular contractile state deteriorated. The left ventricular end-systolic volume increased during acute rejection at a similar level of arterial pressure, however, implying that the end-systolic pressure-volume relation was shifted in a direction indicating depressed left ventricular contractility. This supports the concept that acute rejection with myocyte necrosis depressed left ventricular systolic performance independent of load. Our data indicate that torsional deformation (θ<sub>max</sub>) is more sensitive to such changes in cardiac muscle performance than conventional ejection phase measures of

TABLE 2
Effect of acute cardiac allograft rejection with myocyte necrosis on torsional deformation characteristics in 12 transplant recipients

<table>
<thead>
<tr>
<th>Patient</th>
<th>θ&lt;sub&gt;max&lt;/sub&gt; (degrees)</th>
<th>+dΩ/dt&lt;sub&gt;max&lt;/sub&gt; (deg/sec)</th>
<th>−dΩ/dt&lt;sub&gt;max&lt;/sub&gt; (deg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Rej</td>
<td>Post</td>
</tr>
<tr>
<td>1</td>
<td>22.9</td>
<td>7.9</td>
<td>15.0</td>
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<tr>
<td>2</td>
<td>24.9</td>
<td>21.9</td>
<td>30.7</td>
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<td>3</td>
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<td>23.7</td>
</tr>
<tr>
<td>4</td>
<td>11.3</td>
<td>9.4</td>
<td>9.2</td>
</tr>
<tr>
<td>5</td>
<td>23.7</td>
<td>21.9</td>
<td>24.2</td>
</tr>
<tr>
<td>6</td>
<td>29.8</td>
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<td>7</td>
<td>15.0</td>
<td>4.8</td>
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<td>8</td>
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<td>9</td>
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<tr>
<td>11</td>
<td>26.3</td>
<td>19.5</td>
<td>18.0</td>
</tr>
<tr>
<td>12</td>
<td>14.4</td>
<td>14.5</td>
<td>16.2</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>21.1±5.2</td>
<td>16.0±5.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20.2±5.9</td>
</tr>
</tbody>
</table>

Pre = prerejection. Rej = acute rejection with myocyte necrosis. Post = postrejection; θ<sub>max</sub> = left ventricular torsional deformation amplitude for the maximally deforming marker site; +dΩ/dt<sub>max</sub> = peak rate of left ventricular systolic torsion; −dΩ/dt<sub>max</sub> = peak rate of left ventricular diastolic recoil.

<sup>a</sup>p < .05 compared with pre- and postrejection values by Tukey’s multiple comparison test.
TABLE 3

Effect of acute rejection on left ventricular regional torsional deformation amplitude in 12 transplant recipients

<table>
<thead>
<tr>
<th>Marker location</th>
<th>Pre-rejection (n = 14)</th>
<th>Rejection with myocyte necrosis (n = 14)</th>
<th>Post-rejection (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical segments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>15.3 ± 8.6</td>
<td>12.5 ± 7.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17.2 ± 8.6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anterior</td>
<td>12.4 ± 6.2</td>
<td>11.4 ± 5.1</td>
<td>12.5 ± 6.1</td>
</tr>
<tr>
<td>Lateral</td>
<td>13.4 ± 8.9</td>
<td>9.4 ± 5.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.7 ± 5.9</td>
</tr>
<tr>
<td>Midventricular segments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>6.1 ± 3.9</td>
<td>6.2 ± 3.8</td>
<td>7.5 ± 5.7</td>
</tr>
<tr>
<td>Anterior</td>
<td>6.6 ± 3.7</td>
<td>6.2 ± 3.2</td>
<td>6.6 ± 3.0</td>
</tr>
<tr>
<td>Lateral</td>
<td>7.3 ± 4.8</td>
<td>6.3 ± 4.1</td>
<td>6.7 ± 4.3</td>
</tr>
<tr>
<td>Septal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.7 ± 4.0</td>
<td>5.9 ± 4.6</td>
<td>6.3 ± 2.7</td>
</tr>
</tbody>
</table>

Results expressed as mean ± SD.

<sup>a</sup>In patient 2, there was no marker of the mid-septal wall; thus, for this marker site, n = 12 for pre-rejection and rejection with myocyte necrosis and n = 10 for post-rejection.

<sup>b</sup>p < .05, <sup>c</sup>p < .005 compared with pre-rejection by Tukey’s multiple comparison test; <sup>d</sup>p < .05 compared with rejection with myocyte necrosis by Tukey’s multiple comparison test.

The relative insensitivity of the peak recoil rate to this type of myocardial injury is an intriguing and unexpected result. We predicted a priori that, like a stretched spring in which the restoring forces are proportional to the stiffness of the spring (or spring constant, k) and the displacement, the peak recoil rate would be highly dependent on the amount of left ventricular torsion. We assume that shortening of contractile elements within the obliquely oriented fibers deforms the chamber in the manner described and stretches elastic elements within the myocardium during systole. As a result, mechanical energy would be stored in these elastic elements during systole. Inactivation of the myofilaments during the isovolumetric relaxation phase releases this energy, allowing rapid unwinding of the deformed ventricle. Although it is reasonable to assume that the rate of diastolic recoil should be dependent on the extent to which the elastic elements are stretched, our results suggest that other factors may also be important. It is possible that the rejection process, which produces considerable myocardial edema and, ultimately, fibrosis, may increase the stiffness of the elastic elements, thereby maintaining the restoring forces when these elements are stretched less. Alternatively, the rejection process may decrease the viscous drag that opposes the restoring forces acting on these elements. Additional studies are required to identify precisely the actual determinants of the diastolic recoil rate, to understand the role (if any) of such events on left ventricular filling, and to verify the intriguing possibility that torsional recoil may

CARDIAC PUMP PERFORMANCE SUCH AS STROKE VOLUME AND EJECTION FRACTION.

As shown in Table 2, the apically located marker sites were more sensitive to acute rejection episodes than the midventricular markers. Torsional deformation angle increases as a function of distance from the reference minor axis. This is a predictable outcome, given our

FIGURE 6. Postoperative course of patient 2 during the initial 107 days. Values of θ<sub>max</sub> (ordinate) for this patient obtained in the presence (open circles) or absence (closed circles) of rejection with myocyte necrosis are plotted against the number of days after transplantation (abscissa). Adjustments in the immunosuppressive therapy are indicated at the top of the figure. ATG = antithymocyte globulin.

TABLE 4

Sensitivity, specificity, and accuracy of θ<sub>max</sub> as an index of acute cardiac allograft rejection with myocyte necrosis

<table>
<thead>
<tr>
<th>Biopsy status</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>13/14 = 93 ± 7%</td>
<td>20/31 = 65 ± 14%</td>
<td>33/45 = 73 ± 13%</td>
</tr>
<tr>
<td>Negative</td>
<td>1/13 = 7%</td>
<td>20/20 = 100%</td>
<td>21/33 = 53 ± 13%</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, and accuracy are expressed as mean ± 95% confidence limits.

TP = true positive; FN = false negative; FP = false positive; TN = true negative. θ<sub>max</sub> = left ventricular deformation amplitude for the maximally deforming marker site.
reflect changes in the elastic and/or viscous properties of the myocardium.

Limitations. Although these data constitute the first reported measurements of left ventricular torsional velocities, it must be acknowledged that the values of the normal human left ventricle may differ from those of the transplanted human heart in the early postoperative setting; furthermore, as discussed previously, the results may be highly dependent on the depth and location of the markers and ventricular size. Although it would seem that these factors might preclude intersubject comparisons, our conclusions, which are based solely on serial studies in the same subject, should be generally valid.

Another potential limitation in the interpretation of these data relates to the fact that we were unable to control left ventricular loading conditions. Fortunately, significant changes in either preload (end-diastolic volume) or the arterial pressure opposing contraction did not occur. Preliminary studies from our laboratory, moreover, suggest that \( \theta_{\text{max}} \) is relatively insensitive to afterload manipulation with methoxamine and preload augmentation with normal saline.\(^\text{15}\)

Although the mean data on torsional deformation (\( \theta_{\text{max}} \)) showed a significant decline during rejection, it must be pointed out that several patients showed very little or no change (table 2). Therefore, the clinical value of this technique is uncertain. Additional studies in larger numbers of subjects are required to provide more precise sensitivity and specificity results before this myocardial marker technique can be advocated for routine clinical use as an adjunctive method for surveillance of rejection.

Although cardiac biopsy remains the accepted method of choice for detection of rejection, our study raises some questions regarding this method. In several instances, such as the example shown in figure 6, large decreases in \( \theta_{\text{max}} \) preceded histopathologic evidence of treatable rejection episodes by up to 1 week. Likewise, increases in \( \theta_{\text{max}} \) occurred before resolution of rejection as judged histologically. Although the example cited above would have represented a false-positive result in our study, it is possible that such decreases in \( \theta_{\text{max}} \) may reflect the occurrence of rejection episodes before histologic evidence of cell death. After the onset of the rejection process, it seems likely that myocyte dysfunction would precede necrosis of the cell; thus a lag between functional and histologic manifestations of rejection may have adversely influenced our results, given our histologic definition of rejection, which required the presence of myocyte necrosis.

Finally, it is unlikely that false-negative biopsy findings (i.e., missed episodes of myocyte necrosis) significantly influenced our results. Whereas the histopathologic involvement of certain disease processes may be limited to one ventricle while sparing the other, histologic sectioning of cardiac allografts with ongoing chronic rejection have consistently shown a relatively uniform process affecting the right and left ventricles equally (personal communication with Margaret E. Billingham, M.D.). This histologic picture was observed in the first cardiac allografts of patients 5 and 7. We believe, therefore, that the results of our right ventricular endomyocardial biopsies accurately reflect the status of the left ventricle. This is further supported by the high degree of concordance between our histologic and torsional data. To minimize the possibility of false-negative results, a minimum of four biopsy specimens per study were evaluated by an expert cardiac pathologist without knowledge of the myocardial marker data.

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