

# Left Ventricular Function Before and After Diltiazem in Patients With Coronary Artery Disease

TOMOYUKI MURAKAMI, MD, OTTO M. HESS, MD, HANS P. KRAYENBUEHL, MD

Zurich, Switzerland

Left ventricular contraction, relaxation and diastolic mechanics were investigated before and after intravenous administration of 15 mg of diltiazem in 15 patients with coronary artery disease. High fidelity left ventricular pressure measurements were performed in all 15 patients, with simultaneous biplane cineangiography in 13. The time constant of left ventricular isovolumic pressure decay was calculated from the linear relation of left ventricular pressure and its rate of change with time (negative dP/dt). Frame by frame volume analysis through one cardiac cycle was completed to construct volume-time and pressure-volume curves before and after the administration of diltiazem.

After diltiazem, left ventricular peak systolic pressure decreased from 124 to 113 mm Hg ( $p < 0.001$ ), while left ventricular end-diastolic pressure and heart rate were not altered. Maximal positive dP/dt also remained unchanged. End-diastolic volume was not changed after diltiazem, but end-systolic volume increased from 48

to 52 ml/m<sup>2</sup> ( $p < 0.025$ ); as a result, ejection fraction decreased slightly from 57 to 55% ( $p < 0.025$ ). The time constant of left ventricular pressure decay and maximal negative dP/dt decreased from 58 to 54 ms ( $p < 0.025$ ) and from -1,404 to -1,321 mm Hg/s ( $p < 0.025$ ), respectively. Peak early diastolic filling rate increased from 621 to 752 ml/s ( $p < 0.01$ ) in association with an increase in filling volume during the first half of diastole from 60 to 68% ( $p < 0.005$ ). No consistent displacement of the diastolic pressure-volume curve was observed after diltiazem.

This study indicates that diltiazem reduces afterload and depresses myocardial contractility in patients with coronary artery disease. In contrast, it improves left ventricular relaxation, which may contribute in part to the enhancement of early diastolic filling. However, left ventricular passive diastolic properties remain unaltered.

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Calcium channel antagonists block the slow channel by inhibiting the slow inward current carried by calcium ions. Since calcium ions play an important role in activating contractile proteins, interference with the transport of calcium ions by these agents produces a negative inotropic effect in myocardium and vasodilation in vascular smooth muscle. Diltiazem, one of the calcium antagonists, has recently been shown to be effective in reducing systolic determinants of myocardial oxygen consumption and improving exercise tolerance in patients with coronary artery disease (1-3). However, there is little information concerning its effects on left ventricular function, especially on left ventricular relaxation and diastolic mechanics, in these patients. Left ventricular relaxation, or pressure decay, is an energy-dependent process influenced by a complex interaction be-

tween loading conditions, inactivation (which is a process of calcium uptake by the sarcoplasmic reticulum) and the uniformity of distribution of loading conditions and inactivation (4). Diltiazem could alter left ventricular relaxation by affecting some of these determinants of relaxation. Moreover, this alteration in left ventricular relaxation potentially influences diastolic mechanics, such as diastolic filling and the pressure-volume relation. Therefore, the purpose of this study was to evaluate the effect of diltiazem on left ventricular contraction, relaxation and diastolic mechanics in patients with coronary artery disease.

## Methods

**Study patients.** The subjects of this study were 15 men with coronary artery disease (>50% diameter narrowing); 6 had single vessel, 1 had double vessel and 8 had triple vessel disease. The mean age was 51 years (range 41 to 63). Fourteen of the 15 patients had a history of myocardial infarction (4 anterior and 10 inferior). Informed consent was obtained from all patients.

From the Department of Internal Medicine, Medical Policlinic, Cardiology, University Hospital, Zurich, Switzerland. Manuscript received June 5, 1984; revised manuscript received September 24, 1984, accepted October 18, 1984.

Address for reprints: Tomoyuki Murakami, MD, Department of Internal Medicine, Medical Policlinic, Cardiology, University Hospital, Raemistrasse 100, 8091 Zurich, Switzerland.

**Cardiac catheterization.** Patients underwent right and left heart catheterization in the fasting state. Premedication consisted of 10 mg of chlorthalidone administered orally 1 hour before catheterization. Eleven patients were receiving long-term medication with a beta-receptor blocking agent, which was discontinued either 24 hours (seven patients) or 12 hours (four patients) before the study. Ten patients were receiving the calcium antagonist, nifedipine; it was withdrawn either 24 hours (two patients) or 12 hours (eight patients) before the study. Eleven patients were taking a long-acting nitrate; it was withdrawn either 24 hours (1 patient) or 12 hours (10 patients) before the study.

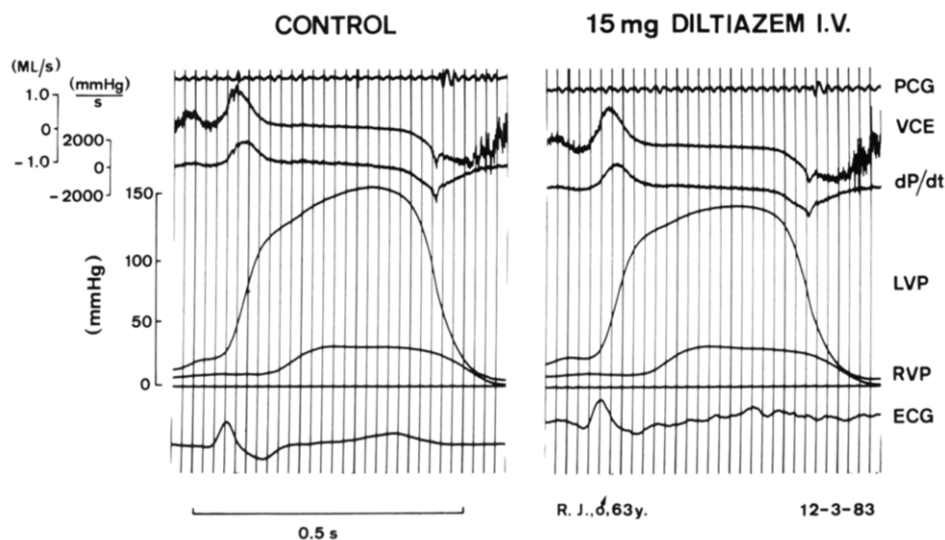
*Left ventricular pressure* was measured with a Millar pigtail angiographic micromanometer introduced through the right femoral artery. Left ventricular pressure, the first derivative of left ventricular pressure ( $dP/dt$ ), an intracardiac phonocardiogram from the micromanometer signal and an intracardiac electrocardiogram from a right-sided electrode catheter were recorded at a paper speed of 250 mm/s (Electronics for Medicine, model VR12) (Fig. 1). The micromanometer pressure tracing was superimposed on the conventional pressure tracing.

*Simultaneous biplane left ventricular cineangiography* was performed in the 30° right anterior oblique and 60° left anterior oblique projections at a filming rate of 50 frames/s. Volumes were calculated using the area-length method. Each angiographic frame had a digital time that corresponded to time marks on the pressure recordings.

**Study protocol.** After placement of the catheters, routine measurements of right and left heart hemodynamics at rest were made. Baseline left ventricular angiography and simultaneous high fidelity left ventricular pressure measurements were then performed. After the first ventriculogram, a pause of 15 minutes was permitted for dissipation of the hemodynamic and myocardial effects of the contrast agent. Then 15 mg of diltiazem was injected intravenously

at a rate of 5 mg/min (47 to 77  $\mu\text{g}/\text{kg}$  per min). Ten minutes after the initiation of the injection, intracardiac pressure measurements and left ventricular cineangiography were repeated. The time interval between the first and the second angiogram was 25 minutes. Two patients were excluded from the volume analysis because cineangiography had not been performed at baseline or after diltiazem. All patients were found to have a left ventricular regional wall motion abnormality (in 14 patients on the baseline angiogram, and in 1 who did not undergo baseline angiography on the rest echocardiogram). Five patients showed akinesia and nine showed hypokinesia in the regions of the wall corresponding to those of myocardial infarction; one patient who had not had a previous myocardial infarction demonstrated anterior hypokinesia. Finally, coronary arteriography was performed by the Judkins technique.

**Data analysis.** All beats analyzed were sinus beats, and postextrasystolic beats were excluded. Pressure tracings were digitized for an entire cardiac cycle by an electronic digitizer (Numonics Corporation) interfaced with a digital computer (PDP, model 11/10). A previously described program (5) produced a printout of pressure and  $dP/dt$  values, dividing one cardiac cycle into 130 time intervals. The time constant of isovolumic relaxation and the extrapolated baseline pressure (pressure at  $dP/dt = 0$ ) were calculated, respectively, as the negative reciprocal of the slope and the intercept of the linear regression of pressure and the negative  $dP/dt$  coordinates during the isovolumic relaxation period. The isovolumic relaxation period was defined as the period beginning immediately after maximal negative  $dP/dt$  and ending when pressure decreased to 5 mm Hg above left ventricular end-diastolic pressure (6). The mean correlation coefficient of the linear relation between left ventricular pressure and negative  $dP/dt$  was  $-0.994$  both in the control state (range 0.983 to 0.999) and after diltiazem administration (range 0.985 to 0.999). In 13 patients with pressure recordings and



**Figure 1.** Pressure tracings in the control state and 10 minutes after 15 mg of diltiazem intravenously (I.V.). In this patient, left ventricular peak pressure (LVP) decreased by 16 mm Hg after the administration of diltiazem. End-diastolic pressure did not change. ECG = electrocardiogram; ML/s = muscle lengths per second; PCG = phonocardiogram; RVP = right ventricular pressure; VCE = the first derivative of left ventricular pressure ( $dP/dt$ ) divided by pressure (P).

simultaneous cineangiography, volume-time and pressure-volume curves were constructed every 20 ms throughout one cardiac cycle in the baseline state and after diltiazem administration. Stroke work (SW) in g/m<sup>2</sup> was calculated from the equation: SW = A × 0.0136, where A is the area enclosed by the pressure-volume loop as determined by planimetry. In this study, the time of end-diastole was defined as the beginning of the rapid increase in left ventricular pressure immediately after the onset of the QRS complex. End-systole was defined as the angiographically determined point of aortic valve closure or the point of the second heart sound.

The method for analyzing diastolic mechanics has been reported previously (7). The time of mitral valve opening was 20 ms before the first frame showing the entry of unopacified blood into the left ventricle; the pressure at this timing was termed "mitral opening pressure" and was considered to be an index of atrial driving pressure. The time interval from mitral valve opening to end-diastole was taken as the left ventricular filling time. This filling time was divided into a first and second half; mid-diastolic pressure and volume and the ratio of the volume increase during the first and second half of diastole to the total filling volume (maximal diastolic volume minus volume at mitral valve opening) were calculated. In addition, instantaneous diastolic filling rates were calculated every 20 ms after mitral valve opening. To minimize error due to random noise in the left ventricular volume curve, raw data were smoothed by the convolution method (8) according to the formula:

$V(t) = [v(t - 20) + 2 \cdot v(t) + v(t + 20)]/4$ , where t is the time from mitral valve opening (ms), and v(t) and V(t) are raw and smoothed instantaneous left ventricular volume (ml), respectively. Then diastolic filling rate (fr) at time t was calculated (in ml/s) from the equation:  $fr(t) = [V(t + 20) - V(t - 20)]/0.04$ . The greatest value occurring early in diastole was termed the "peak filling rate." Pressures and volumes at three diastolic points (lowest diastolic pressure, mid-diastole and end-diastole) were averaged, and the mean diastolic pressure-volume curve was constructed. End-diastolic volume index, end-systolic volume index and ejection fraction were calculated in the usual fashion.

**Statistics.** Comparisons of hemodynamic and angiographic variables between the control state and diltiazem administration were performed by a paired t test. Differences were considered significant when the p value was less than 0.05. Data are presented as mean values ± 1 standard deviation.

## Results

Left ventricular pressure and relaxation data are presented in Table 1, and volume data and data obtained from pressure-volume loops in Table 2. Figure 1 demonstrates representative pressure tracings. Examples of pressure-dP/dt, volume-time and pressure-volume relations in the same patient are shown in Figures 2 and 3.

**Systolic function.** Left ventricular systolic pressure decreased from 124 to 113 mm Hg (p < 0.001) after the

**Table 1.** Left Ventricular Pressure and Derived Data in 15 Patients

Case	HR (min <sup>-1</sup> )		LVEDP (mm Hg)		LVSP (mm Hg)		LVESP (mm Hg)		+dP/dt max (mm Hg/s)		-dP/dt max (mm Hg/s)		T (ms)		P <sub>B</sub> (mm Hg)	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
	1	64	65	4	5	110	106	98	86	1,182	1,126	1,240	1,226	61	50	-18
2	55	61	11	13	105	97	94	82	1,306	1,132	1,178	1,191	55	50	-13	-9
3	75	64	14	16	108	98	108	83	1,281	1,174	1,071	1,058	62	55	-9	-6
4	67	55	14	13	143	113	83	76	1,501	1,303	1,301	1,071	97	94	-38	-32
5	68	71	26	23	166	150	114	90	1,535	1,496	1,841	1,598	53	51	-15	-10
6	53	53	14	18	126	124	111	108	1,360	1,366	1,494	1,414	51	51	-11	-8
7	54	50	17	17	139	130	86	82	1,326	1,290	1,313	1,323	65	54	-12	-7
8	82	80	14	15	118	98	85	72	1,601	1,402	1,502	1,261	45	44	-6	-5
9	64	61	6	8	112	108	86	88	1,449	1,365	1,383	1,365	56	54	-12	-10
10	67	68	10	6	124	118	102	85	1,207	1,297	1,481	1,422	59	51	-11	-10
11	74	75	11	11	131	126	87	90	1,418	1,396	1,571	1,628	45	40	-8	-7
12	61	60	13	10	114	95	81	70	1,423	1,141	1,395	1,116	43	51	-1	-4
13	81	81	3	6	113	114	96	94	1,533	1,787	1,399	1,385	48	50	-13	-16
14	62	74	12	13	141	112	83	68	1,376	1,346	1,526	1,367	71	56	-20	-10
15	78	72	7	14	112	110	74	73	1,476	1,430	1,365	1,386	54	54	-10	-10
Mean	67	66	12	13	124	113	93	83	1,398	1,394	1,404	1,321	58	54	-13	-10
±SD	±9	±10	±6	±5	±17	±15	±12	±11	±123	±160	±183	±170	±13	±12	±8	±7
p Value	NS		NS		<0.001		<0.001		NS		<0.025		<0.025		<0.01	

Data are presented in the control state (C) and after the administration of diltiazem (D). HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVESP = left ventricular end-systolic pressure; LVSP = left ventricular systolic pressure; P<sub>B</sub> = extrapolated baseline pressure; T = time constant of the decrease in left ventricular pressure.

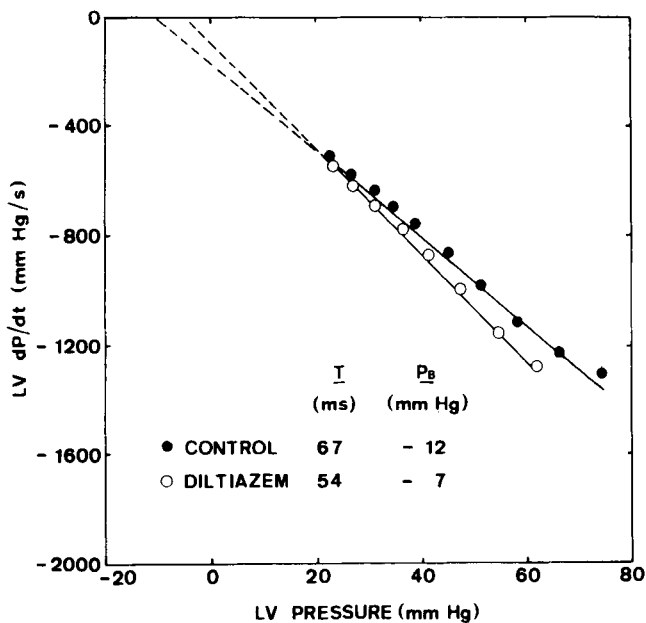
**Table 2.** Angiographic and Derived Data in 13 Patients

Case	EDV (ml/m <sup>2</sup> )		ESV (ml/m <sup>2</sup> )		EF (%)		SW (g/m <sup>2</sup> )		fp (ml/s)		TFV (ml)		V <sub>1</sub> (%)		V <sub>2</sub> (%)	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
3	116	113	52	52	55	54	83	55	575	625	119	116	63	72	37	28
4	135	125	71	70	47	44	74	60	600	750	138	126	69	72	31	28
5	102	101	41	42	60	58	110	98	775	875	122	120	65	65	35	35
6	103	106	37	40	64	62	83	82	500	675	127	130	65	68	35	32
7	140	144	61	70	56	52	107	97	700	775	137	135	61	66	39	34
8	111	122	47	55	58	55	75	82	650	850	120	125	60	73	40	27
9	94	87	31	37	67	58	44	30	500	475	99	85	54	71	45	29
10	159	161	67	65	58	60	86	78	1,175	1,050	170	177	76	76	24	24
11	108	114	45	48	59	58	87	78	675	825	118	113	60	65	40	35
12	111	107	49	49	56	54	62	55	600	675	108	109	67	67	33	33
13	99	106	44	52	55	51	77	66	400	450	115	104	43	54	57	46
14	102	108	42	42	59	62	82	81	525	950	136	145	53	63	47	37
15	87	99	43	50	51	49	57	63	400	800	93	106	48	75	52	25
Mean	113	115	48	52	57	55	79	71	621	752	123	122	60	68	40	32
±SD	±20	±20	±12	±11	±5	±5	±18	±19	±200	±172	±30	±22	±9	±6	±9	±6
p Value	NS		<0.025		<0.025		<0.01		<0.01		NS		<0.005		<0.005	

EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; fp = peak filling rate; SW = stroke work; TFV = total filling volume; V<sub>1</sub> and V<sub>2</sub> = % volume increase during the first and the second half of diastole, respectively. Other abbreviations as in Table 1.

administration of diltiazem, while end-diastolic pressure and heart rate did not change. Although end-diastolic volume remained unchanged after diltiazem administration, end-systolic volume increased from 48 to 52 ml/m<sup>2</sup> ( $p < 0.025$ )

**Figure 2.** Relation between negative dP/dt and pressure. Left ventricular (LV) pressure and negative dP/dt coordinates from the isovolumic relaxation period are shown. The time constant (T) of relaxation and the extrapolated baseline pressure (P<sub>B</sub>) are derived from the linear relation of pressure and negative dP/dt as its reciprocal of the slope and its intercept at dP/dt = 0. In this case, diltiazem decreased the time constant from 67 to 54 ms and increased the extrapolated baseline pressure from -12 to -7 mm Hg.



in association with a significant decrease in end-systolic pressure from 93 to 83 mm Hg ( $p < 0.001$ ). As a result, ejection fraction slightly decreased from 57 to 55% ( $p < 0.025$ ). Maximal positive dP/dt decreased slightly but not significantly from 1,398 to 1,349 mm Hg/s. Diltiazem lowered stroke work from 79 to 71 g/m<sup>2</sup> ( $p < 0.01$ ).

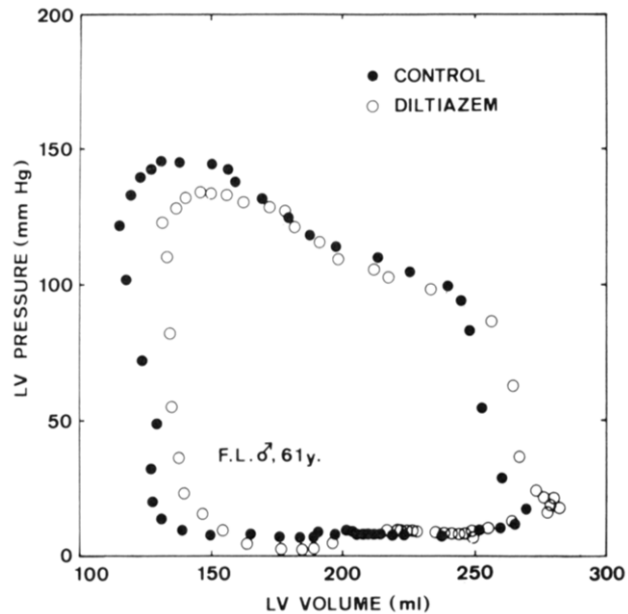
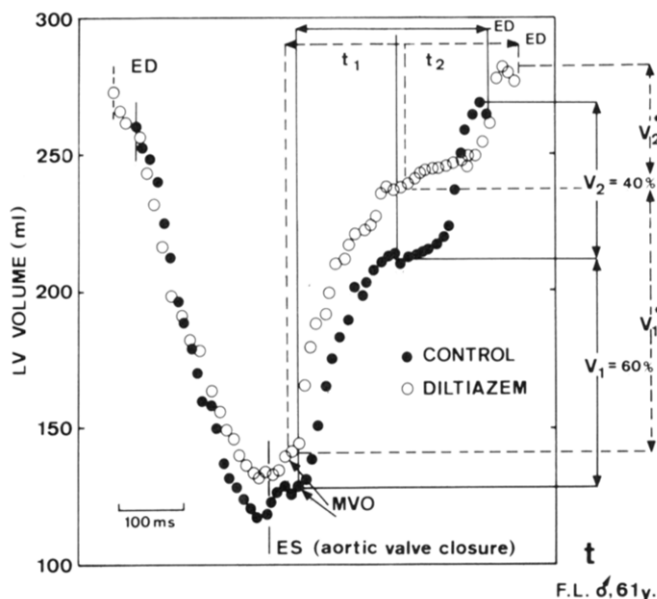
**Isovolumic relaxation.** Peak negative dP/dt decreased from -1,404 to -1,321 mm Hg/s ( $p < 0.025$ ). The time constant of left ventricular relaxation decreased from 58 to 54 ms ( $p < 0.025$ ) and extrapolated baseline pressure increased from -13 to -10 mm Hg ( $p < 0.01$ ) after the administration of diltiazem.

**Diastolic mechanics.** Diltiazem enhanced early diastolic filling. It caused an increase in peak early diastolic filling rate from 621 to 752 ml/s ( $p < 0.01$ ) and percent of filling volume during the first half of diastole from 60 to 68% ( $p < 0.005$ ). Total filling volume did not change. Although there was no significant change in either mitral opening pressure or lowest diastolic pressure after the administration of diltiazem, mid-diastolic pressure increased from 5 to 8 mm Hg ( $p < 0.01$ ). Volumes at both lowest diastolic pressure and mid-diastole were augmented from 136 to 148 ml ( $p < 0.025$ ) and from 177 to 193 ml ( $p < 0.005$ ), respectively (Table 3).

Diltiazem did not displace significantly either the position or the slope of the mean diastolic pressure-volume curve (Fig. 4). Four patients showed a slight rightward shift of the entire pressure-volume loop (Fig. 3).

## Discussion

**Systolic function.** The potency of calcium channel antagonists in causing myocardial depressant, vasodilative or



chronotropic effects may vary depending on the drug used and its dosage (9). Under conditions of the present study, our data demonstrate that diltiazem reduces afterload, but does not alter either preload or heart rate. Although left ventricular regional function was not assessed in this study, it seems that diltiazem depresses myocardial contractility because end-systolic volume increased and ejection fraction decreased despite a reduction in afterload. An increase in end-systolic volume in association with a decrease in end-systolic pressure (right downward shift of the end-systolic pressure-volume relation) also suggests depressed myocardial contractility after diltiazem administration.

It is possible that the observed negative inotropic effect of diltiazem is pronounced during intravenous injection and different from the effect of oral administration; thus, further investigation is required regarding such a difference. The dosage of diltiazem used in the study is, however, thought to be sufficient to inhibit the myocardial activation process, which may result from a reduction in the concentration of intracellular calcium ions due to interference in the transport of these ions by diltiazem. As is indicated by a reduction in stroke work, the effects of diltiazem on systolic performance apparently contribute in reducing the determinants of

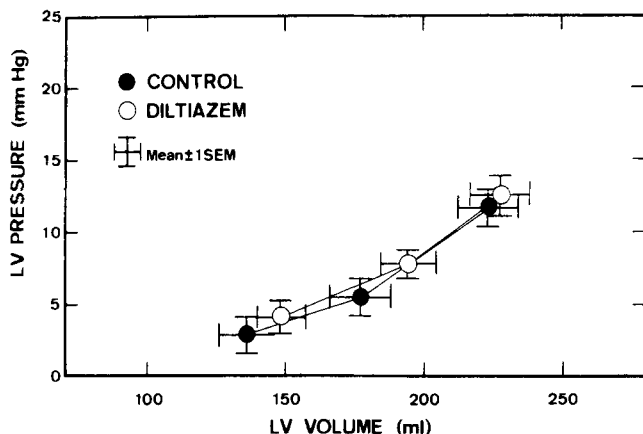
**Figure 3.** Volume-time (left) and pressure-volume (right) curves through one complete cardiac cycle for the same patient are shown. **Left,** Left ventricular (LV) filling time from the mitral valve opening (MVO) and the subsequent end-diastole (ED) were divided into the first ( $t_1$ ) and second ( $t_2$ ) half of diastole. The ratio of volume increase during each filling period to total filling volume (maximal diastolic volume minus volume at mitral valve opening) was also calculated ( $V_1$  and  $V_2$ ). After diltiazem, the peak filling rate increased from 700 to 775 ml/s and was associated with an augmentation of the percent volume increase during the first half of diastole from 60 to 68%. **Right,** The pressure-volume loop was shifted slightly rightward, reflecting depressed systolic performance after diltiazem in this patient. However, its diastolic portion was not shifted significantly. ES = end-systole.

myocardial oxygen consumption in patients with coronary artery disease. Another important determinant of myocardial oxygen consumption, peak systolic wall stress, is unlikely to change after the administration of diltiazem because the decrease in left ventricular systolic pressure may be antagonized by the increase in left ventricular end-systolic dimension.

**Isovolumic relaxation.** In conscious dogs, Karliner et al. (10) demonstrated that factors that augment the extent and

**Table 3.** Diastolic Pressure and Volume Data in 13 Patients

	Mitral Opening Pressure (mm Hg)	Lowest Diastolic Pressure (mm Hg)	Volume at Lowest Pressure (ml)	Pressure at Mid-Diastole (mm Hg)	Volume at Mid-Diastole (ml)
Control	16 ± 10	3 ± 4	136 ± 36	5 ± 8	177 ± 40
Diltiazem	18 ± 7	4 ± 4	148 ± 33	8 ± 4	193 ± 36
p Value	NS	NS	<0.025	<0.01	<0.005



**Figure 4.** Left ventricular (LV) diastolic pressure-volume relation in 13 patients. A mean diastolic pressure-volume curve was constructed. Averaged values of pressures and volumes were derived from three diastolic points: the point at the lowest diastolic pressure, at mid-diastole and at end-diastole. No significant change in either the position or the slope of the pressure-volume curve was observed after diltiazem, although the pressure-volume coordinates were shifted slightly up and to the right.

velocity of myocardial fiber shortening also enhance the rate of isovolumic left ventricular relaxation. In the intact dog heart, Gaasch et al. (11) and others (6) found a close relation between the index of the rate of isovolumic left ventricular relaxation and end-systolic loading conditions. The data from these studies suggest that interventions that provide more deformation of the ventricular shape during contraction are associated with an increment in the relaxation rate. Because diltiazem increases end-systolic volume and, thus, decreases the magnitude of deformation as the net result of interaction between negative inotropic effect and afterload reduction, slower left ventricular relaxation would be expected to result. In our study, however, diltiazem led to a decrease in the time constant of relaxation, indicating a more rapid left ventricular isovolumic pressure decay.

Recently, Brutsaert et al. (4) observed that myocardial relaxation is regulated by a complex interplay of three major determinants: load, inactivation and uniformity of distribution of loading conditions. It is possible that a lower calcium ion concentration in the region of myofibrils, which results from blockade of calcium entry by diltiazem and causes an inhibition of activation, in turn, contributes to rapid uptake of calcium by the sarcoplasmic reticulum (acceleration of inactivation) and thereby augments relaxation. The potential increase in sympathetic discharge resulting from the afterload reduction caused by diltiazem may provide another possible explanation for accelerated relaxation. Kawai et al. (12) observed a suppressive effect of calcium channel antagonists (diltiazem, verapamil and nifedipine) on sinoatrial nodal function experimentally, which is modified in the clinical setting by augmented sympathetic ac-

tivity depending on the vasodilative effect of each agent. Therefore, although contractile function was depressed and heart rate was unaltered after the administration of diltiazem in this study, it is possible that augmented sympathetic nerve activation due to afterload reduction minimizes more profound negative inotropic and masks negative chronotropic effects that are produced primarily by diltiazem administration. The decrease in the time constant of left ventricular pressure decay despite an increased end-systolic volume suggests that accelerated inactivation is a prominent effect with the dose of diltiazem used in this study.

Our data demonstrate an opposite tendency of the directions of changes in the time constant and another index of pressure decay, namely, maximal negative  $dP/dt$ . It is unlikely that the mathematical model we used is inappropriate for calculating a time constant because we observed a high correlation in the linear relation between pressures and negative  $dP/dt$ . However, previous investigators (10,13) pointed out that maximal negative  $dP/dt$  is primarily influenced by the level of aortic pressure and is not a valid measure of left ventricular relaxation during acute alterations in afterload. The decrease in maximal negative  $dP/dt$  that we observed may merely reflect an afterload reduction caused by diltiazem, and not a slower isovolumic relaxation.

*Diltiazem could accelerate relaxation by reducing myocardial ischemia in patients with coronary artery disease.* Although dynamics in coronary circulation were not evaluated in this study, previous studies (14,15) have shown that diltiazem increases coronary blood flow to the subendocardium and border ischemic zones in the presence of coronary artery stenosis in animals. Such an increase in coronary blood flow with diltiazem, in combination with a decrease in the determinants of myocardial oxygen consumption as demonstrated in this study, may improve the imbalance between myocardial oxygen supply and demand in patients with coronary artery disease and influence isovolumic pressure decay in two ways: 1) by promoting inactivation, and 2) by improving asynchronous wall motion of the left ventricle. However, the presence or absence of an impairment in the inactivation process or a regional wall motion abnormality due to a persistent ischemia in our patients is not certain.

**Diastolic filling.** There has been considerable controversy over whether or not calcium antagonists can alter the filling dynamics and contribute to improved cardiac function in patients with hypertrophic cardiomyopathy. Some investigators (16-19) showed that verapamil enhances peak early diastolic filling rate in association with a rapid left ventricular pressure decay, while others (20) demonstrated the opposite effects.

*Diltiazem also enhances early diastolic filling*, as suggested by the increases in peak filling rate and percent of filling volume during the first half of diastole. An early diastolic phenomenon such as peak filling rate could be

affected by an alteration in isovolumic relaxation; accelerated relaxation by diltiazem may contribute in part to an enhancement of early diastolic filling. In a recent comparative study on the effects of three calcium channel antagonists in conscious and ischemic dogs, Urquhart et al. (9) observed an increase in peak diastolic filling rate only after verapamil or nifedipine administration, while they did not observe such an increase with similar dosages of diltiazem. The reasons for the discrepancy between their results and ours might be related to the differences in species, protocol, relative dosage and methods for evaluation, since in their study no consistent changes in either systolic (unchanged global or regional ejection fraction) or diastolic function were produced by diltiazem.

*Left atrial driving pressure has been considered to be another important determinant of diastolic filling (7).* Instead of this pressure, we assessed mitral opening pressure, which is a reasonable alternative to the driving pressure. However, no significant change was observed in the mitral opening pressure either before or after diltiazem administration. Our data demonstrate that the extrapolated baseline pressure is increased slightly but significantly after the administration of diltiazem. Whether or not this increase in baseline pressure reflects an alteration in relaxation or filling dynamics is not certain, but it may be due to the reduction of elastic recoil observed with an increase in end-systolic volume after diltiazem (21). As described previously (22), although the extrapolated baseline pressure helps in characterizing isovolumic pressure decay, which is inadequately predicted by a time constant alone, further work will be required regarding its physiologic implications.

**Diastolic pressure-volume relation.** Despite alterations in isovolumic pressure decay and early diastolic filling, diltiazem administration does not produce a subsequent displacement of diastolic pressure-volume relations. Accelerated relaxation would be expected to displace the diastolic pressure-volume curve downward. However, the enhanced filling rate in early diastole after the administration of diltiazem moves the pressure-volume relation upward on the rest pressure-volume curve. This explains the significant increase in mid-diastolic pressure and volume after diltiazem. There appears to be no significant change in passive elasticity of the left ventricle after diltiazem since there was no alteration in the slope of the individual or mean pressure-volume curves (Fig. 4). In this study, diltiazem displaced the end-diastolic pressure-volume relation slightly rightward in four patients and, thus, it may have importantly affected their left ventricular preload.

The effects of diltiazem observed in this study might have been influenced by the medications taken by the patients before entering the study, especially when these had been withdrawn only 12 hours before the study. No significantly different responses to diltiazem administration, however, were observed among patients in whom cardiovascular

medications such as beta-adrenergic blocking agents or calcium channel antagonists had been withdrawn 12 hours before the study and those who were not taking these medications or in whom they had been withdrawn 24 hours before the study.

*In summary,* in patients with coronary artery disease, diltiazem inhibits myocardial activation but accelerates its inactivation processes. The former may result in depressed contractility and the latter in more rapid relaxation of the left ventricle in association with enhanced early diastolic filling. These alterations are not accompanied by a change in the passive diastolic properties of the left ventricle.

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