Improvement in regional wall motion and left ventricular relaxation after administration of diltiazem in patients with coronary artery disease

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ABSTRACT To assess the effect of diltiazem on left ventricular systolic regional wall motion and diastolic function in patients with coronary artery disease (CAD), 22 patients underwent biplane left ventricular cineangiography before and after intravenous diltiazem (plasma concentration 154 ± 12 ng/ml). Left ventricular and right ventricular pressures were measured by micromanometer-tipped catheters. Regional wall motion was assessed quantitatively with an area ejection fraction technique. Diltiazem decreased mean arterial pressure 11.5% (p < .0001) and heart rate 6.8% (p < .005); it increased cardiac index 8.8% (p < .025) and global ejection fraction 9.1% (p < .0001). However, left ventricular end-diastolic pressure increased 14.2% (p < .001) and the left ventricular end-systolic pressure-volume (P-V) ratio decreased 8.8% (p < .02). Diltiazem decreased the time constant of left ventricular relaxation by 14.3% (p < .002), despite lack of change in the left ventricular diastolic P-V relationship, in 16 patients. Diltiazem caused a significant increase in area ejection fraction in 53% of hypokinetic areas supplied by diseased arteries compared with 13% of normokinetic areas supplied by diseased arteries (p < .0001). Response of ejection fraction to diltiazem in areas supplied by normal coronary arteries was less (p < .05) than that in hypokinetic areas supplied by arteries affected by disease. In conclusion, diltiazem improves regional wall motion abnormalities in patients with CAD and the improvement is associated with better left ventricular relaxation but not with a change in the diastolic P-V relationship. Global indexes of left ventricular systolic performance are favorably influenced by diltiazem, despite a mild negative inotropic effect.


DILTAZEM HYDROCHLORIDE is a calcium-channel blocker that is effective in the therapy of exertional1,2 and variant3 angina pectoris. Like other calcium-channel blockers, it has complex cardiovascular effects4-6: it dilates peripheral and coronary arteries, is a negative inotropic agent, and depresses conduction in the atrophicventricular and sinus nodes. The primary hemodynamic effect of intravenous or oral diltiazem is peripheral vasodilation, usually occurring without reflex sympathetic stimulation so that there is no change or a decrease in heart rate.6-7 The consequent decrease in the rate-pressure product is thought to be a major mechanism by which diltiazem exerts its protective effect in patients with exercise-induced angina pectoris.1-7 Other mechanisms that might protect the myocardium from ischemia have not been demonstrated conclusively. Measurements of total coronary blood flow have shown little change after diltiazem,7-8 and it has not been possible to demonstrate a clinically apparent negative inotropic effect of the drug4,9,10 except during acute myocardial ischemia7 or in an animal preparation of high-output congestive heart failure.11

Early in the course of coronary artery disease (CAD), patients develop abnormalities of regional left ventricular contraction12,13 and alterations in diastolic function14,15 even in the absence of myocardial infarction. Given the critical role that calcium plays in the processes of cardiac contraction and relaxation, one might expect that the calcium-channel blockers might affect these abnormalities of systolic and diastolic function seen in patients with CAD. Studies2,16,17 have shown that diltiazem improves resting left ventricular global ejection fraction and attenuates the hemodynamic and global ejection fraction abnormalities that develop during exercise-induced angina, but there has been no comprehensive evaluation of the effects of
diltiazem on systolic and diastolic ventricular function in patients with CAD. We designed this investigation to assess the effects of diltiazem on left ventricular systolic regional wall motion, left ventricular relaxation, and diastolic compliance in patients with CAD.

Methods

Patient population. Twenty-two patients undergoing cardiac catheterization for the evaluation of chest pain syndromes comprised the study population. All were men and their mean age was 56.5 ± 8.6 (range 41 to 71) years. Criteria for exclusion from the study were presence of unstable angina, acute myocardial infarction within 3 months of catheterization, severe congestive heart failure or hypotension, valvular heart disease, atrial fibrillation, uncontrolled arrhythmias, and second- or third-degree atrioventricular block. All cardiovascular medications except long-acting nitrates were discontinued at least 48 hr before catheterization. Long-acting nitrates were discontinued at least 12 hr before the study. The experimental protocol was approved by the Clinical Investigation Committee of The Milton S. Hershey Medical Center, and all patients participating gave informed consent.

Experimental protocol. All patients underwent catheterization, while they were in the fasting state and without premedication, from the femoral approach. Arterial pressure was measured with a cannula inserted into the left radial artery. Baseline right heart pressures were measured with a flow-directed pulmonary artery catheter inserted percutaneously into the right femoral vein. Cardiac output was measured by indicator-dilution technique. The flotation catheter was then exchanged for a No. 7F micromanometer-tipped catheter (Millar Instruments, Inc.), which was positioned in the right ventricle. A No. 8F micromanometer-tipped pigtail injection catheter was then inserted percutaneously into the right femoral artery and advanced to the left ventricle.

Both micromanometer-tipped catheters were calibrated to external transducers, and the calibration was checked at intervals throughout the study. The 0 mm Hg reference level for the external transducer was at the midchest level. All measurements were made during a held, gentle, submaximal inspiration. When performed properly, such a respiratory maneuver results in stable intracardiac pressures. We confirmed that each patient performed the maneuver properly by observing respiratory motion fluoroscopically and intracardiac pressures during pressure recordings. We collected the pressure data on an Electronics for Medicine VR12 recorder set at a 2500 Hz filter and interfaced with an Electronics for Medicine Catheterization Laboratory Computer with a sampling rate of 200 Hz.

After measuring baseline intracardiac pressures, we performed biplane 30 degree right anterior oblique/60 degree left anterior oblique left ventricular cineangiography with 40 ml of 66% diatrizoate meglumine and 10% diatrizoate sodium (Renografin-76) injected at a rate of 12 ml/sec. Film speed was 60 frames/sec. Pressures were measured during the left ventricular cineangiographic examination, and an electrically triggered cine tracer marked the x-ray film and sent a timing signal to the VR12 recorder to allow for simultaneous measurement of pressure and volumes.

After a rest period of 15 to 20 min, intracardiac pressures were again measured to confirm that hemodynamics had returned to baseline. Previous studies have documented that such a rest period eliminates any effects of the radio-iodinated contrast agent from the first left ventricular cineangiogram on the systolic and diastolic left ventricular function as determined at the second cineangiographic examination. We then administered diltiazem intravenously as an initial bolus of 0.25 mg/kg followed by a continuous infusion of 0.0014 mg/kg/min for 10 min. The continuous infusion was increased every 2 min by 0.0014 mg/kg/min as necessary to maintain a fall in mean arterial pressure of approximately 10% from baseline. Plasma diltiazem levels were measured before and after the infusion. At the end of 10 min, when systemic arterial pressure was stable, we repeated intracardiac pressure measurements and then obtained a second biplane left ventricular cineangiogram with the use of an identical dose of contrast agent.

After the completion of the protocol, all patients underwent selective coronary angiographic examination by the femoral approach.

Data analysis. We analyzed hemodynamic and volumetric data from the first adequately opacified sinus beat within the first five cardiac cycles after injection of contrast agent and did not use postmature beats. Left ventricular cineangiographic film frames were projected with a Vanguard XR-35 projector and the left ventricular silhouettes were digitized with a Graf-Pen ultrasonic digitizer interfaced with a PDP 11/05 computer. Right and left anterior oblique grids obtained at the time of each study were also digitized to correct for x-ray magnification and distortion. For each patient, the two left ventricular cineangiograms were projected in random order and the investigator was blinded as to their order and identity. Volumes were determined by the biplane area-length method. We measured volumes serially every 33.3 msec.

The digitized pressure data were stored on a magnetic disk for analysis by the PDP 11/05 computer. Simultaneous left ventricular pressures and volumes from the time of minimal diastolic pressure to end-diastolic (post-a wave) pressure were fitted to the polynomial equation

\[ P = aV^2 + bV^3 + cV^4 + dV^5 + e \]  

(1)

where \( P \) = left ventricular pressure (mm Hg) and \( V \) = left ventricular volume index (ml/m²). We used multiple linear analysis of the control and diltiazem diastolic pressure-volume (P-V) relationships to assess the adequacy of the P-V fits for each experimental condition. To determine the short-term effect of diltiazem on the left ventricular P-V relationship, we then performed a multiple linear regression analysis of the combined data with the following equation:

\[ P = aV^2 + bV^3 + cV^4 + dV^5 + e + f(DTZ) + g(DTZ \times V) \]  

(2)

where DTZ = 0 during the control state and DTZ = 1 during the drug study. The coefficients a, b, c, d, and e in equation 1 are not necessarily identical to those in equation 2. This type of P-V analysis is a modification of that described by Glantz. Linear regression analysis can tell us whether the terms \( f(DTZ) \) and \( g(DTZ \times V) \) contribute significantly to the diastolic P-V relationship. If \( f(DTZ) \) is statistically significant, then diltiazem causes a significant shift in the intercept of the P-V fit; if \( g(DTZ \times V) \) is statistically significant, then diltiazem causes a significant shift in the slope of the diastolic P-V fit.

The polynomial relationship is an empiric fit between pressure and volume during diastole and thus makes no assumptions about the physiologic interaction of pressure and volume. As a consequence, the coefficients of the equation do not represent indexes of ventricular chamber stiffness. We used such an approach rather than the more traditional exponential analysis because we wanted to evaluate the effect of diltiazem on the entire period of left ventricular filling. The left ventricular diastolic P-V relationship approximates an exponential function only during passive filling when elastic properties of the left ventricle are of paramount importance. Deviation from the exponential occurs during rapid filling and at end-diastole.
when viscous properties of the left ventricle are apparent.\textsuperscript{24} Using the polynomial fit we were able to quantify the shifts in the overall left ventricular diastolic P-V relationship caused by diltiazem and using linear regression analysis we were then able to determine whether shifts in the left ventricular diastolic P-V relationship in individual patients were statistically significant (figure 1). This contrasts to previous studies of left ventricular diastolic function in which investigators used grouped data\textsuperscript{25-27} to evaluate the effects of an intervention on left ventricular diastolic P-V relationships or assessed the individual P-V fits visually.\textsuperscript{28-30} The advantages of the polynomial approach have been discussed previously.\textsuperscript{22}

To assess the effect of diltiazem on left ventricular relaxation, we measured the time constant (T) of the negative monoeponential pressure decay during isovolumetric left ventricular relaxation. T was derived according to the method suggested by Craig and Murgo\textsuperscript{31} and verified by Thompson et al.\textsuperscript{32} Pressure was measured during isovolumetric relaxation every 5 msec from maximum negative dP/dt to a pressure that was 5 mm Hg above the left ventricular end-diastolic pressure of the next beat and fit to the equation

\[ P(t) = (P_0 - P_b) e^{-t/T} + P_b \]

where \( P \) = pressure; \( t \) = time; \( P_0 \) = pressure at \( t = 0 \); \( P_b \) = base pressure if isovolumetric left ventricular pressure decay continued indefinitely (\( t = \infty \)); \( T \) = time constant. By taking the derivative, the equation is transformed to

\[ \text{dP/dt} = P(t)/T + P_b/T \]

resulting in a linear relationship between dP/dt and P with a slope that is the negative reciprocal of \( T \). \( T \) is then derived by linear regression analysis. The validity of such a model depends on how well the model describes the physiologic system. Others have reported that isovolumetric left ventricular relaxation is not exactly a negative monoeponential decay.\textsuperscript{33} Consequently, for each beat analyzed we determined the correlation coefficient of the linear relationship between \( T \) and left ventricular negative dP/dt. We also used least squares analysis to reconstruct the original equation (the monoeponential equation) from the calculated \( T \). The SEE of such an analysis indicates how closely the mathematic model actually fits the raw pressure data. We measured at least 25 beats in every patient. In all cases an \( R \) value greater than .95 and an SEE less than 1.7 mm Hg were obtained, indicating that in our patients, \( T \) accurately described the time constant of left ventricular relaxation. Because recent work has suggested that \( T \) is load dependent,\textsuperscript{33} we assessed the effects of diltiazem-induced changes in load on \( T \) by linear regression analysis. The other index of left ventricular relaxation measured was maximum negative dP/dt.

We evaluated left ventricular systolic function by measuring the ejection phase indexes of global ejection fraction and mean velocity of circumferential fiber shortening (Vcf), the isovolumetric index of maximum positive dP/dt, and the left ventricular end-systolic P-V ratio.\textsuperscript{34}

In addition to global left ventricular systolic function, we assessed regional wall motion with a quantitative area ejection fraction technique.\textsuperscript{35} The left ventricle was divided into eight areas. End-diastolic and end-systolic left ventricular silhouettes were identified with use of frame-by-frame analysis. For each area

\[ \text {Area EF} = \frac{\text{End-diastolic area} - \text{end-systolic area}}{\text{End-diastolic area}} \]

where EF is ejection fraction. Normokinesis was considered to be present when the area ejection fraction was within 1 SD of the normal mean value for our laboratory; hypokinesis was defined as an area ejection fraction of less than 1 SD of the normal mean value. A statistically significant change in area ejection fraction caused by diltiazem was defined as a change beyond the 95% confidence intervals of random variability in this value as deter-
mined in our laboratory.36 Such an approach allowed us to quantitate significant changes in regional wall motion not only in individual patients, but also in individual left ventricular regions.

Significant CAD was defined as a coronary stenosis of greater than 70% of luminal diameter. For each patient, the relationship between regional CAD and myocardial area was documented. Those areas jeopardized by CAD were defined as CAD areas. The effect of diltiazem on area ejection fraction and its relation to CAD areas was determined by chi-square analysis.

To assess the influence of baseline left ventricular function on the results, we divided the patients into two groups according to the presence or absence of baseline left ventricular dysfunction, as defined by the range of normal values for our laboratory. The criteria used were an elevated left ventricular end-diastolic volume index (≥ 100 ml/m²), elevated left ventricular end-diastolic pressure (≥ 17 mm Hg when measured during ventriculography), or a depressed global ejection fraction (< 0.54).

To compare data obtained at control and after diltiazem in individual patients, we used the paired t test. Group comparisons of continuous data were evaluated with the t test for differences between group means or, when multiple comparisons were made, analysis of variance. All data are mean ± SEM.

Results

Clinical characteristics. Twenty of the 22 patients had CAD. All had stable angina pectoris and 14 had suffered prior myocardial infarction. Multivessel CAD was common: 13 patients had three-vessel disease, four had two-vessel disease, and three had one-vessel disease. Left ventricular asynergy was present in 19 of the 20 patients with CAD and in neither of the patients with normal coronary arteries. The amount of left ventricle jeopardized by CAD averaged 65.9 ± 6.2%.

The two patients with normal coronary arteries had atypical chest pain and normal resting left ventricular function. They have been included in the study because eliminating their data from the analysis did not alter the results.

Effect of diltiazem on hemodynamics and left ventricular volume. Table 1 shows that diltiazem caused significant decreases in mean arterial pressure (11.5%), left ventricular systolic pressure (13.5%), calculated systemic vascular resistance (20.8%), and heart rate (6.8%). Cardiac output increased 8.8% and left ventricular stroke volume index increased 16.7%. Significant changes in the ejection phase indexes of left ventricular function indicated an improvement in left ventricular systolic performance: Global ejection fraction increased 9.1% from 0.55 ± 0.02 to 0.60 ± 0.02 and left ventricular mean Vcf increased 10.3%. In addition, left ventricular end-systolic volume index decreased by 7.6%. The findings indicate that diltiazem given intravenously reduced afterload acutely and improved global left ventricular systolic performance. The extent of improvement in left ventricular systolic function as assessed by percentage increase in global ejection fraction correlated with the percentage decrease in left ventricular systolic pressure (R = .564, p < .01).

Despite the improvement in global left ventricular systolic performance, diltiazem had some intrinsic negative inotropic effects (table 1). The significant fall

| TABLE 1 | Hemodynamics and left ventricular volumes and function before and after diltiazem (n = 22) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | C               | D               | % Change       | p value         |
| Heart rate (beats/min) | 68.7 ± 3.3 | 64.0 ± 2.6 | −6.8           | <.005           |
| Mean systemic arterial pressure (mm Hg) | 101.3 ± 2.6 | 89.6 ± 2.0 | −11.5          | <.0001          |
| LV systolic pressure (mm Hg) | 141.2 ± 4.2 | 122.1 ± 3.9 | −13.5          | <.0001          |
| LV end-diastolic pressure (mm Hg) | 17.6 ± 1.1 | 20.1 ± 1.0 | +14.2          | <.001           |
| LV maximum positive dp/dt (mm Hg/sec) | 1470 ± 66 | 1315 ± 53 | −10.5          | <.0001          |
| LV maximum negative dp/dt (mm Hg/sec) | −1782 ± 87 | −1655 ± 88 | −7.1           | <.02            |
| T (msec) | 68.5 ± 7.3 | 58.7 ± 5.5 | −14.3          | <.002           |
| Pp (mm Hg) | −14.2 ± 2.8 | −7.7 ± 2.3 | +45.8          | <.0001          |
| RV systolic pressure (mm Hg) | 29.0 ± 1.8 | 30.7 ± 1.6 | +5.9           | <.03            |
| RV end-diastolic pressure (mm Hg) | 9.3 ± 0.7 | 10.0 ± 0.6 | +7.5           | NS              |
| Cardiac index (1/min/m²) | 3.20 ± 0.14 | 3.48 ± 0.12 | +8.8           | <.025           |
| Systemic vascular resistance (dyne·sec·cm⁻³) | 1290 ± 52 | 1022 ± 39 | −20.8          | <.0001          |
| LV end-diastolic volume index (ml/m²) | 86.9 ± 3.3 | 91.8 ± 3.3 | +5.6           | <.005           |
| LV end-systolic volume index (ml/m²) | 39.7 ± 2.6 | 36.7 ± 2.4 | −7.6           | <.002           |
| LV stroke volume index (ml/m²) | 47.2 ± 1.9 | 55.1 ± 2.5 | +16.7          | <.001           |
| LV global EF | 0.55 ± 0.02 | 0.60 ± 0.02 | +9.1           | <.0001          |
| LV mean Vcf (circ/sec) | 1.07 ± 0.09 | 1.18 ± 0.08 | +10.3          | <.025           |
| LV end-systolic P-V ratio | 3.29 ± 0.24 | 3.00 ± 0.20 | −8.8           | <.02            |

All data are mean ± SEM.
C = control; D = diltiazem; LV = left ventricular; RV = right ventricular; EF = ejection fraction.
of 10.5% in left ventricular maximum positive dP/dt may have reflected the decrease in afterload rather than negative inotropy, but the left ventricular end-systolic P-V ratio also decreased by 8.8% after diltiazem. Diltiazem increased left ventricular end-diastolic pressure significantly (14.2%) from 17.6 ± 1.1 to 20.1 ± 1.0 mm Hg. This increase in pressure was paralleled by a mild increase in right ventricular systolic pressure, but occurred without any significant change in end-diastolic pressure in the right ventricle. In addition to the increase in left ventricular end-diastolic pressure, diltiazem also significantly increased the left ventricular end-diastolic volume index by 5.6%.

**Effect of diltiazem on the left ventricular diastolic P-V relationship and left ventricular relaxation.** We were able to generate left ventricular diastolic P-V fits in 20 of the 22 patients. In the other two patients, the cine tracer failed, preventing us from correlating simultaneous left ventricular pressures and volumes. In the 20 patients, the diastolic P-V fits to polynomial equation 1 for both control and diltiazem P-V curves were excellent, with the correlation coefficients ranging from .955 to .996. The mean correlation coefficient for these left ventricular diastolic P-V relationships was .976 ± .002. When the data obtained at control and after diltiazem were combined and analyzed with polynomial equation 2, the correlation coefficients ranged from .956 to .988, with a mean of .972 ± .002. Thus, combining the two sets of data to create a single polynomial equation did not degrade the "goodness" of fit of the diastolic P-V analysis.

In 16 of the 20 patients there was no change in the left ventricular diastolic P-V relationship after diltiazem (figure 1, A). In three patients there was an upward shift after diltiazem caused by a change in slope in two patients (figure 1, B) and a change in intercept in one patient. In none of these three patients did right ventricular end-diastolic pressure increase more than 1 mm Hg after diltiazem. In one patient there was a downward shift in the intercept of the left ventricular diastolic P-V relationship after diltiazem. This patient experienced no change in right ventricular end-diastolic pressure after diltiazem. Thus, in most patients diltiazem had no effect on the left ventricular diastolic P-V relationship, despite increasing left ventricular end-diastolic pressure and volume.

Diltiazem improved left ventricular relaxation significantly (table 1), shortening T by 14.3% (p < .002). T decreased in 18 of the 22 patients. The improvement in relaxation rate was not accompanied by an increase in left ventricular maximum negative dP/dt, perhaps because of the load dependency of maximum negative dP/dt. The effect of load on T is illustrated in figure 2, A; the changes in T did not correlate with changes in left ventricular pressure (R < .200). We obtained similar results when T was compared with left ventricular end-diastolic pressure or end-systolic volume. P_e, the asymptote of the monoeponential equation describing isovolumetric relaxation, was negative in patients at rest (P_e = −14.2 ± 2.8 mm Hg) and became less negative (by 45.8%) after diltiazem. Changes in P_e were unrelated to changes in left ventricular end-systolic volume (R = .294).

**Influence of baseline left ventricular function on the effects of diltiazem.** Thirteen patients had abnormal and nine normal baseline left ventricular function. There were no significant differences in the effects of diltiazem on hemodynamic variables, left ventricular volumes, global left ventricular systolic function, or left ventricular relaxation in the two groups of patients. However, the three patients in whom there was an upward shift in the left ventricular diastolic P-V relationship after diltiazem all had normal baseline left
ventricular function and the one patient in whom the shift was downward had abnormal baseline left ventricular function. Figure 3 demonstrates that the change in left ventricular end-diastolic pressure correlated weakly with the baseline left ventricular end-diastolic pressure (R = -.777, p < .02). Thus, the negative inotropic effect of diltiazem was somewhat less apparent at higher baseline levels of left ventricular end-diastolic pressure. On the other hand, figure 4 illustrates that changes in left ventricular end-diastolic volume and global ejection fraction were completely unrelated to the baseline values. Figure 2, B, shows that the effect of diltiazem on left ventricular relaxation was strongly correlated with the baseline relaxation rate (R = -.777, p < .001). Diltiazem improved left ventricular relaxation the most when baseline T was markedly prolonged.

**Effect of diltiazem on left ventricular systolic regional wall motion.** We were able to analyze regional wall motion in 21 of the 22 patients. One patient shifted his position between cineangiograms, preventing evaluation of comparable areas for the control and diltiazem studies. There were 47 areas supplied by normal coronary arteries or in which CAD was nonocclusive and there were 121 areas supplied by arteries with significant CAD. Response of area ejection fraction was unrelated to regional CAD in general: there was significant improvement in area ejection fraction in 40 (33%) CAD areas after diltiazem compared with 13 (28%) areas supplied by normal arteries (p = NS). A significant decrease in area ejection fraction after diltiazem was noted in only four areas: two CAD areas with resting hypokinesis and two areas supplied by normal coronary arteries with resting normokinesis.

Of the 121 CAD areas, baseline contraction was normal in 60 and hypokinetic in 61. After diltiazem, there was a significant increase in area ejection fraction in 32 (53%) hypokinetic CAD areas compared with only eight (13%) normokinetic CAD areas (p < .001). This is reflected in the magnitude of the area ejection fraction response to diltiazem, as depicted in figure 5. In the normokinetic CAD areas, area ejection fraction increased from $0.51 \pm 0.015$ to $0.53 \pm 0.017$ after diltiazem, a small but statistically significant (p < .02) improvement. In the hypokinetic CAD areas there was a larger increase in area ejection fraction from $0.33 \pm
0.014 to 0.42 ± 0.014 (p < .0001). When both regional CAD and resting wall motion abnormalities were taken into consideration, the percent increase in area ejection fraction in the hypokinetic CAD areas after diltiazem was significantly greater than the percent increases in the hypokinetic areas supplied by normal arteries or the normokinetic CAD and “non-CAD” areas (figure 6). Figure 7 illustrates the effect of diltiazem on regional wall motion abnormalities in a patient with a 90% stenosis of the proximal right coronary artery. The inferior wall hypokinesis (areas 4 and 5) that was present at baseline improved significantly after diltiazem.

**Plasma diltiazem levels.** No patient had a measurable level of diltiazem during the control study. At the time of the postdiltiazem left ventricular cineangiographic study the mean plasma diltiazem level was 154 ± 12 ng/ml.

**Discussion**

**Effects of diltiazem on global left ventricular systolic function.** The results of this study indicate that diltiazem has complex effects on cardiac function in patients with CAD. The plasma diltiazem levels achieved in our patients were similar to those reported in studies of patients taking oral diltiazem for the therapy of angina pectoris. Thus, the hemodynamic effects that we have documented here are probably comparable to those that can be expected in clinical practice.

Our data confirm the results of others that diltiazem improves such afterload-dependent indexes of global left ventricular systolic performance as ejection fraction, cardiac index, and stroke volume index. On the other hand, we found in our patients that diltiazem did have some intrinsic negative inotropic effects, causing a decrease in the left ventricular end-systolic P-V ratio in conjunction with an increase in left ventricular end-diastolic pressure and volume. In addition, it is possible that the slower heart rate after diltiazem, by lengthening the diastolic filling period, resulted in some increase in left ventricular end-diastolic volume. Our findings are in contrast to those reported recently by Walsh et al. in a group of patients with congestive heart failure. In their patients, left ventricular filling pressure decreased after diltiazem and a negative inotropic effect was not demonstra-
able. Differences in both method and patient populations most likely account for the discrepant results. Walsh's patients had a greater decrease in arterial pressure than our patients and their baseline left ventricular function was much worse. Of interest, therefore, is our finding that the negative inotropic effect of diltiazem tended to be least apparent in those patients with the highest resting left ventricular end-diastolic pressures (figure 3).

Effect of diltiazem on abnormalities of diastolic function in patients with CAD. Previous investigations have demonstrated that left ventricular relaxation is often slowed and left ventricular compliance diminished in patients with CAD. Although abnormalities are most marked during episodes of acute myocardial ischemia when the left ventricular diastolic P-V relationship shifts upward acutely and left ventricular relaxation is prolonged, they are also present at rest. In some cases, myocardial scarring may account for the resting abnormalities in diastolic function; in others, the pathophysiologic mechanism is uncertain. It has been suggested that chronic ischemia is present; however, no myocardial lactate production is noted in patients with stable angina pectoris when they are studied in the asymptomatic state. Braunwald and Kloner recently hypothesized the concept of the "stunned myocardium," in which posts ischemic myocardium is depleted of ATP reserves and calcium metabolism is deranged, to account for the left ventricular systolic regional wall motion abnormalities that occur in patients with CAD in the absence of myocardial infarction or active ischemia. Because left ventricular relaxation depends on calcium sequestration in the sarcoplasmic reticulum of myocardial fibers and is an energy-dependent process, the stunned myocardium may not only result in abnormalities of contraction but also those of relaxation.

The beneficial effect of diltiazem on diastolic function in our patients was confined to early diastolic events, with a significant improvement in left ventricular relaxation rate as measured by T. Diltiazem may have influenced relaxation in several ways. First, relaxation is a process often dependent on load. In our patients, the effects of diltiazem on load were variable, with a decrease in afterload and an increase in load at end-diastole. Although we found no relationship between T and systolic or end-diastolic pressure, it is possible that had we measured a more sensitive index of load, such as wall stress, we might have found a relationship. Second, impairment of calcium sequestration may prolong the myocardial inactivation process in patients with CAD, leading to delayed relaxation. Although the effects of diltiazem on intracellular calcium metabolism are unknown, it is possible that the drug improved left ventricular relaxation by direct effects on myocardial inactivation. Third, left ventricular relaxation rate depends on the degree of uniformity of contraction throughout the ventricle. In patients with CAD, Gibson et al. have demonstrated localized delays in left ventricular relaxation with resting asynchrony. Thus, the improvement in systolic regional wall motion after diltiazem may have led to an increase in left ventricular relaxation rate.

In contrast to our results with diltiazem, Ludbrook et al. found that nifedipine did not affect left ventricular relaxation. The differing results may in part be related to the different methods used for calculating T, different mechanisms of action of the two drugs, or to the different patient populations in the two studies. Most of our patients had left ventricular asynchrony, whereas most patients in the previous study did not. The effect of diltiazem on left ventricular relaxation in our patients was greatest in those with the most abnormal baseline left ventricular relaxation rate (figure 2, B). Therefore, the difference between the previous study and ours may in part be one of degree. It is of interest to note that nifedipine did improve left ventricular relaxation in patients with hypertrophic cardiomyopathy, a condition in which left ventricular relaxation is seriously deranged.

We found that, in addition to its effect on T, diltiazem also significantly altered P_b, but how P_b is related to left ventricular relaxation is uncertain. Yellin et al. have reported that left ventricular pressure becomes negative if the mitral valve orifice is occluded transiently and left ventricular relaxation is allowed to continue uninterrupted by left ventricular filling. They reported that the extent of left ventricular relaxation correlated inversely with left ventricular end-systolic volume, with more negative pressure at smaller end-systolic volumes. Our finding that P_b is usually less than zero is in agreement and is supported by the work of Thompson et al. However, we found no correlation between P_b and left ventricular end-systolic volume. If P_b did represent the extent of left ventricular relaxation, then it should have become more negative as T shortened and relaxation rate increased. Our results with diltiazem were the opposite: P_b became less negative after diltiazem. Others have reported similar directional changes in P_b and T. It is therefore probable that P_b does not represent the extent of left ventricular relaxation but rather is a theoretic term that contributes to the mathematic description of left ventricular pressure decay during isovolumetric relax-
ation. The interaction of left ventricular filling with left ventricular relaxation most likely invalidates any direct calculation of the extent of left ventricular relaxation in the intact heart.

The lack of effect of diltiazem on the left ventricular diastolic P-V relationship was unexpected given the drug’s beneficial effect on left ventricular relaxation. In our patients, left ventricular relaxation may not have been sufficiently impaired in the resting state to affect the left ventricular diastolic P-V relationship. Other factors that may shift the left ventricular diastolic P-V relationship acutely, such as right ventricular diastolic dynamics and coronary perfusion, were probably not affected by diltiazem. Diltiazem did not alter right ventricular diastolic pressure in our patients; therefore, ventricular interaction was not important. This is in contrast to studies of nifedipine and nitroglycerin in which downward shifts in the left ventricular diastolic P-V relationship occurred in conjunction with decreases in right heart pressures. We did not measure coronary perfusion, but two recent studies have suggested that total coronary sinus flow does not change after intravenous diltiazem in patients with CAD. The upward shifts in the left ventricular diastolic P-V relationship in three patients with normal baseline left ventricular function remain unexplained. These three patients had no clinical characteristics or hemodynamic responses to diltiazem that distinguished them from the other patients with normal left ventricular function at baseline. Similarly, the reason for the downward shift in the left ventricular diastolic P-V relationship after diltiazem in one patient with abnormal baseline left ventricular function is unknown, since he had hemodynamic responses to the drug similar to those of the other patients with abnormal baseline function.

Systolic regional wall motion response to diltiazem. Given the beneficial effect of diltiazem on global left ventricular relaxation and the known association between abnormalities of relaxation and contraction in patients with CAD, it is not surprising that the drug significantly improved area ejection fraction in hypokinetic areas supplied by diseased arteries (figures 5 to 7). The increase in area ejection fraction in hypokinetic areas did not occur at the expense of normokinetic areas because the latter did not decrease area ejection fraction after diltiazem. Reversal of resting systolic regional wall motion abnormalities has been reported previously after administration of nitroglycerin, but not after the administration of other calcium-channel blockers. Vliestra et al. reported no change in regional wall motion after administration of intravenous verapamil. Two studies have shown that nifedipine did not alter resting wall motion abnormalities in patients with CAD, although it did prevent exercise-induced abnormalities. The differences reported here may relate to varying mechanisms of action of the three agents, methodologic differences among various studies, and the differing patient populations.

Several mechanisms may have contributed to the favorable effect of diltiazem on left ventricular systolic regional wall motion. The improvements in regional systolic contraction may have correlated with more rapid local left ventricular relaxation. Ludbrook et al. noted improvement in regional left ventricular relaxation associated with reversal of regional wall motion abnormalities after administration of nitroglycerin in patients with CAD. We did not measure regional relaxation and this must be considered a limitation of our study, but the increase in global left ventricular relaxation rate after diltiazem that was associated with improvement in regional left ventricular systolic function does support the concept that in our patients, relaxation and contraction abnormalities in CAD areas were interrelated.

The arterial vasodilating effect of diltiazem contributed to the improvement in global left ventricular systolic function and may have played a role in increasing regional contraction as well. Our analysis of regional left ventricular systolic contraction suggests that other factors were also important, because clinically evident increases in area ejection fraction occurred primarily in left ventricular areas that were supplied by stenosed coronary arteries and were hypokinetic at rest. If the improvements were secondary only to afterload reduction, area ejection fraction would be expected to increase similarly in all regions. Mechanisms that might account for the ability of diltiazem to improve regional contraction selectively in asynergic areas of the left ventricle supplied by diseased arteries include effects on regional coronary blood flow, calcium metabolism, and ATP utilization. Although intravenous diltiazem does not alter total myocardial blood flow, Bache and Dymek have shown that it partially corrects the derangement in the subendocardial/subepicardial flow ratio that occurs in a dog preparation of acute myocardial ischemia. Moreover, Malacoff et al. showed that another calcium-channel blocker, nifedipine, improves regional myocardial flow distal to stenosed coronary arteries. Nifedipine also prevents the accumulation of intracellular calcium that occurs during acute myocardial ischemia. Of note, therefore, is the observation of Weishaar et al. in a dog preparation of regional ischemia that diltiazem reduces ATP depletion, diminishes lactate production, and improves con-
tractility in the ischemic area of the left ventricle. No studies have been performed to evaluate the effects of a calcium-channel blocker on regional left ventricular function in a preparation that simulates the stunned myocardium, which was likely present in the patients studied here. But if the stunned myocardium does represent a postischemic state in which coronary flow is marginal, ATP is depleted, and calcium metabolism is deranged, then diltiazem might potentially exert its beneficial effects through any of the mechanisms described above.

In conclusion, intravenous diltiazem in a dose that provided a plasma level comparable to that reported for effective therapy of angina pectoris improved global left ventricular systolic performance, regional wall motion, and left ventricular relaxation rate in patients with CAD. The favorable effects of diltiazem on left ventricular performance occurred despite evidence of a mild negative inotropic effect. The improvement in regional contraction was confined to areas supplied by diseased arteries in which there was resting hypokinesis. The increase in left ventricular relaxation rate occurred without any overall effect on the left ventricular diastolic P-V relationship.

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