Effects of Diltiazem and Nitroglycerin on Left Ventricular Diastolic Properties in Patients with Coronary Artery Disease

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SUMMARY

To determine the effects of diltiazem (DTZ) and nitroglycerin (NTG) on left ventricular (LV) diastolic relaxation and filling in patients with coronary artery disease (CADpts), LV graphy and time constant (Tc) of LV isovolumic pressure decay were studied before and 5 min after intravenous DTZ (10 mg) in 16 CADpts and sublingual NTG (0.3 mg) in 11 CADpts. Diastolic regional ventricular filling dynamics were quantitated by segmental area-time curves during early-, mid- and late-filling periods. After NTG, LV systolic pressure (LVSP), end-diastolic pressure (EDP) and end-diastolic volume (EDV) decreased. Early-filling rate (EFR) decreased (165 ± 82 to 122 ± 61 ml/sec/m^2) due to a decrease in the regional early-filling rate in the normokinetic area and late-filling rate (LFR) increased (95 ± 38 to 145 ± 45 ml/sec/m^2), while LV peak positive dp/dt, peak LVSP/end-systolic volume (ESV) ratio, Tc and mid-filling rate (MFR) were unchanged. After DTZ, LVSP decreased and EDV increased. EFR increased. EFR increased (127 ± 54 to 166 ± 60 ml/sec/m^2) due to an enhanced regional early-filling rate in the mildly hypokinetic area, while EDP, LV peak positive dp/dt, peak LVSP/ESV ratio, Tc, MFR and LFR were unchanged. From these results, it was postulated that NTG caused a decrease in LV early filling and an increase in LV late filling, probably due to LV preload reduction. In contrast, DTZ caused significant improvement of LV early filling particularly in the mild hypokinetic area. Thus, DTZ but not NTG was able to relieve local myocardial dysfunction secondary to a stenosed coronary artery during the filling

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period, resulting in clinical improvement in CADpts.

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DILTIAZEM, one of the calcium slow channel blocking agents, has been shown to be effective in the relief of coronary spasm in patients with variant angina.[1] Even in patients with exertional angina, diltiazem has been shown to reduce the frequency of anginal attacks and to improve exercise tolerance.[2] These effects were mainly due to coronary vasodilation[3] and reduction in myocardial oxygen demand.[4] Recently, early detection of impaired diastolic properties have been emphasized in the evaluation of ventricular function in patients with coronary artery disease.[5] The diastolic abnormalities in patients with coronary artery disease and hypertrophic cardiomyopathy have been shown to be favorably modified by the administration of calcium channel blocking agents.[6-8] Whether diltiazem alters left ventricular relaxation and diastolic filling in patients with coronary artery disease, however, has not been investigated using simultaneous measurement of left ventricular pressure and volume. This study was designed to assess the acute hemodynamic effects of diltiazem on left ventricular relaxation and diastolic filling in patients with coronary artery disease and moderately depressed left ventricular function. To appreciate more fully the actions of this agent, the effects of nitroglycerin on diastolic properties were compared with those of diltiazem.

Patients and Methods

This study included 27 patients with coronary artery disease who underwent diagnostic cardiac catheterization. All patients had clinical and electrocardiographic evidence of myocardial infarction which had occurred within 6 months before study. These patients were in sinus rhythm, and patients with hypertension or valvular heart disease were excluded from this study. All cardioactive drugs were discontinued for at least 24 hours before the start of this observation. Complete informed consent was obtained from each patient and no unfavorable complication occurred during this study. We investigated 16 patients before and after the administration of diltiazem and 11 patients before and after that of nitroglycerin. The details of the 2 groups are listed in Table I.

Study protocol:

Cardiac catheterization was performed via the femoral approach with

Table I. Summary of Clinical Data

	Nitroglycerin	Diltiazem
Patient	11	16
Age (years)	54±8	54±9
Sex	9M, 2F	14M, 2F
CAD (number of patients)		
1V	8(6LAD, 2RCA)	10(8LAD, 1RCA, 1CX)
2V	3(2LAD+RCA, 1LAD+CX)	4(4LAD+CX)
3V	0	2
Previous MI (number of patients)		
Inferior	3	4
Anterolateral	8	12

Values represent mean±SD.

Abbreviations: MI=myocardial infarction; V=coronary vessel with luminal stenosis more than 75%; LAD=left anterior descending artery; RCA=right coronary artery; CX=circumflex artery.

the patient in a fasting state without premedication. Left ventricular pressure was recorded using a high fidelity micromanometer-tipped catheter (Millar Instrument). The micromanometer system was calibrated electronically against a mercury manometer before insertion and after withdrawal of the catheter. Left ventriculography was performed with single plane 35 mm cineangiography at 60 frames/sec in the right anterior oblique projection (Philips Poly-diagnost C). A bolus of 35 ml of Iodamide Sodium Maglumine (Conraxin-H) was injected via the 8F pigtail catheter at a rate of 12 ml/sec with cine film exposed at 60 frames/sec. During cineventriculography study, high fidelity left ventricular pressure and peak positive dp/dt were calculated by using a computer system (Philips ACS). Control left ventriculography with simultaneous measurement of left ventricular pressure was initially performed. After a pause of 30 min to allow for dissipation of the hemodynamic and myocardial depressant effects of contrast agents, simultaneous hemodynamic and angiographic studies were obtained in 16 patients with coronary artery disease 10 min after intravenous administration of 10 mg infused over a period of 5 min and in 11 patients with coronary artery disease 5 min after sublingual administration of 0.3 mg nitroglycerin. Coronary arteriography was then performed in all patients using the Judkins technique.

Measurements and computations:

For evaluation of left ventricular function, cine films were projected to a video camera and ventricular silhouettes were outlined with a light pen on a video screen. A computer system (Philips LVV100) calculated volumes applying Simpson's rule. The patients with both premature and post pre-

mature beats during and after left ventriculography were excluded from this study. All analyses were performed within the first three normal sinus beats following the commencement of injection of contrast agents, when the effects of contrast agents on myocardial function are negligible.[9] The angiographic ejection fraction was calculated according to the standard formula.[10] Volume data were corrected for the body surface area. For the purpose of regional wall motion analysis, left ventricular silhouette was divided into 8 segments, as we previously reported in detail.[11] The long axis extended from the midpoint of the aortic orifice to the apex, and three vertical lines to the long axis at quarter-length intervals divided the left ventricular silhouette into 8 segments. Each regional area was calculated by the computer system at 8 positions around the left ventricular contours, that is, anterobasal (segments 2 and 3), apical (segments 4 and 5), inferior (segments 6 and 7) and inferobasal (segment 8). Segmental wall contraction was calculated as follows: %segmental wall contraction=Ad−As/Ad×100 (Ad=the area of each segment in end-diastole, As=the area of each segment in end-systole). The normal values for %segmental wall contraction were then used to define abnormally contracting segments.[11] The mild hypokinetic areas and severe hypokinetic areas were defined as those where the %segmental wall contractions were more than two standard deviations and four standard deviations lower than the mean value of normally contracting left ventricle, respectively.

Global ventricular filling was quantitated with frame-by-frame angiographic volumes from the end of the isovolumic relaxation period to end-diastole. A three point moving average filter was applied. The end of the isovolumic relaxation period was noted as the point where pressure declined to the level of the left ventricular end-diastolic pressure.[12] The time from the end of the isovolumic relaxation period to end-diastole is referred to the left ventricular filling time. This filling time was divided into three equal intervals. The mean filling rates of each interval were calculated before and after administration of drugs. These filling rates were termed early-filling, mid-filling and late-filling rate.

Regional ventricular filling was quantitated by the velocity of the regional outward wall motion during the filling period which was determined by examining the frame-by-frame angiographic area of each segment against time. Using the same time references of global ventricular filling, the mean velocities of regional outward wall motion during the early-, mid- and late-filling periods were calculated in each segment and termed the regional early-filling rate, regional mid-filling rate and regional late-filling rate, respectively. There are known limitations of all reference systems for quantitating regional

wall motion analysis. Therefore, for assessing regional outward wall motion characteristics, segments 1 and 8 adjacent to the valves were excluded from analysis.

The index of left ventricular relaxation, time constant (Tc), was calculated with a microcomputer (SANYO MBC 220) from the point of the peak negative dp/dt to the time at which pressure decreased to the level of the left ventricular end-diastolic pressure of the preceding beat.[12] Tc was derived from an exponential curve fitting with a variable asymptote.[13] Thus, $P(t)=ae^{bt}+c$, where P(t)=pressure at time, t=time after peak negative dp/dt and c=the asymptote. $Tc=-1/b$.

Statistical methods:

Statistical analysis of the data was performed with Student's t-test for paired and unpaired analysis. Values were expressed as mean±SD and $p<0.05$ was considered significant.

Results

1. Global left ventricular hemodynamics (Table II)

Hemodynamic results after administration of diltiazem and nitroglycerin are shown in Table II. Heart rate remained unchanged after diltiazem and increased from a control value of 68±9 to 74±11 beats/min ($p<0.05$) after nitroglycerin. Both diltiazem and nitroglycerin administration were associated with decreases in left ventricular systolic pressure from 130±19 to 125±18 mmHg (diltiazem) and from 130±16 to 112±15 mmHg (nitroglycerin). Nitroglycerin produced a decrease in left ventricular minimal pressure (6±4 to 3±3 mmHg), left ventricular end-diastolic pressure (19±8 to 12±6 mmHg), end-diastolic volume (108±29 to 95±34 ml/m²) and end-systolic volume (55±25 to 49±29 ml/m²). After diltiazem, end-diastolic volume increased slightly but significantly from 96±25 to 101±26 ml/m² ($p<0.05$) and end-systolic volume tended to be lower, resulting in an increase of ejection fraction (53±11 to 57±11%, $p<0.01$). There were no changes in left ventricular minimal pressure and end-diastolic pressure after diltiazem. Left ventricular peak positive dp/dt, peak left ventricular systolic pressure/end-systolic volume ratio and Tc remained unchanged following either diltiazem or nitroglycerin administration.

2. Left ventricular global filling dynamics (Table II, Figs. 1 and 2)

Representative left ventricular filling curves obtained at rest and after administration of nitroglycerin are presented in Fig. 1. After nitroglycerin, the left ventricular diastolic early-filling rate decreased from 165±82 to 122 ±61 ml/sec/m² and the late-filling rate increased from 87±39 to 141±39 ml/

Table II. Effect of Nitroglycerin and Diltiazem on Left Ventricular Hemodynamics

	Nitroglycerin (n=11)		Diltiazem (n=16)	
	before	after	before	after
HR (beats/min)	68±9	74±11*	69±9	68±8
LVSP (mmHg)	130±16	112±15***	130±19	125±13*
LVPmin (mmHg)	6±4	3±3***	8±5	8±5
LVEDP (mmHg)	19±8	12±6***	19±9	20±8
EDV (ml/m²)	108±29	95±35***	96±25	101±26*
ESV (ml/m²)	55±25	49±29*	44±17	42±18
EF (%)	53±13	54±14	53±11	57±11*
LV(+)dp/dt (mmHg/sec)	1613±326	1583±383	1328±269	1357±253
peak LVSP/ESV	3.0±1.4	3.2±1.6	3.5±1.6	3.6±1.7
Tc (msec)	90±24	85±17	75±12	73±13
EFR (ml/sec/m²)	165±82	122±61*	127±54	166±60***
MFR (ml/sec/m²)	84±62	79±43	79±52	87±59
LFR (ml/sec/m²)	87±39	141±39	120±53	126±50

Abbreviations: HR=heart rate; LVSP=left ventricular systolic pressure; LVPmin=left ventricular minimal pressure; LVEDP=left ventricular end-diastolic pressure; EDV=end-diastolic volume; ESV=end-systolic volume; EF=ejection fraction; Tc=time constant of left ventricular pressure decay; peak LVSP/ESV=peak left ventricular systolic pressure/end-systolic volume ratio; EFR=early-filling rate; MFR=mid-filling rate; LFR=late-filling rate. Values represent mean± SD.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$: vs control period.

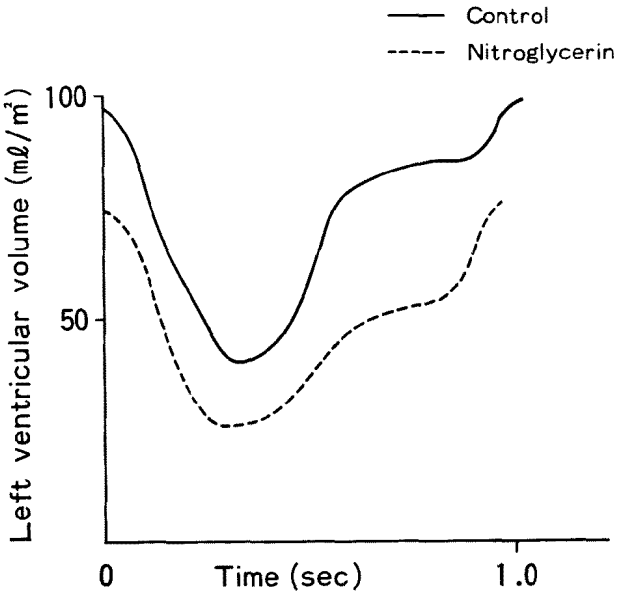

Fig. 1. Volume-time curves obtained at rest during control conditions and after administration of nitroglycerin. Nitroglycerin produced a decrease in early diastolic filling and an increase in late diastolic filling.

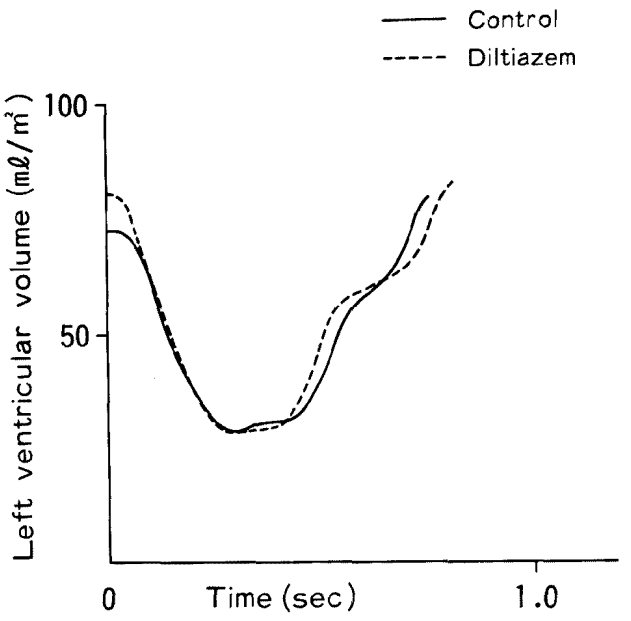

Fig. 2. Volume-time curves obtained at rest during control conditions and after administration of diltiazem. Diltiazem caused an increase in early diastolic filling.

Table III. Effect of Nitroglycerin on Regional Filling Dynamics

	before	after
REFR ($mm^2/sec/m^2$)		
normokinetic areas (12 anterior, 12 apical, 12 inferior)	974±568	756±544***
mild hypokinetic areas (6 anterior, 4 apical, 7 inferior)	472±341	328±327
severe hypokinetic areas (4 anterior, 6 apical, 3 inferior)	120±294	88±149
RLFR ($mm^2/sec/m^2$)		
normokinetic areas (12 anterior, 12 apical, 12 inferior)	479±331	628±393*
mild hypokinetic areas (6 anterior, 4 apical, 7 inferior)	329±284	614±233**
severe hypokinetic areas (4 anterior, 6 apical, 3 inferior)	474±293	767±521*

Abbreviations: REFR=regional early-filling rate; RLFR=regional late-filling rate.
Values represent mean±SD.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$: vs control period.

sec/m^2, while the mid-filling rate was unchanged. Examples of left ventricular filling curves obtained at rest and after diltiazem are presented in Fig. 2. After diltiazem the early-filling rate increased from 127±54 to 166±60 $ml/sec/m^2$, while the mid-filling rate and late-filling rate remained unchanged.

3. Left ventricular regional filling dynamics (Tables III and IV)

Regional filling dynamics after administration of nitroglycerin and

Table IV. Effect of Diltiazem on Regional Filling Dynamics

	before	after
REFR ($mm^2/sec/m^2$)		
normokinetic areas (20 anterior, 12 apical, 16 inferior)	570±382	584±453
mild hypokinetic areas (12 anterior, 8 apical, 11 inferior)	407±321	641±513**
severe hypokinetic areas (3 anterior, 12 apical, 2 inferior)	362±369	509±699
RLFR ($mm^2/sec/m^2$)		
normokinetic areas (20 anterior, 12 apical, 16 inferior)	653±389	640±323
mild hypokinetic areas (12 anterior, 8 apical, 11 inferior)	656±411	538±333
severe hypokinetic areas (3 anterior, 12 apical, 2 inferior)	320±333	390±472

Abbreviations: REFR=regional early-filling rate; RLFR=regional late-filling rate.
Values represent mean±SD.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$: vs control period.

diltiazem are shown in Tables III and IV. After nitroglycerin, the regional early-filling rate in normokinetics areas (12 anterior, 12 apical and 12 inferior) decreased significantly from 974±568 to 756±544 $mm^2/sec/m^2$ ($p<0.001$) and those in mild hypokinetic areas (6 anterior, 4 apical and 7 inferior) and severe hypokinetic areas (4 anterior, 6 apical and 3 inferior) also decreased, but not significantly. The regional late-filling rate increased significantly in all areas. On the contrary, after diltiazem, the regional early-filling rate in mild hypokinetic areas (12 anterior, 8 apical and 11 inferior) increased from 407±321 to 641±513 $mm^2/sec/m^2$. Those in normokinetic areas (20 anterior, 12 apical and 16 inferior) and severe hypokinetic areas (3 anterior, 12 apical and 2 inferior) increased, but not significantly. The regional late-filling rate in all areas remained unchanged.

Discussion

Recently, the study of the diastolic phase in various types of heart disease has been considered to be of special importance in the assessment of left ventricular function.[3] Diastolic filling rates obtained by radionuclide methods have been reported for coronary artery disease patients at rest and during exercise.[14),15] Hammermeister and Warbasse have shown a reduced peak filling rate at rest in a group of patients with coronary artery disease using contrast angiography.[16] There are important differences between contrast left ventriculography and radionuclide ventriculography. Filling rates determined by the radionuclide method are not true volume rates but instead, quantitate filling by changes in the number of end-diastolic counts per unit of time. Furthermore, since the diastolic period in the radionuclide studies include the isovolumic relaxation period, this may result in a false reduction

in left ventricular filling during the first one third of the diastolic phase.

The result of this study indicated that, after nitroglycerin, left ventricular systolic pressure, left ventricular minimal pressure, left ventricular end-diastolic pressure, end-diastolic volume and end-systolic volume decreased. These actions of nitroglycerin suggest an effect of systemic venous vasodilation and, consequently, a reduction in left and right ventricular preload. These findings are consistent with prior observations which have shown that a downward displacement of the left ventricular diastolic pressure-volume relation occurs during vasodilator therapy.[17),18)] Peak positive dp/dt and peak left ventricular systolic pressure/end-systolic volume ratio, indexes of contractility,[19)] remained unchanged. Furthermore Tc, an index of relaxation, was not significantly altered, while the early-filling rate decreased, particularly in the normokinetic area, and the late-filling rate increased. Thus, changes in contraction and relaxation do not appear to constitute the major explanation for the decrease in the early-filling rate and increase in the late-filling rate observed after nitroglycerin. Further, changes in regional filling rates occurred in the normokinetic area perfused by a normal coronary artery rather than in the mild or severe hypokinetic area. Therefore, the observed filling dynamics after nitroglycerin may result not from changes in active contraction and relaxation, but from changes in loading conditions, that is, preload reduction. And increase in the late-filling rate seems to be a compensatory mechanism.

We also demonstrated that, after diltiazem, left ventricular systolic pressure decreased slightly but significantly, and there was a small but significant increase in end-diastolic volume, resulting in an increase in ejection fraction. Although peak positive dp/dt, peak left ventricular systolic pressure/end-systolic volume ratio and Tc were unaltered, diltiazem increased the early-filling rate. Further, we observed a definite improvement of regional filling dynamics in the mild hypokinetic area perfused by a stenosed coronary artery, although there was no significant effect of diltiazem in normokinetic and severe hypokinetic areas. This recovery of regional filling dynamics in the mild hypokinetic area improved global early diastolic filling, resulting in an increase in filling volume. Therefore, an increase in filling volume could derive from the effects of diltiazem on left ventricular filling, producing an increase in end-diastolic volume.

It cannot be ascertained from our study whether diltiazem had no salutary effect on global relaxation or whether such an effect on global relaxation was present but was masked by other actions of the drug. Since the time constant of relaxation also depends on left ventricular loading conditions,[20),21)] Tc may be modulated by diltiazem-induced changes in end-

systolic pressure and end-diastolic volume. However, as shown in our study, the changes in loading condition after diltiazem appeared to be minor. Furthermore, some investigators reported that in patients with coronary artery disease the rate of decrease in isovolumic pressure, an index of global relaxation, may underestimate the severity of a local impairment in relaxation.[22] Therefore, the effects of a therapeutic intervention on left ventricular diastolic properties should have been estimated by using an analysis of regional relaxation.

Although the precise direct effect of diltiazem on left ventricular filling dynamics cannot be definitely ascertained from these preparations, several mechanisms may explain the improvement in left ventricular diastolic early filling after diltiazem. The most important indirect effect of a calcium channel blocking agent is a baroreceptor-mediated reflex which increases beta adrenergic tone in response to the systemic vasodilation produced by these drugs, resulting in both an increase in heart rate and augumentation of myocardial contractility.[23] However, the findings of our study do not appear to support a baroreceptor-mediated positive inotropic effect, because there were no significant changes in peak positive dp/dt, peak left ventricular systolic pressure/end-systolic volume ratio, heart rate and end-systolic volume after diltiazem.

Animal studies demonstrated that diltiazem has potent effects on the coronary circulation and results in increased coronary blood flow,[4] thereby improving ischemia-induced changes in cardiac muscle inactivation and compliance. Furthermore, myocardial relaxation and early diastolic filling might be thought to be partly due to the ability of the sarcoplasmic reticulum to take up calcium.[24] Several studies suggest that calcium slow channel blocking agents alter diastolic filling properties of the left ventricle in patients with cardiomyopathy.[6],[7] Therefore, it is possible that the observed improvement in impaired left ventricular filling during treatment with diltiazem may be related in part to a reduction of calcium influx via the slow channel.

In summary, we studied the effect of diltiazem and nitroglycerin, antianginal agents, on left ventricular relaxation and filling in patients with coronary artery disease. Nitroglycerin administration caused a decrease in early filling, particularly in the normokinetic area, and a compensatory increase in late filling. These effects may be due to left ventricular preload reduction. To the contrary, diltiazem administration caused significant improvement of left ventricular early filling in the mild hypokinetic area. The improvement in filling dynamics observed after diltiazem is unlikely to be due solely to left ventricular systolic unloading. The relief of subendocardial ischemia related to coronary vasodilation or the prevention of calcium

influx may possibly contribute to the beneficial effects of diltiazem on left ventricular filling. Thus, diltiazem could relieve local myocardial dysfunction secondary to a stenosed coronary artery during the left ventricular filling period, resulting in clinical improvement in patients with coronary artery disease.

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