Assessment of regional left ventricular relaxation in patients with coronary artery disease: importance of geometric factors and changes in wall thickness

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ABSTRACT To assess local myocardial relaxation abnormalities in patients with coronary artery disease, left myocardial left ventricular wall stress was computed in nine normal subjects and in 22 patients with coronary artery disease. In normal left ventricles, the rate of decrease in isovolumic local stress was not significantly different from the rate of decrease in isovolumic pressure, and the residual wall stress at the end of isovolumic relaxation was uniformly low. In patients with coronary artery disease, the residual wall stress was increased both in infarcted areas and in noninfarcted areas perfused by stenosed arteries (43 ± 31 and 30 ± 19 kdyne/cm², respectively, vs 9 ± 5 kdyne/cm² in normal areas; p < .001). The rate of decrease in local stress in infarcted areas paralleled the rate of decrease in pressure (48 vs 49 msec; NS), but in ischemic areas the rate of decrease in stress was significantly slower than the rate of decrease in pressure (69 ± 35 vs 48 ± 15 msec; p < .05). It is concluded that in patients with coronary artery disease, indexes based only on the analysis of decreases in isovolumic pressure underestimate the severity of local impairments in relaxation rate and cannot be used to predict the level of residual diastolic wall stress. Circulation 69, No. 4, 696–702, 1984.

ABNORMALITIES in left ventricular relaxation and diastolic filling are more common in patients with coronary artery disease.1–6 Some investigators suggest that these impairments might play an important pathophysiologic role by reducing coronary perfusion and ventricular compliance and by augmenting filling pressures.7 Many studies have therefore been performed to quantify these alterations and their response to interventions such as calcium-antagonist therapy, positive inotropic stimulation, or coronary angioplasty.8–10

For practical reasons, all these studies focused on global indexes of left ventricular relaxation such as the time course of decrease in isovolumic pressure1, 2, 4, 5, 10 or the dynamics of the rapid filling.3, 6, 8, 9 However, experimental and clinical studies in ischemic heart disease have shown asynchronous wall motion and wall thinning during early diastole.11–17 Furthermore, Ludbrook et al.17 observed that in patients with coronary artery disease, impaired global left ventricular relaxation was consistently accompanied by asynchronous protodiastolic wall motion. Such an inhomogeneity of diastolic behavior suggests that global indexes can only imperfectly quantify the abnormalities in diastolic function. Recently, Janz18 proposed a formula to compute local myocardial stress, which could be easily applied to angiographic data. This approach allows changes in geometric factors and wall thickness to be taken into account during assessment of relaxation. The purpose of this study was therefore to compute local myocardial wall stress in normal subjects and in patients with coronary artery disease and to determine whether clinically important information could be derived from this analysis.

Patients and methods

Thirty-one patients were retrospectively selected for this study because their left ventricular angiograms showed a good definition of wall thickness in inferior and anterior left ventricular walls. Of these patients, nine (mean age 46 years, range 37 to 60) who had atypical chest pain but completely normal ventriculograms and coronary arteries were considered normal control subjects. Twenty-two patients (mean age 49 years, range 24 to 68) had significant coronary artery disease defined as stenosis of 75% or greater in at least one major coronary vessel. This group included nine patients with one-vessel disease, six with two-
vessel disease, and seven with a three-vessel disease. Eleven patients had had previous inferior myocardial infarction and six had had anterior myocardial infarction as demonstrated by typical electrocardiographic and enzymatic changes.

All cardioactive drugs were discontinued at least 72 hr before the catheterization procedure. Informed consent was obtained from each patient and no complication occurred as a result of the study.

**Study protocol.** Left heart catheterization was performed through the femoral approach with the patient in the fasting state and without premedication. High-fidelity left ventricular pressure was recorded with a No. 5F micromanometer-tipped catheter (Millar Instruments). Left ventriculography was performed by means of a No. 8F pigtail catheter and single-plane 35 mm cineangiography at 50 frames/sec in the right anterior oblique projection (Philips Polydiagnost C). The hemodynamic variables and a cine frame marker were recorded on magnetic tape (Honeywell 101) and on paper (Honeywell 1858). Left ventricular pressure during ventriculography and the time of the peak of the R wave were also sampled synchronously with frame exposure and displayed in digital form on the corresponding cine frame (Cine Data, Philips).

Ventriculograms were obtained from all patients under basal conditions. In addition, in nine patients with coronary artery disease, 5 mg of the calcium antagonist nicardipine was administered intravenously 10 min after the first ventriculogram was taken. A second ventriculogram was obtained 20 min after nicardipine.

**Measurement and computations.** Both premature and post-premature beats were excluded from analysis. Ventricular silhouettes were outlined frame by frame with a light pen on a video screen. The digitized contours were preprocessed by a computer system (LVV Philips 100). As described previously,”19 this computer derived the correction factor for x-ray magnification, calculated volumes applying Simpson’s rule, and defined the reference coordinate systems used for analysis of wall motion. The preprocessed data were then directed to an HP 21MX computer for smoothing by cubic spline methods and for the computation of various indexes of left ventricular function, including the maximal pressure/volume ratio (Emax), which was taken as the end of systole.20 Local systolic shortening was derived from the smoothed data and expressed as segmental ejection fraction, the reference system being the long axis of the left ventricular silhouette.”19

**Local wall stress computation.** Local average circumferential stress (STi. i = 1 to 10) was computed at 10 positions around left ventricular contours (figure 1). This computation was done frame by frame, starting at the end of systole and ending at the mitral valve opening as indicated by a significant augmentation in left ventricular volume. Local average circumferential stress was calculated as follows: STi = P · ACi/AWi, where P is left ventricular pressure and ACi and AWi are the cross-sectional areas of the cavity and the wall. This formula, developed by Janz,”18 is based on Newton’s third law and uses the thick-wall shell theory and a general representation of ventricular geometry; it yields results agreeing closely with corresponding stresses in a finite element model. The values for local wall thickness used in the above formula were directly determined with calipers from the corresponding cine frames projected on the screen of a Tagarno projector. This procedure ensured better definition of wall thickness than on the video screen; the need for wall thickness measurements on the cine films also explains why only patients with a good definition of the left ventricular wall on the angiograms could be included in the study.

**Assessment of local myocardial relaxation rate.** To characterize the rate of decrease in local stress during isovolumic relaxation, the stress and time data from peak (−dP/dt) to mitral valve opening were fitted into a monoeponential relation by the method of least squares. The time constant Tst (r = .91 to .99) of this relation was used as an index of local relaxation rate. The left ventricular pressure and time data were similarly analyzed and the time-constant Tp of this relation was used to characterize the rate of decrease in isovolumic pressure. The value of the local stress at the end of isovolumic relaxation (residual stress) was also determined for each subject; the end of isovolumic relaxation was taken as the last frame preceding the first significant increase in left ventricular volume (>5 ml/m²).

**Assessment of local systolic force-length relations.** To characterize the force-length relation of the various left ventric-
Results

Local relaxation in normal left ventricles. Figure 2 illustrates the time course of decrease in left ventricular pressure and local stress in one anterior and one inferior segment of a left ventricle. Table 1 summarizes the average local stresses in eight segments of the nine normal ventricles (the segments 1 and 10 adjacent to the valves were excluded from analysis).

As can be seen from table 1 and figure 2, small differences in local wall stress and in the time course of decrease in stress were observed between anterior and inferior walls. End-systolic local stress appeared greater in basal inferior segments than in anterior segments, but the rate of decrease in stress was also slightly faster in these areas, particularly between Emax and peak (−) dP/dt. Accordingly, the residual wall stress was always symmetrically distributed between the anterior and inferior segments (table 1). Furthermore, the residual wall stress was low (mean 9 kdyne/cm², range 1 to 26) in all segments. As also shown in figure 2, neither the decrease in pressure or stress was linearly decreasing with time on a semilogarithmic scale; the characterization of these rates of decrease by the time constant T of a monoexponential relation (r = .91 to .99) can therefore be regarded as only a rough approximation. The use of this index was nevertheless practical to confirm for the whole group the visual impression of figure 2, i.e., that the rates of decrease in stress and in pressure were not significantly different (mean Tp 33 ± 4 msec vs mean Tst 38 ± 9 msec; NS), although the rate of pressure fall was generally slightly faster.

Local relaxation in patients with coronary artery disease. A total of 176 segments (basal segments 1 and 10 excluded) were analyzed in these patients; 138 segments could be classified according to the criteria described below.

Normal segments. The “normal segment” was defined as a segment with a normal systolic shortening and with normal coronary perfusion (i.e., both normal circumflex and left anterior descending arteries for an anterior segment and both normal circumflex and right coronary arteries for an inferior segment). By this definition, normal segments were found in only eight patients with one-vessel disease.

When compared with matched segments sampled in the normal group, these normal segments were found to have normal values of end-systolic wall stress and of residual wall stress (table 2). The time course of decrease in local stress was also normal (figure 3) and, as in the normal ventricles, the time constant Tst was slightly but not significantly slower than the rate of decrease.

![FIGURE 2. Time course of decrease in local stress and left ventricular (LV) pressure (logarithmic scale) in a normal subject, from the maximal pressure/volume ratio (Emax) to mitral valve opening. The arrow indicates the timing of peak (−) left ventricular dP/dt. T = time constant of monoexponential fitting of stress or pressure data after peak (−) dP/dt.](image)

**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>Left ventricular segments</th>
<th>Anterior</th>
<th>Apical</th>
<th>Inferior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>End-systolic wall stress (kdyne/cm²)</td>
<td>95 ± 36</td>
<td>105 ± 43</td>
<td>95 ± 45</td>
<td>49 ± 28</td>
</tr>
<tr>
<td>Residual wall stress (kdyne/cm²)</td>
<td>10 ± 6</td>
<td>11 ± 6</td>
<td>11 ± 6</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>Tst (msec)</td>
<td>39 ± 5</td>
<td>41 ± 8</td>
<td>42 ± 8</td>
<td>46 ± 10</td>
</tr>
</tbody>
</table>

Tst = time constant of decrease in isovolumic stress.
Data are mean ± SD. The average time constant of decrease in isovolumic pressure was 33 ± 4 msec.
TABLE 2
Local wall stress values in patients with coronary artery disease

<table>
<thead>
<tr>
<th></th>
<th>End-systolic wall stress (kdyne/cm²)</th>
<th>Residual wall stress (kdyne/cm²)</th>
<th>Tst (msec)</th>
<th>Tp (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal segments (20 anterior, 12 inferior)</td>
<td>104 ± 66</td>
<td>11 ± 11</td>
<td>41 ± 12</td>
<td>37 ± 14</td>
</tr>
<tr>
<td>Data in normal subjects (32 matched segments)</td>
<td>112 ± 80</td>
<td>10 ± 6</td>
<td>41 ± 10</td>
<td>33 ± 4</td>
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<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Abnormal segments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarcted segments (31 anterior, 23 inferior)</td>
<td>396 ± 176</td>
<td>43 ± 31</td>
<td>48 ± 16</td>
<td>49 ± 15</td>
</tr>
<tr>
<td>Data in normal subjects (54 matched segments)</td>
<td>118 ± 68</td>
<td>9 ± 5</td>
<td>40 ± 9</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.005</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ischemic segments (31 anterior, 21 inferior)</td>
<td>153 ± 92</td>
<td>30 ± 19</td>
<td>69 ± 35</td>
<td>48 ± 15</td>
</tr>
<tr>
<td>Data in normal subjects (52 matched segments)</td>
<td>117 ± 68</td>
<td>9 ± 5</td>
<td>40 ± 9</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Tst = time constant of decrease in isovolumic stress; Tp = time constant of decrease in pressure; n = number of patients.
Data are mean ± SD.

Infarcted segments. "Infarcted" or "scarred" areas were defined as the hypokinetic or akinetic zones supplied by a 100% occluded vessel and located in a territory with electrocardiographic signs of myocardial infarction (Q waves). Figure 3 illustrates the time course of decrease in stress in the scarred area of a left ventricle of a patient with one-vessel disease and anterior myocardial infarction (100% occlusion of the left anterior descending artery). End-systolic wall stress was increased in the scarred area, as was the residual wall stress at the time of mitral valve opening. The rate of decrease in stress, however, appeared very similar to the rate of decrease in pressure or in stress in a normal area. Accordingly, the increased residual wall stress primarily resulted from the increased end-systolic stress and was not caused by delayed relaxation.

Table 2 includes data that confirm these observations for the whole group, and shows that in scarred areas Tst (48 ± 16 msec) was similar to Tp (49 ± 15 msec).

Ischemic segments. "Ischemic segments" were defined as normokinetic or hypokinetic segments of the myocardium perfused by one or two stenosed vessels (≥75% narrowing) but without electrocardiographic evidence of necrosis. Fifty-two segments meeting such criteria (19 hypokinetic and 33 with normal systolic shortening) could be identified. Table 2 indicates that these segments, like the scarred segments, had increased end-systolic and residual wall stresses. However, in contrast to normal and scarred areas, the rate of decrease in stress was slower in these ischemic areas than the rate of decrease in pressure (Tst 69 msec, Tp 48 msec; p < .05). This discrepancy between the rates of decrease in pressure and in stress in scarred and ischemic areas is evident on visual inspection of the raw data of a typical case (figure 4). Figure 4 illustrates that the increased residual wall stress in the ischemic area resulted not only from an increased end-systolic stress but also largely from a reduced rate of decrease in stress.

Local end-systolic stress/area relations in scarred areas and in ischemic areas. Figure 5 illustrates the end-systolic stress/area relation of segment 6 in the nine normal subjects and in infarcted segment 6 of the 11 patients.
with inferior infarcts. As can be seen from this typical example, the relation characterizing the scarred areas had increased slope (1.43 ± 0.32 vs 0.39 ± 0.08 msec; p < .001) and increased intercept (327 vs -58 mm²; p < .01).

Figure 6 similarly illustrates the stress/area relation of segments 2 and 3 in the normal population and in segments 2 and 3 classified as ischemic (six hypokinetic and 10 normokinetic). In this case, no significant difference in slope was found, although the intercepts (35 vs -7 mm²; p < .001) differed slightly.

Effects of nicardipine on local relaxation. After nicardipine, Tst improved from 72 ± 24 to 58 ± 20 msec (p < .02, paired t test) in ischemic segments. In contrast, Tst was unchanged in the normal and scar segments (44 ± 12 vs 44 ± 12 msec; NS) and Tp was only slightly reduced (47 ± 13 to 41 ± 10 msec; NS). The end-systolic stress was significantly lowered in all segments after nicardipine but the residual wall stress decreased more in ischemic segments than in normal areas (-29 vs -4 kdyne/cm²; p < .01).

Discussion

Our data indicate that in patients with coronary artery disease, local myocardial relaxation may be significantly more impaired than expected from the analysis of the decrease in isovolumic pressure exclusively. Our results also call attention to the fact that the level of wall stress during early diastole, a critical factor for coronary perfusion, depends not only on the relaxation rate but also on the absolute level of wall stress at the end of ventricular systole. Before discussing the clinical relevance of these observations, it is important to consider the limitations of local wall stress computations.

Problems in local wall stress computations. The simplified formula derived by Janz used in this study predicts average circumferential stresses that generally agree to within 10% with the corresponding stresses in a finite element model of a ventricle.

However, except for the particular case of the equatorial stress, no direct measurements are available to confirm the physical validity of the derived stresses. Furthermore, this formula does not characterize the variation of stress through the wall; its usefulness may also be limited by errors that may arise in locating lines perpendicular to the endocardial surface (figure 1), which delimit the required cavity and wall areas. The precision of the computation is also likely to decrease when larger areas are used, although it is more practical to limit the number of left ventricular segments under analysis. Similarly, the precision of the computation probably decreases near the apex of the ventricle, where changes in fiber orientations, radii of curvature, and wall thickness are markedly different from those in the equatorial and basal zones. Finally, it must also be acknowledged that local stress computation

FIGURE 4. Time course of decrease in local stress and left ventricular pressure in a patient with right coronary occlusion (scarred area) and stenoses of the left anterior and circumflex arteries (ischemic area). For abbreviations see figure 2.

FIGURE 5. Relations between end-systolic local stress and area in segment 6 of normal subjects and in infarcted segment 6. CAD = coronary artery disease.

FIGURE 6. Relations between end-systolic local stress and area in segments 2 and 3 of normal subjects and in segments 2 and 3 classified as ischemic. CAD = coronary artery disease.
requires a tedious manual digitization of left ventricular wall thickness and contours, with its well-known drawbacks. Because a good definition of the entire left ventricular wall cannot be obtained in all patients (particularly of the inferior wall), our approach cannot be routinely applied unless improved imaging techniques providing a better definition of the left ventricular wall are used.

Considering all these theoretical and practical limitations, it would be naive to claim that the local wall stress figures presented in this study are entirely correct. As pointed out by Mirsky, further direct experimental validations are needed for the Janz formula. Nevertheless, the approach proposed by Janz, despite its likely imprecisions, has the great merit of providing a reasonable way to incorporate the changes in ventricular geometry and wall thickness mathematically in the assessment of ventricular relaxation. A comparable attempt to ameliorate relaxation indexes has been made by Bourdillon et al., using radial stress. Radial stress, however, combines only changes in pressure and wall thickness. In this respect, the Janz approach appears more complete, since it also takes into account the changes in ventricular geometry that consistently occur in early diastole when global relaxation is impaired.

In summary, the local wall stress computations performed in this study can be regarded, at best, as rough approximations of reality. As such, these computations already emphasize highly significant abnormalities in diastolic stress, which could not have been suspected by analyzing left ventricular pressure exclusively. This is probably sufficient to warrant further investigations in this field.

Clinical implications. Although alterations in left ventricular relaxation and diastolic filling have been universally reported in patients with ischemic heart disease, the clinical relevance of these abnormalities still remains controversial. One argument frequently presented to minimize their importance is that the prolongations in the time constant of decrease in pressure observed in these patients are small and should result in only negligible increases in diastolic wall stress.

In this respect, our data represent a new argument in favor of the pathophysiologic role of relaxation abnormalities. The local alterations in early diastolic stress are indeed much greater than could be predicted from the rate of pressure fall. This large discrepancy is caused first by the increased end-systolic stresses in the ischemic and scarred areas, a factor neglected when pressure is analyzed exclusively, and second because of slower relaxation rates in ischemic areas. Accordingly, the analysis of decrease in isovolumic pressure is of limited value in predicting the severity of relaxation abnormalities in patients with coronary artery disease. Attempts to improve the analysis of decrease in left ventricular pressure or of early diastolic filling by using more sophisticated models are probably futile and more emphasis should be put on the analysis of diastolic regional function. This opinion is further supported by the data obtained after administration of nicardipine. After administration of this calcium antagonist, only modest, insignificant changes in global indexes of relaxation such as Tp or peak filling rate were noted, whereas a consistent and great acceleration in relaxation rate was present in ischemic areas.

The fact that myocardial ischemia is generally a regional process and that dysynchronous wall motion occurs in ischemic zones during relaxation was known long before this study. However, the present analysis may help to elucidate some of the mechanisms underlying dysynchronous wall motion in intact human heart. In scarred areas, the rate of decrease in stress always paralleled the rate of decrease in pressure. In addition, the end-systolic stress/area relation of these zones (figure 5) was characterized by a very steep line shifted to the right. The most likely explanation for this peculiar relation is that it represents the passive tension-length relation of a very stiff, noncontractile structure. These data therefore support the hypothesis that infarcted areas mainly behave as purely passive springs and are not responsible for the slower left ventricular pressure fall. These data are also in agreement with the experimental observations of Kumada et al., who did not observe “T” prolongation in the presence of severely ischemic and noncontractile myocardium.

Consequently, in patients with coronary artery disease it is the presence of contracting but underperfused myocardium that is primarily responsible for the alterations in decrease in left ventricular pressure. Figure 6 indicates that the end-systolic tension-length relations of such segments might still be nearly normal. This suggests that relaxation abnormalities are very sensitive markers that could persist for long periods even when acute ischemia is no longer present.

In conclusion, our data suggest that in patients with coronary artery disease the rate of decrease in isovolumic pressure may underestimate the severity of a local impairment in relaxation. The data obtained after calcium-antagonist administration also suggest that local analysis of the effects of a therapeutic intervention is necessary to correctly evaluate its effects on the myocardium at risk.
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References

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