Effect of Volume Loading, Pressure Loading, and Inotropic Stimulation on Left Ventricular Torsion in Humans

David E. Hansen, MD; George T. Daughters II, MS; Edwin L. Alderman, MD; Neil B. Ingels, PhD; Edward B. Stinson, MD; and D. Craig Miller, MD

Background. The transmural distribution of fiber angles and the extent of shortening among obliquely oriented fibers are likely to be major determinants of the twisting motion that accompanies left ventricular (LV) ejection. As such, measurements of torsion may provide useful information about LV contractile function, but other factors, such as ventricular loading conditions, may also regulate this motion.

Methods and Results. Torsion angles (θ) of midventricular and apical regions were measured relative to a reference minor axis near the base in seven human cardiac allografts from biplane radiographic images of metallic midwall markers. Pressure loading with methoxamine (5–10 µk/kg/min) increased LV end-systolic pressure by 41±14 mm Hg (p<0.0001). Volume loading with normal saline raised LV end-diastolic pressure from 9.9±5.2 to 19.6±4.9 mm Hg (p<0.0001). These alterations in LV loading conditions were associated with no change in θ (difference not significant) for any marker site. Inotropic stimulation with dobutamine (5 µg/kg/min) increased values of θ by as much as twofold (p<0.05); this response varied considerably depending on marker location, with the middle and apical inferior wall and the apical lateral wall being the most sensitive. When the marker site associated with the largest torsion angle (θmax) was considered in each patient, dobutamine increased θmax in all cases (25.2±10.5° versus 15.8±7.7°, p<0.001), whereas pressure and volume loading had negligible effects. This 59% increase in θmax was greater than that of conventional load-dependent indexes of LV systolic performance such as stroke volume (16%), ejection fraction (22%), and maximum rate of LV pressure rise (52%).

Conclusions. This component of LV motion is relatively insensitive to alterations in preload and afterload, while changes in contractile state influence LV torsion in a regionally heterogeneous manner. Quantification of LV torsion may, therefore, provide a sensitive and relatively load-independent measure of contractile performance that may prove to be useful in the serial assessment of LV function. (Circulation 1991;83:1315–1326)

Recent studies of the three-dimensional motion of surgically implanted left ventricular (LV) midwall markers demonstrate that the human left ventricle undergoes a characteristic “wringing” motion about the major axis (i.e., ventricular torsion) as it ejects and fills.¹,² Such measurements have potential clinical importance since ventricular torsion decreases in cardiac transplant recipients during acute cardiac allograft rejection; interestingly, changes can be detected very early in the rejection process, when conventional measures of LV systolic and diastolic performance remain unchanged.³ Thus, serial measurements of ventricular torsion may provide a uniquely sensitive method to assess changes in ventricular function.

Unfortunately, there is little information available regarding the factors that may regulate ventricular torsion. For instance, it would be important to know

From the Division of Cardiology (D.E.H.), Vanderbilt University School of Medicine, Nashville, Tenn., the Division of Cardiology (E.L.A.) and Department of Cardiovascular Surgery (E.B.S., D.C.M.), Stanford University School of Medicine, Stanford, Calif., and the Research Institute of the Palo Alto Medical Foundation (G.T.D., N.B.I.), Palo Alto, Calif.

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Address for correspondence: David E. Hansen, MD, Division of Cardiology, CC-2218 Medical Center North, Vanderbilt University School of Medicine, Nashville, TN 36232.

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whether LV torsion is influenced by alterations in loading conditions; it would also be instructive to know if changes in these measurements actually reflect changes in the contractile state of the myocardium. While the complex helical arrangement of myocardial fibers may provide the anatomic basis for LV torsion, it would be difficult to predict precisely how these hemodynamic factors influence this component of LV motion based solely on considerations of fiber geometry and function.

The present study was undertaken to evaluate the manner in which hemodynamic factors influence torsional deformations about the LV long axis in human hearts. Our results demonstrate that volume loading with normal saline and pressure loading with an α-adrenergic vasoconstrictor (methoxamine) have negligible effects on LV torsion, while inotropic stimulation with a β-adrenergic agonist (dobutamine) increases torsional deformations in a regionally nonuniform manner. These findings provide new knowledge regarding the regulation of ventricular torsion that is essential to the proper interpretation of such measurements and support the notion that ventricular torsion is a sensitive indicator of LV contractile function that is relatively independent of loading conditions.

**Methods**

Seven human orthotopic cardiac allograft recipients participated in this study. Informed consent was obtained from each patient for the implantation of intramyocardial markers and for the studies described. The protocols were approved by the Stanford University Committee on the Use of Human Subjects in Research. No complications resulted from these investigations.

**Implantation of LV Midwall Markers**

Twelve helical coils of tantalum wire (0.8×2.2 mm) were implanted 5 mm below the LV epicardial surface at anatomically well-defined sites as previously described. The positions of these midwall markers as viewed from the 30° right anterior oblique (RAO) and 60° left anterior oblique (LAO) radiographic projections are illustrated in Figure 1. The locations and numbering scheme for the markers are provided in Table 1. Two standard surgical clips were attached to the adventitia of the aorta approximately 2 cm above the anulus to mark the position of the aortic valve.

**Patient Selection**

The ventricular torsion studies were performed in the cardiac catheterization laboratory 1 year after surgery, immediately following the annual posttransplant evaluation that all heart transplant patients undergo at our institution. The annual evaluation includes right ventricular endocardial biopsy, right and left heart catheterization using fluid-filled catheters referenced to the midchest level, biventricular angiography, and multplane coronary arteriography. The criteria for inclusion in the study were 1) right atrial pressure less than 8 mm Hg, 2) pulmonary artery pressure less than 40 mm Hg, 3) LV end-diastolic pressure (EDP) less than 15 mm Hg, 4) Fick cardiac index greater than 2.7 l/min/m², 5) LV ejection fraction (EF) greater than 55%, 6) normal regional wall motion as assessed by a computerized biplane radial shortening method, and 7) no significant coronary artery disease (luminal narrowing greater than 50%). Thus, ventricular torsion studies were performed only in patients with normal cardiac allograft function. The right ventricular endocardial biopsies (minimum of four samples) showed no evidence of acute cardiac allograft rejection in all patients, according to previously published criteria.

**Instrumentation**

The patients were mildly sedated with diazepam (10 mg p.o.) and diphenhydramine (50 mg p.o.) administered 30 minutes before the study. Right atrial pacing was performed at twice the diastolic threshold using a 6F bipolar pacing catheter positioned in the right atrial appendage. The atrial pacing rate was set to 120% of the intrinsic baseline heart rate, allowing a constant heart rate throughout the study. A micromanometer-tipped catheter (Millar SPC-450, Houston, Tex.) was centrally positioned in the LV cavity to measure LV intracavitary pressure continuously. The micromanometer was electronically zeroed in a 37°C temperature bath and calibrated with a mercury manometer. Two 9F side-arm sheaths were inserted for intravenous infusion of drugs and fluid and placement of catheters.

**Data Acquisition**

Biplane radiographic images. Biplane cineradiograms were recorded on 35-mm cine film at a rate of 60 frames/sec (16.7-msec intervals) using a General Electric MLX biplane L-U arm system (Milwaukee, Wisc.) with intensifiers in the 9° mode. Standard 30° RAO and 60° LAO projections were used with the
FIGURE 1. Biplane radiographs of left ventricular midwall marker positions. End-diastolic locations of markers in 30° right anterior oblique (top) and 60° left anterior oblique (bottom) projections are numbered according to scheme presented in Table 1.
two x-ray tubes firing alternately every 8.3 msec to avoid image degradation, which occurs when the biplane images are acquired simultaneously. At the completion of each study, biplane radiographic images of a three-dimensional radiographic phantom of known dimensions were obtained to determine magnification and distortion factors. Comparison of radiographic measurements with actual dimensions revealed that distances could be measured to within 0.4 mm and angles to within 1°.

**Pressure recordings.** The LV pressure signal from the micromanometer was recorded at low and high gain on a multichannel recorder system at a paper speed of 100 mm/sec, along with the electronically determined time derivative of LV pressure (dp/dt) and lead II surface electrocardiogram (ECG). To synchronize these recordings with the marker images, an electronic circuit was used to detect the peak R wave signal from the surface ECG and indicate this event on the cine film by triggering a light-emitting diode; a vertical mark was simultaneously put on the paper record by the multichannel recorder.

**Data Analysis.**

The LV pressure tracing was digitized using a Hewlett-Packard x-y digitizer pad (HP-9111A, Palo Alto, Calif.). The digitized LV pressures corresponding to each frame of the cine film were transmitted to an IBM System/36 computer (Armonk, N.Y.) and stored for subsequent use.

Using markers 2–8 (which silhouette the LV chamber in the 30° RAO projection) and the extrapolated position of the aortic valve determined from the aortic clips, LV volume was computed for each frame using the single-plane area–length method of Sandler and Dodge.6 The accuracy of this method has been previously demonstrated by correlation with simultaneously acquired contrast ventriculograms.7 EDP and end-diastolic volume (EDV) were defined as the LV pressure and volume, respectively, at the time of the peak R wave of the ECG. The end-systolic pressure (ESP) and volume (ESV) were defined according to Suga et al8 as the LV pressure and volume, respectively, at the time of the maximum pressure:volume ratio. LV stroke volume (SV) was computed as EDV−ESV and EF as SV/EDV.

**Image processing.** The position of each marker within a three-dimensional laboratory coordinate system (x,y,z) was determined from the biplane images as previously described.1,2 In brief, the center of each marker image (x,y for the 30° RAO projection and y,z for the 60° LAO projection) was manually digitized frame by frame using a modified Vanguard projector (Neptune, N.J.) linked via a vidicon camera to a Hewlett-Packard 1000 microcomputer and Tektronix (Beaverton, Ore.) light pen. Corrections for the magnification and distortion of the imaging system were performed by the computer. These corrected values were subsequently transferred to an IBM System/36 computer where the y,z data were shifted by 8.3 msec, the y coordinates from the two projections were averaged, and three-dimensional coordinates were computed using a parallel-ray approximation.

**Conversion to cylindrical coordinates.** Computation of torsional deformation angles was facilitated by conversion from laboratory coordinates into a cylindrical coordinate system in which the major and minor axes of the ventricle were aligned with the cylindrical longitudinal and radial axes, respectively. As shown in Figure 2, for each frame (occurring at time t) 1) the midpoint between markers 2 and 8 (point M) was determined, 2) the long axis was defined from point M at the base to marker 5 at the LV apex, 3) the origin of the cylindrical coordinate system was placed at point M, 4) a basal reference minor axis was defined as the line through the projection of markers 2 and 8 onto a plane perpendicular to this long axis, passing through M, and 5) the instantaneous position of marker i (where the subscript i indicates the marker site as numbered in Table 1) was defined in terms of the longitudinal distance li(t) from point M, radial distance ri(t) from the long axis, and angular coordinate αi(t) relative to the reference minor axis. This definition of the LV major axis corresponds closely to that used by Streeter3 in his anatomic dissections of the human left ventricle and was considered the torsional axis for the purposes of this study.

![Figure 2. Cylindrical coordinate system used for computation of torsional deformations. Markers 2, 8, and 5 (solid circles) define major and minor axes of this coordinate system. Major axis is line connecting M (midpoint between markers 2 and 8) with marker 5. Reference minor axis is line through projection of markers 2 and 8 onto plane orthogonal to major axis that contains point M. Position of ith marker (open circle) in this coordinate system is expressed in terms of longitudinal distance li(t) from point M, radial distance ri(t) from major axis, and angle αi(t) relative to translated reference minor axis.](image-url)
Computation of torsional deformation angles. The time-varying torsional deformation angle of the ith marker \([\theta_i(t)]\) was computed as \(\alpha_i(t) - \alpha_i(\text{ed})\), where \(\alpha_i(\text{ed})\) is the value of \(\alpha_i(t)\) at end diastole, and the subscript \(i\) indicates the marker site as numbered in Table 1. The peak R wave of the ECG defined end diastole. Counterclockwise direction (as viewed from apex to base) was positive for both \(\alpha_i(t)\) and \(\theta_i(t)\). This definition of torsional deformation is analogous to that proposed by Arts et al\(^9\) and the one used in our earlier studies.\(^1,2\)

For each marker in the middle and apical thirds of the ventricle, values of \(\theta_i(t)\) were plotted at 16.7-msec intervals and the mean peak-to-trough amplitude (\(\theta\)) for three to five beats was computed. For each subject, the initial baseline control values of \(\theta\) were compared and the data of the marker with the greatest \(\theta\) were smoothed using a Fourier filter with a bandwidth of 8 Hz to eliminate high-frequency digitizing noise. We have demonstrated previously that 95% or more of the information in the frequency spectrum of \(\theta_i(t)\) is contained below this frequency.\(^10\) The mean peak-to-trough amplitude of this smoothed torsional deformation curve was then calculated for each experimental condition and designated as \(\theta_{\text{max}}\). This definition of \(\theta_{\text{max}}\) is identical to that of our earlier studies.\(^1,2\)

As in our earlier studies,\(^1,2\) the marker used for the calculation of \(\theta_{\text{max}}\) was invariably located in the apical region because \(\theta\) increases with increasing distance from the reference minor axis at the base. While the specific marker varied from patient to patient, the marker used for the calculation of \(\theta_{\text{max}}\) was not arbitrary since the marker associated with the largest torsional deformation angle under the initial baseline control conditions was consistently used throughout each study.

Protocol

The experimental protocol is illustrated in Figure 3. Simultaneous recordings of biplane marker images and LV pressure were collected over a wide range of preload and afterload, at the baseline contractile state, and with the contractile state increased experimentally with dobutamine. An initial sequence was obtained under baseline conditions (C1) before any pharmacological intervention. This was followed by LV pressure loading, produced by the intravenous infusion of methoxamine at 5–10 \(\mu\)g/kg/min. This \(\alpha\)-adrenergic agonist is a potent vasoconstrictor without significant inotropic effects in this dose range.\(^11\) Data were collected after each 10–20 mm Hg increase in blood pressure during the methoxamine infusion. In general, LV systolic pressure increased by 30–60 mm Hg, allowing data acquisition at two or three different levels of afterload over 15–20 minutes before reaching the peak methoxamine effect (MTX). The systolic blood pressure during methoxamine infusion never exceeded 180 mm Hg in any patient. An intravenous infusion of dobutamine (5 \(\mu\)g/kg/min) was then added while the infusion of methoxamine was continued. During the dobutamine infusion, dP/dt was monitored to follow the inotropic effect of this drug. Once dP/dt increased to a new stable level, additional data were obtained 1) at the peak methoxamine effect (MTX+DOB), 2) after each 10–20 mm Hg decrease in peak LV systolic pressure following discontinuation of the methoxamine infusion, and 3) during the pure dobutamine effect (DOB) after the methoxamine effect had completely waned, as indicated by a stable peak LV systolic pressure for a minimum of 10 minutes. The dobutamine infusion was then discontinued. After LV pressure and dP/dt stabilized (15–20 minutes), postdobutamine control data (C2) were acquired. This was immediately followed by a rapid infusion over 5–10 minutes of 2 l physiological saline. After each 3–5 mm Hg increase in EDP, additional recordings were obtained as EDP was augmented to a maximum value of approximately 20 mm Hg (VOL).
TABLE 2. Hemodynamic Effects of Methoxamine, Dobutamine, and Saline Infusion in Seven Cardiac Allograft Recipients

<table>
<thead>
<tr>
<th>Hemodynamic parameter</th>
<th>Experimental stage</th>
<th>C1</th>
<th>MTX</th>
<th>MTX+DOB</th>
<th>DOB</th>
<th>C2</th>
<th>VOL</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDP (mm Hg)</td>
<td></td>
<td>8.4±4.5</td>
<td>10.7±5.2</td>
<td>12.6±7.8</td>
<td>7.7±5.0</td>
<td>9.9±5.2</td>
<td>19.6±4.9*</td>
<td>8.10</td>
<td>0.0001</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td></td>
<td>174±47</td>
<td>183±52</td>
<td>177±49</td>
<td>164±38</td>
<td>178±44</td>
<td>198±44*</td>
<td>4.80</td>
<td>0.0024</td>
</tr>
<tr>
<td>ESP (mm Hg)</td>
<td></td>
<td>116±9</td>
<td>157±19*</td>
<td>158±27*</td>
<td>125±24</td>
<td>150±17*</td>
<td>156±22*</td>
<td>13.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td></td>
<td>122±43</td>
<td>125±48</td>
<td>103±46*</td>
<td>94±35*</td>
<td>118±43</td>
<td>133±46</td>
<td>8.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SV (ml)</td>
<td></td>
<td>52±11</td>
<td>58±6</td>
<td>74±16*</td>
<td>70±13</td>
<td>60±11</td>
<td>63±21</td>
<td>3.20</td>
<td>0.0197</td>
</tr>
<tr>
<td>EF</td>
<td></td>
<td>0.31±0.08</td>
<td>0.34±0.09</td>
<td>0.44±0.14*</td>
<td>0.44±0.13*</td>
<td>0.36±0.12</td>
<td>0.34±0.15</td>
<td>6.93</td>
<td>0.0002</td>
</tr>
<tr>
<td>P/dtmax (mm Hg/sec)</td>
<td></td>
<td>1,389±172</td>
<td>1,779±198</td>
<td>2,676±382*</td>
<td>2,528±527*</td>
<td>1,657±234</td>
<td>1,649±281</td>
<td>31.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P/Vmax (mm Hg/ml)</td>
<td></td>
<td>1.1±0.5</td>
<td>1.5±0.9</td>
<td>2.1±1.6*</td>
<td>1.8±1.4*</td>
<td>1.3±1.0</td>
<td>1.4±0.8</td>
<td>4.260</td>
<td>0.0048</td>
</tr>
</tbody>
</table>

Data are mean±SD.

C1, premethoxamine control; MTX, peak methoxamine effect; MTX+DOB, peak methoxamine effect with contractile state enhanced by dobutamine; DOB, contractile state enhanced by dobutamine after methoxamine withdrawn; C2, postdobutamine control; VOL, peak volume infusion effect; ESP, left ventricular (LV) end-diastolic pressure; EDV, LV end-diastolic volume; ESV, LV end-systolic pressure; SV, LV stroke volume; EF, LV ejection fraction; P/dtmax, maximum rate of LV pressure rise; P/Vmax, maximum LV pressure-volume ratio. F statistics and corresponding probability values were computed using one-way analysis of variance for repeated measures.

*p<0.05 different from values without this signifier as determined by Newman-Keuls multiple comparison test.

Statistics

All data are expressed as mean±standard deviation (SD) unless specified otherwise. Data from the six experimental stages (defined in Figure 3) were compared by one-way analysis of variance for repeated measures. When indicated by a significant F statistic, a multiple comparison test (Newman-Keuls) was performed to determine which means differed.12

To determine the independent effects of preload (EDV), afterload (ESP), and contractile state (CS) on torsional deformation (θmax), data from each individual were analyzed by multiple linear regression in which data were fitted to an equation of the form

θmax=a₀+a₁×EDV+a₂×ESP+a₃×CS

where a₀, a₁, a₂, and a₃ are the coefficients for the independent variables, a₀ is the constant term, θmax is the dependent variable, and EDV, ESP, and CS are the independent variables. For the purposes of this analysis, CS was equal to either 0 or 1 depending on whether the contractile state was enhanced by dobutamine (i.e., 0=baseline contractile state; 1=high contractile state). For each patient, the value and 95% confidence limits of each coefficient were determined. The group means and SDs of a₀, a₁, a₂, and a₃ were computed, and the null hypothesis (that these coefficients did not differ from 0) was tested using Student's t test for a single sample; p<0.05 was considered to be statistically significant.12

Results

Hemodynamics

Hemodynamic data for each experimental stage are presented in Table 2. Estimates of EF derived from the LV midwall markers were substantially less than those computed from contrast ventriculograms obtained before initiating atrial pacing. The expected decline in EF when the heart rate was increased by pacing partially accounts for this discrepancy; furthermore, the LV midwall marker technique excludes the contribution of subendocardial thickening,13 resulting in an underestimation of EF. Relative changes in the midwall EF and all ventricular volume measurements should be accurate.

Pressure loading. At MTX the average ESP was 41 mm Hg higher (p<0.0001) than at C1. Pressure loading of the left ventricle with this drug had no significant effect on preload (as measured by either EDP or EDV), SV, or dP/dtmax.

Inotropic stimulation. Dobutamine produced a positive inotropic effect manifested by a 52% increase (p<0.05) in dP/dtmax compared with C2. EF also increased (p<0.05) with dobutamine. ESV during dobutamine infusion was less (p<0.05) than control at the same or a slightly greater (difference not significant) level of ESP. While this implies a shift in the end-systolic pressure–volume relation in the direction of an increased contractile state14 (as indicated by the increase in P/Vmax), SV was unchanged because EDV tended to fall (difference not significant).

Volume loading. Volume loading with normal saline increased EDV by 20 ml (p<0.05 versus C2) as ESP rose by slightly less than 10 mm Hg (p<0.05). Since ESV also tended to increase (difference not significant), preload augmentation was associated with an average increase in SV of only 3 ml (difference not significant). ESP and dP/dtmax were also unchanged (not significantly different from values at C2) by volume loading.

Values at C1 and C2 were similar for all variables except ESP, which was higher (p<0.05) at C2. This suggests a small residual methoxamine effect after withdrawal of dobutamine.

Torsional Deformation

The time-varying torsional deformation curve of marker 4 obtained in patient 1 at C1 is shown in Figure 4, along with simultaneously acquired LV
pressure and volume curves. Immediately after the R wave on ECG there was a brief initial clockwise twist, reflected by negative $\theta_4(t)$ values. After the minimum value of $\theta_4(t)$ at 30–50 msec after the R wave, $\theta_4(t)$ increased rapidly during the ejection phase, reaching a maximum near end ejection (i.e., minimum volume). Rapid uncoiling of the ventricle then followed, and this process was completed well before the next contraction. While the amplitude of these torsion curves varied depending on marker location, this characteristic contour of the torsional deformation curves was similar for all markers under all experimental conditions.

In Figure 4, the value of $\theta_4$ for a given beat is considered to be the difference between the maximum and minimum values of $\theta_4(t)$. Since marker 4 was associated with the greatest torsion angle in this patient, $\theta_{\text{max}}$ and $\theta_4$ are equivalent. We chose to quantify torsion as the maximum torsion angle excursion rather than the maximum amplitude relative to the $0^\circ$ torsion reference because the former method resulted in substantially less beat-to-beat variability. This can be appreciated in the four-beat sequence shown in Figure 4, upper panel. The maximum $\theta_4(t)$ varied from 12° to 15° whereas the maximum excursion was more uniform because those beats associated with a reduced maximum $\theta_4(t)$ were preceded by a more negative dip during early systole. This approach was taken in our earlier investigations.1,2

**Hemodynamic responses.** The relation between $\theta_{\text{max}}$ and preload, afterload, and contractile state for patient 1 is illustrated in Figure 5. In this typical example, $\theta_{\text{max}}$ was measured for 21 beats at the baseline contractile state over a wide range of preload (EDV) and afterload (ESP) values. Twelve additional determinations of $\theta_{\text{max}}$ were made over roughly the same range of preload and afterload during inotropic stimulation with dobutamine. The values of $\theta_{\text{max}}$ showed virtually no dependence on either EDV or ESP, but dobutamine produced a

![Figure 4](link)

**Figure 4.** Graphs of time-varying torsional deformation angle [$\theta_4(t)$], volume [$v(t)$], and pressure [$P(t)$] of left ventricle for patient 1 under initial baseline conditions. Upper panel: Values of $\theta_4(t)$ are plotted at 16.7-msec intervals along with curve derived from frequency spectrum using Fourier filter with 8-Hz cutoff. Arrows, electrocardiographic R wave. Middle and lower panels: Simultaneously acquired values of instantaneous $V(t)$ and $P(t)$ are plotted for comparison with torsional events.

![Figure 5](link)

**Figure 5.** Scatterplots of load independence and sensitivity to contractile state of maximum left ventricular (LV) torsion ($\theta_{\text{max}}$) in patient 1. Values of $\theta_{\text{max}}$ are plotted versus LV end-diastolic pressure (left panel) and end-systolic volume (right panel). Beats at baseline levels of contractile state are indicated by open squares. Beats obtained during inotropic stimulation with dobutamine are indicated by solid squares. Horizontal lines represent least-squares linear regression lines for these data.
TABLE 3. Effects of Methoxamine, Dobutamine, and Saline Infusion on Regional Ventricular Torsion Measurements and $\theta_{\text{max}}$ in Seven Cardiac Allograft Recipients

<table>
<thead>
<tr>
<th>Torsion parameter ($^\circ$)</th>
<th>C$_1$</th>
<th>MTX</th>
<th>MTX+DOB</th>
<th>DOB</th>
<th>C$_2$</th>
<th>VOL</th>
<th>$F$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$</td>
<td>4.0±4.3</td>
<td>5.1±3.6</td>
<td>8.8±5.5*</td>
<td>7.9±5.5*</td>
<td>2.2±4.8</td>
<td>4.1±4.0</td>
<td>9.57</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td>$\theta_2$</td>
<td>8.9±5.5</td>
<td>11.5±6.1</td>
<td>19.5±10.6*</td>
<td>17.4±9.1*</td>
<td>7.9±8.5</td>
<td>9.5±7.1</td>
<td>11.29</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td>$\theta_3$</td>
<td>8.3±6.1</td>
<td>6.6±5.1</td>
<td>13.0±9.2*</td>
<td>10.4±9.0</td>
<td>6.6±4.7</td>
<td>7.2±4.6</td>
<td>4.06</td>
<td>0.0062</td>
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<tr>
<td>$\theta_4$</td>
<td>3.4±2.9</td>
<td>2.5±2.5</td>
<td>6.5±3.6*</td>
<td>5.0±3.6</td>
<td>3.6±3.9</td>
<td>4.6±2.8</td>
<td>3.59</td>
<td>&lt;0.0116</td>
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<td>$\theta_5$</td>
<td>2.4±2.7</td>
<td>2.6±2.4</td>
<td>7.8±3.4*</td>
<td>5.3±3.7</td>
<td>4.0±3.7</td>
<td>4.4±2.9</td>
<td>6.65</td>
<td>0.0003</td>
</tr>
<tr>
<td>$\theta_6$</td>
<td>14.4±4.2</td>
<td>11.8±4.3</td>
<td>17.6±8.8*</td>
<td>18.4±7.2*</td>
<td>11.3±7.1</td>
<td>11.4±4.6</td>
<td>6.56</td>
<td>0.0003</td>
</tr>
<tr>
<td>$\theta_{\text{max}}$</td>
<td>-0.3±4.6</td>
<td>-1.9±3.8</td>
<td>6.1±4.3+</td>
<td>-2.1±6.2</td>
<td>-1.1±4.9</td>
<td>-0.5±3.7</td>
<td>12.80</td>
<td>&lt;0.0001</td>
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</table>

Data are mean±SD. C$_1$, premethoxamine control; MTX, peak methoxamine effect; MTX+DOB, peak methoxamine effect with contractile state enhanced by dobutamine; DOB, contractile state enhanced by dobutamine after methoxamine withdrawn; C$_2$, postdobo- 

parallel upward shift in these relations such that the values of $\theta_{\text{max}}$ were substantially greater when the inotropic state was enhanced with dobutamine.

The responses of $\theta$ to methoxamine, dobutamine, and saline infusion are summarized in Table 3. Analysis of variance for repeated measures revealed significant changes in $\theta$ for all markers. Multiple comparison tests indicated that these differences were attributable to inotropic stimulation with dobutamine (MTX+DOB, DOB), while LV pressure loading (MTX) and volume loading (VOL) had no significant effect. This was most clearly observed for the inferior wall ($\theta_1$ and $\theta_2$) and apical third of the lateral wall ($\theta_3$) markers, where approximately twofold increases ($p<0.05$) were observed with dobutamine at both high (MTX+DOB) and normal (DOB) levels of afterload. For the anterior wall ($\theta_4$ and $\theta_5$), midlateral wall ($\theta_1$), and septum ($\theta_{\text{ax}}$) markers, a significant increase in $\theta$ was observed only with dobutamine at the peak methoxamine effect (MTX+DOB); however, there was no significant difference for the two dobutamine stages except in the septal region ($\theta_{\text{ax}}$), where torsion angles were generally small in magnitude and variable in direction (i.e., negative torsion angles were observed in some patients).

As shown in Table 3, $\theta_{\text{max}}$ was responsive to inotropic stimulation with dobutamine but insensitive to alterations in both preload and afterload. Irrespective of the prevailing preload and afterload, values of $\theta_{\text{max}}$ at high contractile states (MTX+DOB and DOB) were greater ($p<0.05$) than values obtained at the baseline inotropic state (C$_1$, MTX, C$_2$, and VOL). No significant differences were found among the C$_1$, MTX, C$_2$, or VOL values of $\theta_{\text{max}}$ or between the MTX+DOB and DOB values. Thus, afterload challenge had no effect on $\theta_{\text{max}}$ at either level of contractile state (difference not significant for C$_1$ versus MTX or for MTX+DOB versus DOB). Likewise, at the baseline contractile state, preload augmentation with normal saline had no effect on $\theta_{\text{max}}$ (difference not significant for C$_2$ versus VOL). Thus, the responses of $\theta_{\text{max}}$ were similar to those of $\theta$, except $\theta_{\text{max}}$ was more sensitive to inotropic stimulation with dobutamine than some $\theta$s (markers 6, 7, 11, and 14).

The results of multiple linear regression analysis are shown in Table 4. The 95% confidence limits for the coefficient of the preload term ($a_1$) included 0 in six of seven patients, indicating that $\theta_{\text{max}}$ is insensitive to EDV. Similarly, the coefficient of the afterload term ($a_2$) was statistically indistinguishable from 0 in five of seven patients, indicating that $\theta_{\text{max}}$ is not significantly influenced by ESP. This contrasts with the results for the coefficient of the contractile state term ($a_3$), which was significantly different from 0 in all patients, with an average increase in $\theta_{\text{max}}$ of 8.9±5.4° ($p<0.005$). Thus, when the independent effects of preload, afterload, and contractile state are simultaneously considered, $\theta_{\text{max}}$ is found to depend strongly on contractile state while being statistically independent of preload and afterload.

Discussion

As proposed by Streeter,3 the helical nature of myocardial fibers suggests that systolic torsion and diastolic recoil are important characteristics of LV contraction and relaxation. Indeed, a twisting motion about the LV long axis of the base with respect to the apex was observed in this study and in previous canine15 and human1,4 studies. In an earlier investigation, we found that LV torsion declined in transplanted human hearts during acute cardiac allograft rejection with necrosis while traditional measures of LV pump performance (SV, EF, and peak filling rate) were unchanged.2 This suggested that torsion is a sensitive index of LV contractile function. In the present study, we tested more directly the possibility that the amount of LV torsion is modified by changes in myocardial contractility. We also wanted to determine the sensitivity of our torsion measurements to changes in LV loading conditions. We found that
pressure loading with an α-adrenergic vasoconstrictor (methoxamine) and volume loading with saline had little effect on LV torsion, whereas inotropic stimulation with dobutamine increased torsion, at least in specific, well-defined regions.

Theoretical Considerations

The fiber architecture of the myocardium provides the conceptual framework for this study. Circumferentially oriented fibers reduce the LV minor axis dimension as they shorten, which is clearly important in the process of ventricular ejection. The action of longitudinally oriented fibers contributes to shortening of the LV major axis. Shortening of obliquely oriented fibers is likely to result in a reduction of both the longitudinal and circumferential axes but also would be expected to exert a torque on the ventricle. The torque produced by the circumferentially oriented fibers (helix angle θ) should be negligible. With increasing fiber obliquity, the amount of torque should increase, becoming maximal for fibers that wind from the base to the apex with a helix angle of 45°. The amount of torque should decline as fiber angle increases beyond 45°, again becoming negligibly small for longitudinal fibers (helix angle 90°). The amount of torque exerted by oblique fibers also depends on the radius of curvature, with torque increasing as distance from the LV major axis becomes greater. If the net twist reflects the balance between the opposing actions of the obliquely oriented subepicardial and subendocardial fibers (subepicardial and subendocardial fibers wind from the base to the apex in opposite directions), then factors that change this balance change total twist. If the simultaneous torques produced by the subepicardial and subendocardial fibers change equally, the amount of twist is unchanged. Thus, the amount of twisting is likely to depend on the distribution of fiber angles across the wall and the extent of fiber shortening in subepicardial versus subendocardial zones. Coupling between fibers of different layers and ventricular geometry are other potentially important factors.

Preload Independence of LV Torsion

These data demonstrate that LV torsion changes minimally as LV filling pressure is raised from 10 to 20 mm Hg by volume expansion (Table 2). The multiple linear regression analysis predicted an average increase in θ\textsubscript{max} of only 0.012° for each 1-ml increase in EDV, which was not statistically significant. Thus, unlike conventional measures of LV systolic performance (e.g., dP/dt\textsubscript{max} EF, cardiac output, SV, and stroke work), which are known to be regulated, in part, by the Frank-Starling mechanism, alterations in preload appear to have little to no influence on LV torsion. Since these conventional measurements of LV systolic performance did not change significantly with preload augmentation in this study, we cannot discern whether LV torsion is necessarily more load independent.

It is not immediately obvious why LV torsion should be so insensitive to preload. The dependence of LV pump performance characteristics on preload is widely recognized. This important mechanism seems to have its basis in the ultrastructure of contractile proteins, with the amount of overlap between actin and myosin filaments being a critical determinant of myocardial force generation. Clearly, the amount of LV torsion observed must depend on other factors since the amount of fiber shortening almost certainly increased with volume loading in our study, although torsional deformation remained unchanged.

Volume expansion has a complex effect on the transmural distribution of sarcomere lengths. As the ventricle enlarges, all sarcomere lengths increase, but sarcomeres of different layers are stretched by different amounts. As demonstrated by Yoran et al as the anterior wall of the canine left ventricle, sarcomere lengths of subepicardial fibers exceed those of subendocardial fibers at normal LV filling pressures. At higher LV filling pressures, equal to those achieved by saline infusion in our study, the normal transmural gradient in sarcomere lengths is abolished.
implying greater recruitment of sarcomeres in the subendocardial zone. This probably reflects the fact that the inner radius changes to a greater extent than the outer radius with increasing volume.\textsuperscript{9,13}

The obliquity of helical fibers may be altered by volume expansion as well. It is well known that the left ventricle assumes a more spherical geometry as it dilates.\textsuperscript{18,19} According to the mathematical formulas of Sallin,\textsuperscript{20} this would decrease the obliquity of helical fibers. Indeed, Streeter et al\textsuperscript{21} found that helix angles of fibers within the canine LV free wall differed in the systolic and diastolic states. In the inner layers, fiber obliquity decreased as the cavity expanded, whereas fiber obliquity increased in the outer layers. The work of Covell and Waldman\textsuperscript{22} is also consistent with Sallin’s\textsuperscript{20} prediction of a decrease in fiber obliquity as the ventricle expands. These investigators used high-speed biplane cineradiography of transmural columns of beads to study transmural deformations in the anterior wall of the canine left ventricle.\textsuperscript{22} As LV filling pressure was increased from 2.5 to 9.5 mm Hg, all finite strains through the wall increased and the directions of greatest shortening rotated counterclockwise, from $-45^\circ$ to $-18^\circ$ (relative to circumferential).

It is possible that the preferential recruitment of subendocardial sarcomeres and conversion of subepicardial fibers to a more longitudinal shortening pattern (which would both tend to reduce the amount of torsion) counteracts the effect of increased fiber shortening as LV filling pressure is raised, minimizing preload effects on torsional deformation. While our methods do not provide measurements of actual fiber shortening or obliquity, we believe that this is a plausible, but obviously unproven, mechanism underlying the insensitivity of maximum LV torsion to alterations in preload. Additional studies are required to clarify this mechanism.

\textit{Afterload Independence of LV Torsion}

Dobutamine, at a dose yielding an average increase in the ESP of slightly more than 40 mm Hg, had little or no effect on torsional deformation about the LV long axis (Table 3). Again, this result may seem somewhat surprising in light of the well-known reduction in the rate and extent of fiber shortening when afterload is increased.\textsuperscript{23,24} This might occur if LV pressure loading had a \textit{nonuniform} effect on transmural fiber shortening. The amount of torsion may have been maintained despite overall reduced fiber shortening if shortening of the subendocardial fibers was reduced to a greater extent than that of the subepicardial fibers. Alternatively, changes in ventricular size and geometry as LV pressure load increased may have altered the fiber angles within the LV wall. If subendocardial fibers assumed a more circumferential or longitudinal orientation in response to LV pressure loading or if subepicardial fibers approached the optimum obliquity of $-45^\circ$, the amount of torsion may have been maintained even in the presence of overall reduced fiber shortening. Additional studies that provide information regarding the effects of increased pressure load on LV transmural fiber dynamics are clearly required to determine the precise mechanism by which LV torsion remains unaltered over this range of afterload. Again, since afterload challenge with methoxamine did not significantly alter our conventional measurements of LV systolic performance, we cannot claim that LV torsion is necessarily less sensitive to afterload.

\textit{Sensitivity to Contractile State}

Our measurements of LV torsion appear to be quite sensitive to inotropic stimulation, although the response is regionally heterogeneous. As shown in Table 2, dobutamine significantly increased standard hemodynamic measures of LV systolic performance (EF, $P/\Delta t_{\text{max}}$, $P/V_{\text{max}}$), confirming dobutamine’s positive inotropic effect in this study. A significant dobutamine effect on $\theta$ was observed for each marker (Table 3). For some markers, this effect was observed only with simultaneous infusion of methoxamine; however, even for these markers, it is likely that this was \textit{predominantly} a dobutamine effect since there was no significant difference between $\theta$s with dobutamine administered either alone (DOB) or in combination with methoxamine (MTX+DOB) and since methoxamine had no significant effect on these measurements in the absence of dobutamine as seen by comparison of the initial control ($C_i$) and methoxamine alone (MTX) data. These results are consistent with those of an earlier study from this laboratory that suggested a dependence of torsional deformation amplitude on inotropic state, using an atrial pacing protocol that permitted the effects of rate-related changes in contractile state to be evaluated at similar levels of load.\textsuperscript{1}

It is also interesting to note that these torsion measurements appear to be more sensitive to inotropic stimulation than the conventional indexes of LV systolic performance. For example, compared with postdobutamine control ($C_i$) values, dobutamine (DOB) increased SV by 16%, EF by 22%, $P/V_{\text{max}}$ by 38%, and $P/\Delta t_{\text{max}}$ by 52%, whereas a 59% increase in $\theta_{\text{max}}$ was observed. This might explain why $\theta_{\text{max}}$ was more sensitive to the effects of acute cardiac allograft rejection than conventional measurements of LV pump function (e.g., EF, SV, and peak filling rate) in our previous study.\textsuperscript{2} The relative insensitivity of LV torsion measurements to ventricular loading conditions may also enhance the ability to discriminate changes in the intrinsic myocardial contractility since compensatory changes in preload and afterload normally influence LV pump characteristics.

\textit{Nonuniform Response to Dobutamine}

Torsion of the inferior and lateral walls appeared to be somewhat more sensitive to the effects of dobutamine than torsion of the anterior wall. The septum behaved differently from these sites in that $\theta_3$ and $\theta_4$ were generally much smaller in magnitude and were often opposite in direction. Thus, the
response to inotropic stimulation was regionally heterogeneous. This is consistent with other studies of ventricular torsion from our laboratory. Our data suggest that the apical markers of the inferior and lateral walls are the most sensitive sites to track in studies that employ such measurements of LV torsion as indexes of LV contractility. It is unlikely, but conceivable, that the variable response to dobutamine in the present study is simply a manifestation of regional differences in β-adrenergic receptor densities or coupling in these denervated hearts. While it is known that such regional differences in adrenergic function exist in samples of LV myocardium from normal canine and human cadaver hearts, we have no information regarding such differences in these transplanted human hearts. In the canine studies of Lew and LeWinter, however, propranolol did not abolish regional and directional differences in midwall segmental function, suggesting that regional differences in LV contraction dynamics may have their origin in other factors. Important differences in the extensibility of the anterior and posterior walls, as well as a greater influence of longitudinal fibers on midwall dynamics in the posterior wall, probably account for the regional differences observed by Lew and LeWinter and may be operative in our studies of torsion as well. Regional differences in fiber architecture, as described by Greenbaum et al, may constitute the anatomic basis of these differences in regional function, as previously proposed.

**Limitations**

The potential limitations of our torsional measurements have been discussed in detail elsewhere. Our torsion measurements are clearly influenced by marker location and possibly by the depth of penetration at the time of placement. Although this limits our ability to make intersubject comparisons, our myocardial marker technique should provide a great deal of precision in studies, such as this one, which are based exclusively on intrasubject comparisons. As previously discussed, the use of heart transplant recipients has certain potential disadvantages. The transplanted human heart is subject to ischemia at the time of procurement and implantation and to additional myocardial injury in the form of allograft rejection postoperatively. While acute rejection diminishes maximum LV torsion, normalization generally occurs with successful treatment of rejection episodes. Although all of our patients experienced at least one rejection episode, none had evidence of rejection at the time of study as proven by endomyocardial biopsy. Moreover, Borow et al have shown that LV contractility and contractile reserve are normal in such subjects. The transplanted human heart model, therefore, should provide results that are generally applicable. The model has the advantage that these denervated hearts have blunted cardiovascular reflexes mediated by baroreceptors. For this reason, sympatholytic and vagolytic agents were not administered, although we cannot entirely exclude any humorally mediated effects of baroreceptors.

The eventual validation of these findings in nonsurgical patients will require noninvasive methods to quantify LV torsion. Echocardiography, which has been employed in dogs and humans, provides limited information since this technique measures the rotation of only a few structures such as the papillary muscles and since the precision of such measurements is questionable. More recently, noninvasive quantification of LV torsion in normal humans has been accomplished using a magnetic resonance imaging technique called myocardial tagging. This technique is most promising for eventual widespread clinical application.

Finally, pharmacological manipulation of preload, afterload, and contractility can produce mixed hemodynamic effects. As shown in Table 2, the primary effect of methoxamine was an increase in ESP; potential increases in preload due to venoconstriction were not an important factor since a significant increase in EDP and EDV did not occur. Likewise, dobutamine primarily elevated dP/dtmax with, at most, modest preload and afterload effects. Finally, infusion of saline had the desired effect of increasing preload, with significant increases in both EDP and EDV. This preload challenge may have had minimal negative inotropic effects, however, since dP/dtmax failed to increase as expected with increasing preload. Despite any potential or actual mixed hemodynamic effects of these interventions, our conclusions regarding the load insensitivity of maximum LV torsion and its dependence on contractile state should be valid since they were based on multiple linear regression analysis, which considered the independent contributions of these hemodynamic factors. These results, nevertheless, require confirmation using nonpharmacological methods that permit preload and afterload parameters to be varied independently.

In conclusion, these data demonstrate that ventricular loading conditions have negligible effects on LV torsion, whereas the amount of torsion depends on the contractile state of the myocardium. The experimental findings can be reconciled with the known or predicted effects of these hemodynamic factors on the shortening and obliquity of fibers comprising the myocardium and on ventricular geometry. Thus, measurements of LV torsion may provide an index of myocardial contractile function that is relatively load independent without manipulation of loading conditions, major assumptions regarding LV geometry, or the use of an LV catheter.

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