Alterations in Left Ventricular Diastolic Twist Mechanics During Acute Human Cardiac Allograft Rejection

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Background. Contraction of obliquely oriented left ventricular (LV) fibers results in a twisting motion of the left ventricle. The purpose of this study was to assess the effects of acute human cardiac allograft rejection on LV twist pattern and the twist-volume relation.

Methods and Results. Tantalum markers were implanted into the LV midwall in 15 transplant recipients to measure time-varying, three-dimensional chamber twist using computer-assisted analysis of biplane cinefluoroscopic images. Twist was defined as the mean longitudinal gradient of circumferential rotation about the LV long axis. When plotted against normalized percent ejection fraction (%EF), the resulting twist-normalized %EF relation could be divided into three phases. In systole, LV twist was linearly related to ejection of blood. In contrast, diastolic untwist was characterized by early rapid recoil with little change in LV volume, followed by more gradual untwisting when the bulk of diastolic filling occurred. During 10 acute rejection episodes in 10 patients, maximum twist, peak systolic twist rate, and the slope of the systolic twist-normalized %EF relation did not change. In contrast, the slope of the early (first 15% of filling) diastolic twist-normalized %EF relation (M_{early-dia}) decreased significantly (−0.194±0.062 [prerejection] versus −0.103±0.054 rad/cm [rejection], p=0.0003), resulting in a prolonged t_{1/2} (time required to untwist by 50% [20±5% versus 28±5% of diastole], p=0.0003) and decrease in percent untwisting at 15% diastolic LV filling (62±11% versus 36±13%, p=0.0003). Therefore, a greater proportion of LV untwisting occurred later in diastole during rejection, as reflected by an increase in the slope (M_{mid-dia}) of the middle to late (from 15 to 90% filling) diastolic twist-normalized %EF relation (−0.018±0.009 versus −0.030±0.010 rad/cm, p=0.0015). Peak rate of untwist was not affected. With resolution of rejection, M_{early-dia} and percent untwist during early diastole returned to baseline levels (p=NS versus baseline). There was also a trend for M_{mid-dia} to return toward prerejection values (p=NS versus baseline), but this change did not reach statistical significance compared with rejection values.

Conclusion. Acute cardiac allograft rejection is associated with altered diastolic twist mechanics in the absence of any demonstrable systolic abnormalities. During rejection, myocardial edema and other factors may result in intrinsic changes of the elastic properties of the myocardium, thereby leading to modification of recoil forces responsible for the early, rapid unwinding of the deformed ventricle. (Circulation 1991;83:962–973)

Anatomical studies have confirmed that the orientation of left ventricular (LV) fibers changes smoothly from a left-handed helix in the subepicardium to a right-handed helix in the subendocardium. Contraction of the obliquely oriented fibers results in a counterclockwise twist of the apex with respect to the base during systole (as viewed from apex) of the left ventricle about its long axis.

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axis.5–9 During systole, global LV twist is linearly related to mean chamber fractional radial shortening in canine hearts.10 This relation, however, is more complex during diastole, when there is early, rapid recoil with little change in chamber dimension, followed by a more gradual untwisting when the bulk of diastolic filling occurs.10 Using magnetic resonance imaging (MRI) radiofrequency-tagging techniques, 50% of LV untwisting was estimated to occur during isovolumic relaxation in normal dogs.11

Our group has demonstrated that acute human cardiac allograft rejection is accompanied by small but statistically significant decreases in torsional deformation and peak systolic torsion rate of the maximally deforming myocardial radiopaque marker; the peak diastolic recoil rate of this particular marker, however, did not change. On the other hand, Doppler echocardiographic12–16 and MRI17 data indicated that acute cardiac rejection results in abnormal early LV diastolic dynamics, without measurable alterations in systolic function. The purpose of the present study was to assess the effects of a reversible myocardial injury—acute cardiac rejection—on the global LV twist pattern and the twist–volume contraction relation using surgically implanted myocardial markers.

Methods

Patients

Fifteen orthotopic cardiac transplantation patients were studied from December 1984 through January 1986 and between March and October 1988. Mean patient age was 43±13 (±1 SD) years. Informed consent was obtained for implantation of intramyocardial markers at the time of cardiac transplantation and for subsequent radiographic studies in accordance with the requirements of the Stanford University Medical Center Committee on the Use of Human Subjects in Research. No complications resulted from the implantation of markers or the subsequent cinefluoroscopic investigations.

Myocardial Marker Implantation

As previously described,6,7 12 tantalum radiopaque helices (0.8×2.2 mm) were inserted into the LV midwall to a depth of approximately 5 mm from the epicardial surface using a specially designed insertor tool. Three markers were positioned in the anterior wall along the left anterior descending coronary artery, one at the apex and three along the posterior descending artery in the inferior LV wall. Three lateral wall markers were implanted midway between the anterior and posterior markers along the obtuse margin, and two additional markers were inserted into the interventricular septum at the basal and midventricular levels via the tricuspid valve. The apical septum was not easily accessible. Two 1×5-mm stainless-steel surgical clips were attached to the adventitia of the aortic root such that the position of the aortic valve could be extrapolated. In this manner, these markers silhouetted the left ventricle as viewed in the 30° right anterior oblique (RAO) and 60° left anterior oblique (LAO) projections.

Postoperative Management

All patients received standard triple-drug immunosuppressive therapy with cyclosporine A, azathioprine, and prednisone; beginning in 1988, prophylactic OKT-3 was also added to the regimen for 2 weeks. The dose of cyclosporine A was adjusted to maintain a trough serum level between 100 and 200 ng/ml. Surveillance of cardiac rejection was based on right ventricular endomyocardial biopsies, which were performed weekly during the first postoperative month, every other week for the next 4–6 weeks, and then monthly for the subsequent 2–3 months. The biopsies were graded according to Billingham’s classification.18 No evidence of rejection was defined as the absence of cellular infiltrate or myocyte necrosis; mild rejection reflected cellular infiltration without myocyte necrosis; moderate rejection demonstrated cellular infiltrate with myocyte necrosis; and severe rejection was accompanied by myocardial hemorrhage. Moderate and severe rejections were treated with pulse methylprednisolone therapy (1 g/day i.v. for 3 days) with biopsies performed weekly until complete resolution of the rejection episode. Management of persistent rejection consisted of a repeat course of methylprednisolone followed by rabbit antithymocyte globulin or OKT-3, if necessary.

Experimental Protocol

On a prospective basis, biplane cineradiographic studies were performed approximately once a week between 41 and 143 days after transplantation. Results were classified into one of three conditions based on histopathological biopsy findings: prerejection, acute rejection with myocyte necrosis (rejection), and complete resolution of rejection (postrejection). All studies performed within 3 days before or after a biopsy indicating acute rejection were included in the rejection group. Data obtained during mild rejection (which did not require specific treatment) were excluded from analysis; experimental parameters from these studies were not statistically different from prerejection values. Only 10 of the 15 patients had a rejection episode that required intensified immunosuppressive therapy during this time period. In two patients, studies were performed before, during, and after a second rejection episode; another patient also had a third episode of rejection. However, because these subsequent rejection episodes were not necessarily independent events, analysis was restricted to the first rejection episode for each patient. Thus, data from a total of 10 rejection episodes in 10 patients were available. During three of these rejection episodes, two abnormal biopsies were obtained as a result of ongoing rejection; results from the corresponding cineradiographic studies were combined in the rejection category. Similarly,
three consecutive biopsies demonstrating moderate rejection occurred during another two rejection episodes. Each of these rejection episodes was considered to have only one abnormal biopsy to avoid biasing the data. Therefore, of the 50 biopsies performed, 10 revealed moderate or severe rejection.

Data Acquisition

All cineradiographic examinations were conducted with patients in the supine position with suspended respiration (at midexpiration) using a General Electric MLX biplane L-U arm system (General Electric Medical Division, Milwaukee, Wis.) with the image intensifiers in the 9-in. boost fluoro-mode and iso-centered on the LV cavity. Simultaneous biplane videofluoroscopic images were recorded at 60 Hz for at least three cardiac cycles in the 30° RAO and 60° LAO projections on Sony U-Matic 5800 3/4-in. videocassette recorders, synchronized with the radiograph pulses by a master sync oscillator. An analog electrocardiographic signal was digitized and recorded in digital format on each individual image using a custom-modified intelligent video controller (Control Video Corp., Campbell, Calif.); the peak R wave signal was detected electronically and defined end-diastolic frames. At the end of each cineradiographic study, images of a lead grid containing 1-cm squares and a three-dimensional helical radiographic phantom with known dimensions were recorded to determine radiographic distortion and magnification factors. The two-dimensional coordinates of each marker in each projection (x,y) were identified, tracked, and digitized using a computerized myocardial marker detection system (model RS-20, Hewlett-Packard, Palo Alto, Calif.) equipped with Matrox MVP-/AT/NP image processing board (Dorval, Quebec, Canada) based on custom-designed image-processing and digitization software developed in our laboratory. Digital data from the two views were later merged to yield the three-dimensional x,y,z coordinates of each marker every 16.7 msec. Accuracy and reproducibility of myocardial marker positions can be measured with a mean overall error of 0.3±1.3 mm using this system.19

Data Analysis

Hemodynamic computations. LV volume was computed for each frame by a modification of the single-plane (RAO), area–length method of Sandler and Dodge20 using marker data, which has been validated previously in our laboratory using contrast left ventriculography.21 For each cardiac cycle, end diastole was defined as the time of peak electrocardiographic R wave and end systole was defined as the time of minimum LV volume. Ejection fraction (EF) was calculated as [(EDV–ESV)/EDV]·100%, where EDV and ESV are end-diastolic and end-systolic LV volumes, respectively.

Computation of left ventricular twist. LV twist was calculated by a modification of the method of Beyar et al.19 Cartesian coordinates (x,y,z) were first transformed into a local cylindrical coordinate (r,θ,z) system. To measure LV twist with respect to the base, marker coordinates underwent translation and rotation in each frame such that the midpoint of the chord connecting the anterobasal and posterobasal markers was positioned at the origin and the long axis (defined as a line passing through the origin and the apical marker) was aligned with the z axis. For each marker, the circumferential rotational angle change [θ(t)] relative to end diastole was computed on a frame-by-frame basis (Figure 1); positive angle change was defined as a counterclockwise rotation as viewed from the apex. For each frame, this rotational angle change was plotted as function of the distance (cm) of each marker from the apical marker along the LV long axis. At any given time, instantaneous chamber twist was defined as the average longitudinal gradient of circumferential rotation (rad/cm) (i.e., the slope of the linear regression of individual marker rotation [θ(t)] versus longitudinal distance from the apex [z−z̄]). Figure 2 illustrates calculation of LV chamber twist at end systole: The circumferential rotation of each marker relative to its end-diastolic position was plotted versus its distance along the z axis from the apex. In this example, the end-systolic twist (represented by the slope) was −0.039 rad/cm (r=0.929, SEM=0.005 rad/cm, 90% confidence limits=−0.051 to −0.027 rad/cm, p<0.0001). Negative twist indicates counterclockwise twisting of the apex with respect to the base (as viewed from the apex). Twist data (with respect to time) were smoothed using a running three-point average. Maximum twist (Twav), defined as the maximum amplitude of negative LV twist, and the time

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**Figure 1.** Schematic of internal reference system for computation of marker rotation about the long axis defined by the line segment passing through the apical marker and bisecting the chord connecting the anterobasal and posterobasal markers. Counterclockwise circumferential rotational angle change at time (t) relative to end diastole (ED), as viewed from apex to base, was considered positive. Global twist describes the longitudinal gradient of θ(t) for all markers.
required for the left ventricle to untwist 50% of $T_{max}$
($\tau_{1/2}$) (expressed as percent of diastole, adjusting for
heart rate, from the time of $T_{max}$) were then calculated.
The first derivative of twist with respect to time
($dT/dt$) was computed using a Fourier series (by fitting
the curve to the Fourier series and then taking the
analytical derivative of the cosine and sine terms), as
were the peak LV systolic twist rate ($dT/dt_{max}$) and
peak diastolic untwist rate ($dT/dt_{max}$). To correct for
possible changes in heart rate, $dT/dt_{min}$ and $dT/dt_{max}$
were normalized by multiplying by the RR interval
($N_{d}dT/dt_{min}$ and $N_{d}dT/dt_{max}$, respectively).

Twist-normalized percent ejection fraction relation.
EF (relative to end diastole) was normalized to the
end-systolic value: Normalized percent EF
($\%EF=EF/EF_{end-systole}$ (ranging from 0 at end diastole
to 1.0 at end systole)). When plotted against LV
twist, the resulting twist-normalized %EF relation
was divided into three phases with corresponding
slopes of the twist-normalized %EF relation as de-
formed by Beyar et al.13: $M_{systole}$ is slope from peak
positive twist to $T_{max}$ during systole, $M_{early-dia}$ is slope
from 1.0 to 0.85 normalized %EF in early diastole,
and $M_{mid-dia}$ is slope from 0.85 to 0.10 normalized
%EF in middle to late diastole. In addition, percent
untwist at 15% diastolic filling was calculated.

To determine the accuracy of the calculated frame-
to-frame normalized LV volume changes, LV volume
computed using a multiple three-dimensional tetra-
hedral model was also used for determination
of normalized %EF. This method used all available
markers, which contrasts to the previously validated
single-plane (RAO) LV volume. LV volume within
the 12-marker structure was divided into 13 adjacent
tetrahedra with coordinates of the four vertices,
x$_{i}$,y$_{i}$,z$_{i}$ ($i=1-4$). The volume (vol.) of each tetrahedron
was calculated as one sixth of the absolute value of
the following determinant:

\[
\begin{vmatrix}
  x_1 & y_1 & z_1 & 1 \\
  x_2 & y_2 & z_2 & 1 \\
  x_3 & y_3 & z_3 & 1 \\
  x_4 & y_4 & z_4 & 1 \\
\end{vmatrix}
\]

and total LV volume was computed as vol$_{tot}=vol_1+vol_2+\ldots+vol_{13}$. When the tetrahedral volume change
was normalized to span from 0 at end diastole to 1.0 at
end systole, the resulting normalized %EF was essen-
tially identical to that obtained using the single-plane,
area-length method (slope=1.01±0.01, x intercept=
0.01±0.06, r=0.98±0.01, $p<10^{-3}$). Accordingly,
the twist versus normalized %EF relation was the same
using either method to determine LV volume.

**Statistical Analysis**

All values are given as mean±1 SD. For each
rejection episode, prerejection and postrejection val-
ues represent the mean of three to nine beats ob-
tained during one to three studies. Rejection values
were also based on three to nine beats, depending on
how many abnormal biopsies and cinefluoroscopic
studies were obtained during rejection. Mean data
for all conditions were compared by repeated-meas-
ures analysis of variance (rm-ANOVA); an F statistic
corresponding to an $\alpha$ error of less than 0.05 was
considered statistically significant. If a significant
difference was detected by rm-ANOVA, Student’s $t$
 test for paired observations with the Bonferroni
correction for multiple comparisons was used to
determine which individual changes were significant.
An adjusted probability of less than 0.05 was consid-
ered significant. Sensitivity, specificity, and predic-
tive accuracy were calculated as follows:

\[
\text{Sensitivity}=P_T/(P_T+N_T)
\]

\[
\text{Specificity}=N_T/(P_F+N_T)
\]

\[
\text{Predictive accuracy}=(P_T+N_T)/(P_T+N_T+N_F+P_F+N_T)
\]

where $P_T$ is true-positive, $N_T$ is true-negative, $P_F$
is false-positive, and $N_F$ is false-negative. The “true”
standard was judged to be the biopsy result.

**Results**

The pattern of LV twist during the cardiac cycle
was similar in all patients (Figure 3, top panel).
Figure 3. Representative plots showing left ventricular twist dynamics (top panel) with corresponding chamber volume (bottom panel) during one cardiac cycle. Beginning at end diastole (t=0), there is an initial small clockwise twist of the apex with respect to the base (as viewed from the apex). The left ventricle then undergoes a counterclockwise twist, reaching a maximum negative amplitude (T_{max}) near end systole (ES) (within 14±30 msec) as defined by the minimum volume (min vol). Diastole is characterized by an early, rapid recoil followed by a more gradual diastolic untwist. T_{1/2}, time for the left ventricle to untwist to one half of T_{max} (expressed as percent of diastole); dT/dt_{min}, peak systolic twist rate; dT/dt_{max}, peak diastolic untwist rate.

Typically, there was an initial clockwise twist (0.007±0.004 rad/cm) followed by counterclockwise twist during systole, which reached a maximum amplitude near end systole (within 14±30 msec) (Figure 3, bottom panel). Diastole was subdivided into two phases at the most frequently observed inflection point of the diastolic twist-normalized %EF relation: early, rapid diastolic recoil (first 15% of chamber filling) followed by slower diastolic untwist (clockwise). Figure 4 graphically depicts the twist-normalized %EF relation for the beat shown in Figure 3. During systole, there was an initial small clockwise twist (A) followed by a linear relation between chamber counterclockwise twist and ejection (A to B). The relation between untwist and volume expansion during diastole, however, was more complex. There was an early, steep, rapid clockwise untwist (B to C) associated with only a small amount of normalized filling (15–20%). The remaining middle to late diastolic filling period was characterized by slower clockwise untwist of the left ventricle (C to D). These two phases of diastole were subdivided at 15% of normalized volume filling (i.e., 0.85 on the abscissa).

Figure 4. Plot of twist-normalized percent ejection fraction (%EF) relation using data shown in Figure 2 (sampling every 16.7 msec). After an initial clockwise chamber twist (A), the relation is relatively linear during systole (○) from A to B. In contrast, diastole (●) can be divided into two separate phases, each displaying a different slope. There is an early, rapid recoil (B to C) with little chamber filling (15–20% of normalized EF), followed by a slower chamber untwist relative to ventricular filling (C to D). M_systole, slope between minimum and maximum twist (A to B); M_{early-diast}, slope between end systole (normalized %EF, 1.0) and mid diastole (normalized %EF, 0.85) (B to C); M_{mid-diast}, slope between mid-diastole and late diastole (normalized %EF, 0.10). Left ventricular untwist during early diastole (first 15% chamber filling) is expressed as percent of maximal twist.

Average T_{max} values at end systole during baseline conditions (prerejection) for all patients are summarized in Table 1. Overall mean T_{max} was −0.048±0.011 rad/cm, a value similar to that reported in normal canine hearts using myocardial markers. The overall extent of regional heterogeneity, as reflected by the average correlation coefficient (r=−0.758±0.099), tended to be less in this human study during baseline conditions than that reported by Beyar et al in dog

| Table 1. Baseline (Prerejection) Left Ventricular End-Systolic Twist |
|-----------------------|------|------|------|
| Patient | T_{max} (rad/cm) | r | p |
| 1 | −0.036 | −0.636 | 0.048 |
| 2 | −0.058 | −0.803 | 0.003 |
| 3 | −0.054 | −0.677 | 0.023 |
| 4 | −0.030 | −0.806 | 0.005 |
| 5 | −0.062 | −0.606 | 0.048 |
| 6 | −0.051 | −0.912 | <0.001 |
| 7 | −0.051 | −0.708 | 0.023 |
| 8 | −0.034 | −0.803 | 0.004 |
| 9 | −0.060 | −0.861 | 0.002 |
| 10 | −0.049 | −0.769 | 0.007 |

Mean±1 SD | −0.048±0.011 | −0.758±0.099 |

T_{max}, amplitude of chamber twist at end systole. Twist is calculated as the slope of the least-squares linear regression of the circumferential rotation of all markers relative to end diastole as a function of distance from the apex along the long axis.
TABLE 2. Parameters Describing Systolic and Diastolic Left Ventricular Twist for All Patients During Prererejection (Baseline) Conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline value (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (rad/cm)</td>
<td>$-0.048 \pm 0.011$</td>
</tr>
<tr>
<td>$dT/dt_{\text{max}}$ (rad/cm/sec)</td>
<td>$-0.312 \pm 0.064$</td>
</tr>
<tr>
<td>$N-dT/dt_{\text{max}}$ (rad/cm)</td>
<td>$-0.210 \pm 0.049$</td>
</tr>
<tr>
<td>$dT/dt_{\text{max}}$ (rad/cm/sec)</td>
<td>$0.331 \pm 0.070$</td>
</tr>
<tr>
<td>$N-dT/dt_{\text{max}}$ (rad/cm)</td>
<td>$0.223 \pm 0.057$</td>
</tr>
<tr>
<td>$\tau_{1/2}$ (%)</td>
<td>$19.9 \pm 5.1$</td>
</tr>
</tbody>
</table>

$n$, number of patients; $T_{\text{max}}$, maximum negative twist at end systole; $dT/dt_{\text{max}}$, peak systolic twist rate; $N-dT/dt_{\text{max}}$, peak systolic twist rate normalized by RR interval; $dT/dt_{\text{max}}$, peak diastolic untwist rate; $N-dT/dt_{\text{max}}$, peak diastolic untwist rate normalized by RR interval; $\tau_{1/2}$, percentage of diastole required for the left ventricle to untwist 50% of $T_{\text{max}}$.

Values are given as mean±1 SD.

Hearts ($r=0.694 \pm 0.104$). The mean baseline parameters characterizing LV twist for all patients are shown in Table 2. $\tau_{1/2}$, expressed as percent of diastole, was 20±5%, which is lower than the 50% untwist estimated previously to occur during isovolumic relaxation in dog hearts11 (assuming that the duration of isovolumic relaxation is approximately 10% of diastole). Table 3 summarizes the prerrejection values for each patient of the twist-normalized %EF relation during systole and the two diastolic phases. During early diastole, the twist-normalized %EF relation ($-0.194 \pm 0.062$ rad/cm) was steeper than that in systole or mid diastole ($p=0.0003$). The overall degree of untwist occurring in early diastole was 62±11%.

Hemodynamic parameters for the prerrejection, rejection, and postrejection conditions are summarized in Table 4. Although there was a trend toward higher heart rates and lower EFs (due to relatively larger ESV) during rejection, these changes did not reach statistical significance.

The effect of rejection on LV twist is illustrated in Figure 5. In this example, although rejection did not significantly affect the systolic twist pattern ($T_{\text{max}}$ decreased from 0.037 to 0.031 rad/cm and $dT/dt_{\text{min}}$ changed negligibly), the rate of early diastolic untwist was markedly reduced, resulting in a prolongation of $\tau_{1/2}$ (from 15% to 26%) and a reduction in $dT/dt_{\text{max}}$ (from 0.34 to 0.20 rad/cm/sec). Successful treatment of rejection resulted in a return of these parameters toward prerrejection values ($\tau_{1/2}=22\%$ and $dT/dt_{\text{max}}=0.27$ rad/cm/sec). Figure 6 graphically depicts these effects on the twist-normalized %EF relation in the same patient. In this case, rejection was associated with a 67% decrease in the slope during the early diastolic phase (from $-0.147$ to $-0.049$ rad/cm), a 28% decrease in untwisting during this period (from 74% to 53%), and a 46% increase in the slope during the middle to late diastolic phase (from $-0.011$ to $-0.016$ rad/cm).

With resolution of rejection, these values returned toward baseline (Mearly-early = $-0.146$ rad/cm, Mmid-early = $-0.010$ rad/cm, percentage untwist during early filling=70%) in this patient.

TABLE 3. Baseline (Prererejection) Characteristics of Twist-Normalized Percent Ejection Fraction Relation During Systole and Two Phases of Diastole

<table>
<thead>
<tr>
<th>Patient</th>
<th>Systole</th>
<th>Early diastole</th>
<th>Mid diastole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (rad/cm)</td>
<td>$r$</td>
<td>Slope (rad/cm)</td>
</tr>
<tr>
<td>1</td>
<td>$-0.033$</td>
<td>$-0.972$</td>
<td>$-0.166$</td>
</tr>
<tr>
<td>2</td>
<td>$-0.057$</td>
<td>$-0.991$</td>
<td>$-0.242$</td>
</tr>
<tr>
<td>3</td>
<td>$-0.055$</td>
<td>$-0.981$</td>
<td>$-0.200$</td>
</tr>
<tr>
<td>4</td>
<td>$-0.029$</td>
<td>$-0.980$</td>
<td>$-0.099$</td>
</tr>
<tr>
<td>5</td>
<td>$-0.063$</td>
<td>$-0.995$</td>
<td>$-0.196$</td>
</tr>
<tr>
<td>6</td>
<td>$-0.058$</td>
<td>$-0.992$</td>
<td>$-0.197$</td>
</tr>
<tr>
<td>7</td>
<td>$-0.061$</td>
<td>$-0.992$</td>
<td>$-0.278$</td>
</tr>
<tr>
<td>8</td>
<td>$-0.046$</td>
<td>$-0.982$</td>
<td>$-0.095$</td>
</tr>
<tr>
<td>9</td>
<td>$-0.075$</td>
<td>$-0.991$</td>
<td>$-0.202$</td>
</tr>
<tr>
<td>10</td>
<td>$-0.053$</td>
<td>$-0.990$</td>
<td>$-0.267$</td>
</tr>
</tbody>
</table>

| Mean±SD | $-0.053 \pm 0.014^*$ | $-0.987 \pm 0.007$ | $-0.194 \pm 0.062$ | $-0.950 \pm 0.038$ | $-0.018 \pm 0.009^*$ | $-0.900 \pm 0.095$ |

Systolic slope was computed from minimum to maximum twist. Early diastole is defined by the period of first 15% diastolic filling beginning at end systole; mid diastole is the remainder of diastole before atrial contraction defined as 90% chamber filling.

*p=0.0003 versus early diastole; fp=0.0003 versus systole and early diastole.

TABLE 4. Effects of Acute Allograft Rejection on Hemodynamic Variables (n=10)

<table>
<thead>
<tr>
<th></th>
<th>Prererejection</th>
<th>Rejection</th>
<th>Postrejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>90±7</td>
<td>92±8</td>
<td>96±14</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>182±56</td>
<td>178±59</td>
<td>169±53</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>118±46</td>
<td>122±50</td>
<td>109±38</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>64±17</td>
<td>57±11</td>
<td>60±22</td>
</tr>
<tr>
<td>EF (%)</td>
<td>37±8</td>
<td>33±6</td>
<td>35±8</td>
</tr>
</tbody>
</table>

n, number of rejection episodes; HR, heart rate; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction.

No significant differences were detected between the three conditions for these five variables. Values are given as mean±SD.
Figure 5. Scatterplots of effect of acute cardiac rejection with myocyte necrosis on time-varying left ventricular chamber twist at 16.7-msec intervals in a representative study. Each curve represents one cardiac cycle between two successive electrocardiographic R waves. In this example, compared with prerejection (top panel), time for untwist to one half of maximum twist \( (T_{50}) \) increased, and peak diastolic recoil \( (dT/dt_{\text{min}}) \) decreased with acute rejection (middle panel). In contrast, end-systolic twist \( (T_{\text{syst}}) \) was reduced slightly, and peak systolic twist rate \( (dT/dt_{\text{max}}) \) remained unchanged. Chamber twist–untwist pattern returned toward baseline after successful treatment of rejection episode (bottom panel).

Table 5 summarizes the effect of acute allograft rejection on the LV twist parameters \( (n=10) \). None of the variables characterizing systolic twist \( (T_{\text{max}}, dT/dt_{\text{min}}, N-dT/dt_{\text{min}}, \text{or slope of the systolic twist-normalized } \%EF \text{ relation } (M_{\text{max}})) \) were affected by rejection. In contrast, diastolic changes, particularly during the early diastolic filling phase, were large. The slope of the twist-normalized \%EF relation during early diastole \( (M_{\text{early-diastole}}) \) declined significantly (from \(-0.194\pm0.062 \) to \(-0.103\pm0.054 \) rad/cm, \( p=0.0003 \)), resulting in a prolongation of \( T_{50} \) (from \( 20\pm5\% \) to \( 28\pm5\% \), \( p=0.0003 \)) and reduction of untwist at \( 15\% \) of diastolic filling (from \( 62\pm11\% \) to \( 36\pm13\% \), \( p=0.0003 \)). A greater portion of LV untwisting, therefore, occurred during the remainder of diastole, as reflected by an increase in the slope of the twist-normalized \%EF relation \( (M_{\text{mid-diastole}}) \) during middle to late diastole (from \(-0.018\pm0.009 \) to \(-0.030\pm0.010 \) rad/cm, \( p=0.0015 \)). Somewhat surprisingly, rejection had no substantial effect on \( dT/dt_{\text{max}} \), the maximum rate of overall recoil (\( 0.311\pm0.070 \) to \( 0.315\pm0.102 \) rad/cm/sec, \( p=\text{NS} \)). After correcting for heart rate, \( N-dT/dt_{\text{max}} \) also did not change. Resolution of rejection was associated with normalization of \( M_{\text{early-diastole}} \) and percent of untwist during early diastole (\( p=\text{NS} \) versus baseline). Although there was a trend for \( M_{\text{mid-diastole}} \) to return toward baseline, this change was not statistically different from rejection values. The effects of acute rejection.

Figure 6. Plots of effects of acute cardiac allograft rejection (with myocyte necrosis) on left ventricular twist-normalized percent ejection fraction (%EF) relation in the same patient as shown in Figure 5. Compared with prerejection (top panel), acute rejection (middle panel) was associated with a decrease in the slope during early diastole (B to C in Figure 3). Consequently, the slope of the mid-diastolic relation increased with rejection. Resolution of rejection resulted in a return to prerejection diastolic twist dynamics (bottom panel). ○, ○, Systole and diastole, respectively.
TABLE 5. Summary of Effects of Acute Cardiac Rejection With Myocyte Necrosis on the Variables Characterizing Systolic and Diastolic Left Ventricular Twist (n=10)

<table>
<thead>
<tr>
<th></th>
<th>Prerejection</th>
<th>Rejection</th>
<th>Postrejection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T_{max} (rad/cm)</td>
<td>-0.048±0.011</td>
<td>-0.048±0.016</td>
<td>-0.051±0.010</td>
</tr>
<tr>
<td>dT/dt_{min} (rad/cm/sec)</td>
<td>-0.312±0.064</td>
<td>-0.299±0.095</td>
<td>-0.298±0.091</td>
</tr>
<tr>
<td>N-dT/dt_{min} (rad/cm)</td>
<td>-0.210±0.049</td>
<td>-0.196±0.059</td>
<td>-0.188±0.051</td>
</tr>
<tr>
<td>M_{systole} (rad/cm)</td>
<td>-0.053±0.014</td>
<td>-0.052±0.013</td>
<td>-0.045±0.035</td>
</tr>
<tr>
<td><strong>Diastole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dT/dt_{max} (rad/cm/sec)</td>
<td>0.331±0.070</td>
<td>0.315±0.102</td>
<td>0.305±0.077</td>
</tr>
<tr>
<td>N-dT/dt_{max} (rad/cm)</td>
<td>0.223±0.057</td>
<td>0.207±0.067</td>
<td>0.194±0.049</td>
</tr>
<tr>
<td>τ_{1/2} (% diastole)</td>
<td>19.9±5.1*</td>
<td>27.6±5.2</td>
<td>27.8±9.2*</td>
</tr>
<tr>
<td>M_{early-diastole} (rad/cm)</td>
<td>-0.194±0.062*</td>
<td>-0.103±0.054</td>
<td>-0.186±0.073*</td>
</tr>
<tr>
<td>M_{mid-diastole} (rad/cm)</td>
<td>-0.018±0.009*</td>
<td>-0.030±0.010</td>
<td>-0.023±0.012</td>
</tr>
<tr>
<td>Untwist-15% filling (%)</td>
<td>61.6±10.6*</td>
<td>36.0±13.0</td>
<td>53.6±12.1*</td>
</tr>
</tbody>
</table>

n, number of rejection episodes; T_{max}, maximum negative twist; dT/dt_{max}, peak systolic twist rate; N-dT/dt_{min}, peak systolic twist rate normalized by RR interval; M_{systole}, slope of systolic twist-normalized percent ejection fraction (%EF) relation; dT/dt_{min}, peak diastolic recoil rate; N-dT/dt_{max}, peak diastolic untwist rate normalized by RR interval; τ_{1/2}, time for untwisting 50% of T_{max}; M_{early-diastole}, slope of early diastolic twist-normalized %EF relation; M_{mid-diastole}, slope of mid-diastolic twist-normalized %EF relation; Untwist-15% filling, percent left ventricular untwist during early diastole (15% of chamber filling).

*p=0.0003 versus rejection; †p=0.054 versus prerejection; ‡p=0.0015 versus rejection; §p=0.006 versus rejection. Values are given as mean±SD.

on these four diastolic twist parameters for all patients are summarized in Table 6.

Figure 7 illustrates several changes in M_{early-diastole} in one representative patient. The biopsy on postoperative day 14 revealed evidence of moderate rejection, associated with a marked reduction in M_{early-diastole}. Despite methylprednisolone therapy, a repeat biopsy 8 days later demonstrated ongoing rejection, and the slope of the early diastolic twist-normalized %EF relation was similar to that calculated 1 week earlier. After resolution of rejection as documented by subsequent biopsies, M_{early-diastole} returned to baseline levels.

Because M_{early-diastole} was the variable that returned to prerejection levels, the sensitivity, specificty, and predictive accuracy of this parameter as an indicator of rejection were calculated (Table 7). Because the average coefficient of variation for inter-study M_{early-diastole} for all patients was 27%, a reduction in this magnitude was chosen as the threshold to define rejection. All 10 biopsies showing acute rejection with myocyte necrosis were detected using this criterion, yielding a sensitivity of 100%, a specificity of 95%, and an overall predictive accuracy of 92%.

**Discussion**

The results of the present study demonstrate that the LV twist-untwist pattern in human allografted hearts is similar to that reported previously in normal

TABLE 6. Effects of Acute Cardiac Allograft Rejection on Diastolic Parameters in 10 Transplant Recipients

<table>
<thead>
<tr>
<th>Patient</th>
<th>M_{early-diastole} (rad/cm)</th>
<th>M_{mid-diastole} (rad/cm)</th>
<th>τ_{1/2} (% diastole)</th>
<th>Untwist-15% filling (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Rej</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>1</td>
<td>-0.166</td>
<td>-0.079</td>
<td>-0.114</td>
<td>-0.023</td>
</tr>
<tr>
<td>2</td>
<td>-0.242</td>
<td>-0.172</td>
<td>-0.269</td>
<td>-0.012</td>
</tr>
<tr>
<td>3</td>
<td>-0.200</td>
<td>-0.047</td>
<td>-0.133</td>
<td>-0.012</td>
</tr>
<tr>
<td>4</td>
<td>-0.099</td>
<td>-0.050</td>
<td>-0.109</td>
<td>-0.014</td>
</tr>
<tr>
<td>5</td>
<td>-0.196</td>
<td>-0.088</td>
<td>-0.157</td>
<td>-0.039</td>
</tr>
<tr>
<td>6</td>
<td>-0.197</td>
<td>-0.097</td>
<td>-0.163</td>
<td>-0.009</td>
</tr>
<tr>
<td>7</td>
<td>-0.278</td>
<td>-0.146</td>
<td>-0.266</td>
<td>-0.009</td>
</tr>
<tr>
<td>8</td>
<td>-0.095</td>
<td>-0.035</td>
<td>-0.137</td>
<td>-0.014</td>
</tr>
<tr>
<td>9</td>
<td>-0.202</td>
<td>-0.120</td>
<td>-0.196</td>
<td>-0.023</td>
</tr>
<tr>
<td>10</td>
<td>-0.267</td>
<td>-0.194</td>
<td>-0.316</td>
<td>-0.022</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.194*</td>
<td>-0.103</td>
<td>-0.186*</td>
<td>-0.018†</td>
</tr>
<tr>
<td>±SD</td>
<td>0.062</td>
<td>0.054</td>
<td>0.073</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Pre, prerejection; Rej, rejection; Post, postrejection; M_{early-diastole}, slope of early diastolic twist-normalized percent ejection fraction (%EF) relation; M_{mid-diastole}, slope of mid-diastolic twist-normalized %EF relation; τ_{1/2}, time for untwisting 50% of T_{max}; Untwist-15% filling, percent left ventricular untwist during early diastole (15% of chamber filling).

*p=0.0003 versus rejection; †p=0.0015 versus rejection; ‡p=0.054 versus prerejection; §p=0.006 versus rejection.
canine hearts. At the onset of systole, there is a small clockwise twist of the apex with respect to the base (as viewed from the apex). This may relate to the fact that the subendocardium is electrically activated first; because of the right-handed helical orientation of subendocardial myocytes, this produces clockwise LV twist. Soon thereafter, the nearly orthogonally oriented left-handed helix of subepicardial myocardial fibers becomes activated, causing a counterrotating torque and, consequently, counterclockwise LV twist. This systolic twisting motion is linearly related to ejection of blood (Figure 4). The relation between untwisting and LV filling during diastole was more complex. There was an initial, rapid clockwise untwist (recoil) associated with little chamber filling, which was followed by more gradual untwisting. The observation of Rademakers et al that a small but significant degree of circumferential epicardial segment lengthening occurred during isovolumic relaxation may relate to this rapid LV untwisting during early diastole. The values of T_max and slope of the twist-normalized %EF relation during various phases of the cardiac cycle in this study are consistent with those reported in dogs by other investigators.

Previously, our group reported that cardiac allograft rejection in humans was associated with a small (but significant) decrease in the maximum torsional deformation (\(\Theta_{\text{max}}\)) and peak systolic torsion rate of the maximally deforming myocardial LV marker without measurable changes in peak diastolic recoil rate. It should be noted that in that study, five of 14 rejection episodes were associated with a decrease in \(\Theta_{\text{max}}\) of 10.5% or less, the mean interstudy coefficient of variation; thus, 36% of the positive (abnormal) studies could have been accounted for by random variation alone. In contrast, the results of the present study indicate that systolic LV twist did not change during rejection. Ongoing rejection is a diffuse process involving both left and right ventricles (personal communication, M.E. Billingham); furthermore, LV twist, as calculated by these marker data, should also be a global LV phenomenon. The regional heterogeneity of torsional systolic deformation previously reported using myocardial marker and MRI radiofrequency-tagging techniques was reflected by the correlation coefficient of the twist regression used in this study, which was less than unity. Thus, focusing on a single maximally deforming marker to assess LV twist may increase the sensitivity of such being indicative of rejection, especially when the maximally deforming marker is not in a consistent apical myocardial location among patients. Moreover, detectable LV systolic dysfunction is a relatively late event during rejection, an observation that has been corroborated by recent echocardiographic studies. A decline in \(\Theta_{\text{max}}\) however, is not incompatible with the fact that no change in T_max was observed. It is possible that reduced chamber shortening during rejection can lower \(\Theta_{\text{max}}\) without necessarily altering global LV twist (i.e., longitudinal gradient of circumferential rotation). Thus, \(\Theta_{\text{max}}\) which does not assess interactions among various regions of the left ventricle, may not be an appropriate tool for detection of allograft rejection.

The current data indicate that rejection is more closely related to abnormal LV diastolic mechanics: Initial LV rapid recoil was markedly diminished. Although we previously found no consistent change in peak marker diastolic recoil rate, no other diastolic characteristics (in particular, torsion in relation to LV filling) were examined. As was seen in the case of single myocardial markers, the present findings confirm that the maximum overall untwist rate, dT/dt_max did not change during rejection; however, the overall untwist rate during the first 15% of diastolic filling was significantly lower, as reflected by the decrease (47%) in M_early-diastolic (Table 5). As a result, the degree of LV untwisting during this period decreased 42%, and \(\tau_{1/2}\) was prolonged by 40%. The slope of the mid-diastolic LV twist-normalized %EF relation increased, probably as a consequence of the decreased LV untwisting during early diastole. With resolution of

![Figure 7](http://circ.ahajournals.org/)

**Figure 7.** Plot of postoperative course of one patient during the study period. Values of the slope of the early diastolic twist-normalized percent ejection fraction relation (M_early-diastolic) in the presence (○) and absence (●) of rejection with myocyte necrosis are plotted versus the number of days after cardiac transplantation. Acute rejection was associated with a significantly reduced slope.

**Table 7. Sensitivity, Specificity, and Predictive Accuracy of M_early-diastolic as an Index of Acute Cardiac Allograft Rejection**

<table>
<thead>
<tr>
<th>M_early-diastolic decrease (%)</th>
<th>27%</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy positive</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Biopsy negative</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Specificity</td>
<td>36%</td>
<td>90%</td>
</tr>
<tr>
<td>Predictive accuracy</td>
<td>46%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, and predictive accuracy are expressed as mean±70% confidence limits.

M_early-diastolic: slope of early diastolic twist-normalized percent ejection fraction relation; P_t, true-positive; N_t, false-negative; N_r, true-negative; P_r, false-positive.
rejection, all of these parameters reverted toward baseline values. Only $M_{\text{early-dia}}$ and percent untwist during early filling, however, returned to prerejection levels. The persistent alterations in $\tau_{1/2}$ and $M_{\text{mid-dia}}$ may reflect residual changes in the viscoelastic properties of the myocardium, perhaps due to myocyte necrosis with subsequent myocardial fibrosis.

The full implications of initial diastolic rapid recoil of the left ventricle remain unclear; it may, however, be linked to the early diastolic LV suction effect demonstrated in canine28,29 and human30 hearts. During systole, fiber shortening stores energy in elastic elements, both within the myocardial fibers and in the extracellular collagen matrix. It has been suggested that initial LV untwist represents rapid release of this potential energy.10 Furthermore, the passive LV pressure-volume curve at the smallest LV volumes31 suggest that the energy released may generate large recoil forces that rapidly reduce LV pressure during early diastole. This, in turn, would lead to a larger atrioventricular pressure gradient and thereby augment early diastolic LV filling.28,29,31 It has been suggested that such a higher filling rate may increase LV end-diastolic volume32 and thus enhance systolic function by the Frank-Starling mechanism. We therefore hypothesize that during acute allograft rejection, myocyte necrosis, cellular infiltration and edema, fibrosis, and possibly other factors alter the intrinsic elastic properties of the left ventricle. If these were to reduce either the spring constant, $k$, or the shortening, $x$, of an analogous compressed spring, less potential energy ($kx^2/2$) could be stored at end systole, resulting in a loss of diastolic recoil forces responsible for the early, rapid unwinding of the deformed ventricle. Perturbation of this early, rapid LV untwisting not only would affect diastolic LV dynamics but also might have deleterious implications in terms of systolic LV mechanics.

Acute cardiac allograft rejection is characterized histologically by diffuse perivascular and interstitial infiltration of the myocardium with mononuclear cells.33,34 This eventually becomes manifest as increased LV mass and wall thickness as measured by echocardiography,35–39 leading to decreased static compliance of the LV chamber. It follows that diastolic LV dysfunction may precede detectable systolic abnormalities, as indicated by the findings in the present study. Furthermore, echocardiographic Doppler assessment of acute rejection has demonstrated a significant reduction in isovolumic relaxation time12,14–16 and mitral valve pressure half-time.14–16 The shorter isovolumic relaxation time is thought to be a result of earlier mitral valve opening rather than of delayed aortic valve closure.15,16 Although it has been suggested that this may be related to elevated left atrial pressure, it is possible that abnormal early LV diastolic untwisting, as measured in the present study, may alter papillary muscle geometry such that premature opening of the mitral valve occurs. Similarly, inhibition of rapid early LV diastolic recoil and consequent reduced diastolic suction may decrease the atrioventricular pressure gradient, thereby also shortening the pressure half-time.

Using a 27% decrease in $M_{\text{early-dia}}$ as a criterion for the diagnosis of acute rejection, the calculated sensitivity, specificity, and predictive accuracy of this method are higher than those reported using echocardiography Doppler for isovolumic relaxation time12,16 and pressure half-time.16 It should be noted, however, that $M_{\text{early-dia}}$ decreased by only 9% during one of the subsequent (second) rejection episodes in the same patient. If all second and third rejection episodes were included in the analysis, the resulting sensitivity, specificity, and predictive accuracy would be slightly lower (93±7%, 89±5%, and 90±4%, respectively).

Limitations. Although these observations constitute the first detailed analysis of LV twist pattern and twist–volume change relation in the human heart, it should be acknowledged that these values may not represent those of normal human hearts. Preliminary investigations in our laboratory, however, indicate that nontransplanted human hearts (in patients without coronary or valvular heart disease) also demonstrate a similar LV twist pattern postoperatively; moreover, these results are consonant with those reported in normal dog hearts.10

Global LV twist, a statistically derived mean gradient of circumferential rotation of markers in all LV walls, does not directly address the issue of regional heterogeneity of systolic torsional deformation. The measured data, however, were fairly uniform; although there was a large amount of intersubject variability in the computed parameters, the general pattern of LV twist throughout the cardiac cycle as well as the twist–%EF relation were consistent among patients. Furthermore, such regional differences in rotation about the long axis argue that a more general parameter (LV twist versus a single myocardial locus) be used to assess global phenomena such as acute allograft rejection.

Another potential limitation relates to the fact that the effects of recipient atrial contraction were not taken into account in interpreting these data. The influence of recipient atrial contraction on LV filling has been documented by invasive hemodynamic40 and echocardiographic41 studies. It is possible that early diastolic events may be influenced considerably by mechanical activity of the recipient atrium during late systole. This may be a source of some of the interstudy variability seen in our measurements. Evaluation of all studies at the time of an abnormal endomyocardial biopsy, however, revealed that the relation between LV twist and volume change during early diastole was different compared with baseline measurements in 10 of 10 such cases. Thus, our conclusions, based on repeated assessment in the same subjects, should be valid.

Finally, it should be noted that 15% LV filling was chosen to define the two phases of diastole based on the inflection point (15–20%) of the diastolic twist-normalized %EF curve. To ensure the validity of these results, repeat analysis using a 5% interval
about the 15% LV filling to divide early and middle diastole was performed (e.g., 10% and 20%); the results of these analyses did not change the conclusions reported herein. Moreover, our choice of 15% LV filling is consonant with that reported in normal dogs and is corroborated by the consistently high correlations obtained for the two slopes of the diastolic twist-normalized %EF relation.

Summary

We have demonstrated that twisting of the human left ventricle about its long axis is a function of the phase of the cardiac cycle. With respect to chamber volume change, LV twist is linearly related to ejection during most of systole. In contrast, diastolic untwisting can be characterized by early rapid recoil with little change in volume following slower untwisting during the remainder of diastolic filling. The initial rapid untwisting of the left ventricle may play an important role in the mechanical genesis of diastolic LV suction. In the course of acute cardiac allograft rejection, the amount of LV untwisting during early diastole decreased without any detectable alterations in systolic dynamics. This was reflected by a significant decrease in the slope of the early diastolic twist-normalized %EF relation. This type of analysis holds great promise due to the recent advent of MRI radiofrequency-tagging methods to noninvasively measure LV twist dynamics.

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KEY WORDS • left ventricular twist • transplantation • acute rejection • diastolic left ventricular function
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