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Comparison of the Effects of Nitroprusside and Nifedipine on Diastolic Properties in Patients With Hypertrophic Cardiomyopathy: Altered Left Ventricular Loading or Improved Muscle Inactivation?

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The calcium channel blocking agent, nifedipine, has been shown to improve indexes of left ventricular relaxation, diastolic filling and compliance in patients with hypertrophic cardiomyopathy. The mechanism of action of nifedipine on diastolic properties in patients with hypertrophic cardiomyopathy is unclear and could result from an improvement in myocardial inactivation or from systemic vasodilation and left ventricular unloading. To distinguish between these mechanisms, the effects of nifedipine and the vasodilator nitroprusside on left ventricular diastolic properties were compared in 10 patients with nonobstructive hypertrophic cardiomyopathy using simultaneous micromanometer left ventricular pressure and echocardiographic measurements.

Left ventricular peak systolic pressure was comparable during nitroprusside infusion (132 ± 38 mm Hg) and after nifedipine (132 ± 32 mm Hg). During nitroprusside infusion, the decrease in left ventricular end-diastolic pressure (22 ± 11 to 17 ± 11 mm Hg, $p < 0.05$) was associated with a decrease in left ventricular end-diastolic dimension. In contrast, the decrease in left ventricular end-diastolic pressure after nifedipine (22 ± 11 to 18 ± 10 mm Hg, $p < 0.05$) was associated with no reduction of left ventricular end-diastolic dimensions, suggesting an increase in left ventricular distensibility. Compared with nitroprusside, nifedipine was associated with less prolongation of the left ventricular isovolumic relaxation time and less depression of the peak left ventricular posterior wall thinning rate and peak left ventricular internal dimension filling rate.

These data suggest that the effects of the calcium channel blocker, nifedipine, on diastolic mechanics in hypertrophic cardiomyopathy result not only from systemic vasodilation but also from improved cardiac muscle inactivation.

Prolonged left ventricular isovolumic relaxation, impaired left ventricular filling and diminished left ventricular compliance have been described in patients with hypertrophic cardiomyopathy (1–5). The diastolic abnormalities have been shown to be favorably modified by the administration of calcium channel blocking agents using computer analysis of M-mode echocardiograms (6–8) and gated radionuclide angiograms (9). These observations provide evidence that the symptomatic relief of patients with hypertrophic cardiomyopathy during calcium channel blocking therapy (10–12) may be related to an improvement in left ventricular relaxation and compliance. Improved left ventricular relaxation can result from either changes in ventricular loading or cardiac muscle inactivation (13,14). Alterations in left ventricular compliance can result from alteration of pericardial and right ventricular constraints (15–17) or changed muscle tone (18,19). The beneficial effect of calcium channel blocking agents on diastolic properties in patients with hypertrophic cardiomyopathy could, therefore, be related either to an effect of the calcium channel blocking agent on myocardial inactivation and resting tone or to systemic vasodilation, which alters left ventricular loading during systole and left ventricular external constraints during diastole. To distinguish between these mechanisms, we compared the effects of nitroprusside and nifedipine on left ventricular

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relaxation and filling patterns and diastolic compliance in 10 patients with nonobstructive hypertrophic cardiomyopathy.

Methods

Study group. We studied 10 patients with nonobstructive hypertrophic cardiomyopathy. The diagnosis was based on typical clinical, echocardiographic and angiographic criteria (5). Four patients (Cases 2,3,4 and 6) developed an intraventricular pressure gradient on provocation (Valsalva or postextrasystolic potentiation), and six patients had no evidence of a gradient at the time of the study. Nine patients were in sinus rhythm, and one patient (Case 3) had a paced rhythm. All medications were withheld 48 hours before the study. Each patient gave informed written consent in accordance with the Brigham and Women's Hospital Human Subjects Committee, and no complications occurred as a result of the study. Selective coronary arteriography did not reveal significant coronary artery stenoses in any of the patients studied.

Hemodynamic and echocardiographic studies. Cardiac catheterization was carried out using the brachial or femoral artery approach. Systemic arterial pressure, pulmonary artery wedge pressure and right atrial pressure were measured with a fluid-filled catheter system and strain gauge transducers and referenced to atmosphere at the mid-chest level (20). Left ventricular pressure was recorded with a micromanometer tip catheter (Millar Instruments) calibrated against a mercury reference and matched simultaneously against luminal pressure. Cardiac output was measured by the Fick method.

Echocardiograms of the mitral valve and left ventricular cavity were recorded with an Ekoline 20 system (Smith-Kline Instruments) or a Mark III system (Advanced Technology Laboratories) using a 2.25 MHz transducer. Echocardiograms, phonocardiograms of aortic valve closure and single lead electrocardiograms were recorded on an Irex continutrace 101 multiple channel recorder or a Honeywell 1858 fiberoptic recorder at a paper speed of 100 mm/s. The echocardiograms were obtained simultaneously with hemodynamic measurements. The simultaneous recording of electronic markers and the electrocardiogram on both echocardiographic dimension and left ventricular pressure recordings permitted the simultaneous matching of pressure and dimension data during subsequent data digitization.

Hemodynamic and echocardiographic studies were obtained during the control period, during the intravenous administration of nitroprusside and 20 minutes after sublingual administration of 10 mg nifedipine. Control values were reestablished 15 minutes after the administration of nitroprusside, and repeat hemodynamic measurements were obtained. If control conditions could not be reestablished after the administration of nitroprusside, the patient was excluded from the study.

Data analysis and statistics. Data were analyzed for three consecutive beats in control conditions, during the infusion of nitroprusside and after administration of nifedipine. Quiet respiration was maintained throughout all recordings to minimize respiratory fluctuations.

Left ventricular micromanometer pressure was digitized at 5 ms intervals from the peak of the R wave of the electrocardiogram to the peak of the R wave of the subsequent beat, using a hand-controlled cursor (Graph Pen, SAC, Southport, Connecticut), and data were processed by a Tektronix 4051 computer system. A sixth order polynomial curve was fitted to the digitized left ventricular pressure data. The analysis was started at the left ventricular pressure at peak negative first derivative ($-dP/dt$) and stopped at the left ventricular pressure that was equal to the peak of the V wave of a simultaneously recorded pulmonary artery wedge pressure tracing. A polynomial (sixth order) curve fit (correlation coefficient [r] > 0.99) was performed because of poor agreement ($r < 0.99$) between true data points and points calculated from an exponential fit with non-zero reference pressure (21,22). Similar deviations of isovolumic left ventricular relaxation pressure from a simple monoexponential decay have been reported (23,24). A sixth order polynomial curve fit was chosen as it consistently provided a correlation coefficient higher than 0.99. On a representative example (Case 3, Control T_2), a linear curve fit yielded a correlation coefficient of 0.98 and an exponential curve fit with non-zero asymptote yielded a correlation coefficient of 0.96. A correlation coefficient of 0.99 was observed from a polynomial fit of at least the third order. A sixth order polynomial curve fit provided additional accuracy and avoided variability in the closeness of the fit. The contribution of higher order (> sixth) polynomials to the closeness of the fit was negligible. A "time constant" of left ventricular pressure decay was calculated from the sixth order polynomial as the time needed for the pressure to decrease to 1/e of its value at peak negative dP/dt.

Left ventricular septal wall endocardium and posterior wall endocardium and epicardium were digitized at 5 ms intervals from the peak of the R wave on the electrocardiogram to the peak of the R wave of the subsequent beat to provide instantaneous data on left ventricular posterior wall thickness and internal dimension, and a polynomial (sixth order) was fit to the calculated left ventricular internal dimension data and posterior wall thickness data (8). On the basis of goodness of fit, a sixth order polynomial fit was preferred over a five point parabolic fit for determination of first and second derivatives used to calculate peak left ventricular internal dimension filling (dD_{LV}/dt [mm/s]) or thinning (dPW/dt [mm/s]) rates and the extent of rapid filling ($\triangle D_{LV}$[mm]) or thinning ($\triangle$PW[mm]). Excellent agreement was always observed between the true data points and the points calculated from the polynomial ($r > 0.99$).

The percent fractional shortening of the left ventricular

internal dimension (%FS) was calculated from the following formula: (EDD − ESD)/EDD × 100, where EDD = left ventricular end-diastolic dimension (mm) and ESD = left ventricular end-systolic dimension (mm). Left ventricular isovolumic relaxation time (IVRT [ms]) was calculated as the interval between the first high frequency component of the aortic valve closure sound (A_2) and the opening of the mitral valve leaflets on the echocardiogram (4,6,8). In our laboratory, control values (mean ± standard deviation) of isovolumic relaxation time, peak left ventricular internal dimension filling rate and peak left ventricular posterior wall thinning rate are 60 ± 7, 118 ± 7 and 82 ± 11 mm/s, respectively. Mean isovolumic left ventricular pressure decay rate (△P/IVRT [mm Hg/ms]) was obtained by dividing the isovolumic pressure drop (left ventricular pressure at aortic valve closure minus pulmonary artery wedge pressure at peak V wave) by the left ventricular isovolumic relaxation time.

Left ventricular pressure-internal dimension relations were obtained by computer matching of corresponding left ventricular pressure and internal dimension data points. All data are reported as the mean ± standard deviation and statistical significance (probability [p] < 0.05) was determined using a multiple comparison analysis (Bonferroni method) (25). The interobserver and intraobserver variability coefficients for isovolumic relaxation time, peak internal dimension filling rate and peak posterior wall thinning rate were less than 5%.

Results

Left ventricular and systemic hemodynamics. Individual hemodynamic data obtained during control conditions, during the administration of nitroprusside and after the administration of nifedipine are shown in Table 1. Left ventricular peak systolic pressure was comparable during nitroprusside infusion (132 ± 38 mm Hg) and after nifedipine administration (132 ± 32 mm Hg). Both nitroprusside and nifedipine administration were associated with an increase in heart rate relative to control. Both nifedipine and nitroprusside caused a significant decrease in left ventricular end-diastolic pressure (from 22 ± 11 to 17 ± 11 mm Hg [nitroprusside] and from 22 ± 11 to 18 ± 10 mm Hg [nifedipine]). Mean right atrial pressure was significantly lower only during nitroprusside infusion (7 ± 6 to 5 ± 5 mm Hg) and cardiac index was significantly higher only after nifedipine administration (3.5 ± 1.4 to 4.2 ± 1.7 liters/min per m^2). The time constant T of left ventricular relaxation was significantly reduced during nitroprusside infusion and after nifedipine administration relative to the control period.

Diastolic left ventricular pressure wave forms. In three patients (Cases 1,2 and 3, Table 1), an abnormal early diastolic left ventricular pressure waveform was observed during control conditions with an absent rapid filling phase and a continuous pressure fall into mid-diastole, suggestive of prolonged left ventricular inactivation (Fig. 1). In two patients (Cases 5 and 9), similar waveforms were observed in the postextrasystolic beats under control conditions. These waveforms have been described previously, both at rest (7) and during exercise (26). The administration of nifedipine restored this abnormal pressure waveform to a configuration with a rapid filling phase in early diastole and a continuous pressure rise in mid-diastole.

Echocardiographic assessment of left ventricular function. Echocardiographic data obtained in control conditions, during the administration of nitroprusside and after the administration of nifedipine are shown in Table 2. For the group, the left ventricular end-diastolic internal dimension was significantly smaller during nitroprusside infusion with respect to both control conditions and nifedipine administration. Under equal systolic loading conditions, left ventricular end-systolic internal dimension was comparable during nitroprusside infusion and after nifedipine administration, whereas the percent fractional shortening was significantly higher after nifedipine administration compared with that after nitroprusside. The isovolumic left ventricular relaxation time was significantly shorter after nifedipine (84 ± 25 ms) than after nitroprusside (95 ± 26 ms) despite comparable systolic loading. The mean isovolumic left ventricular pressure decay rate (△P/IVRT) remained unaltered by either nitroprusside infusion or nifedipine administration. Nifedipine was associated with significant improvement in peak posterior wall thinning rate (dPW/dt), peak left ventricular internal dimension filling rate (dD_{LV}/dt), total left ventricular internal dimension change during diastole ($\triangle D_{LV}$) and total left ventricular posterior wall diastolic thickness change (△PW), with respect to both control values and the values obtained during nitroprusside infusion.

The decrease in left ventricular end-diastolic pressure during nitroprusside infusion was accompanied by a decrease in left ventricular end-diastolic internal dimension (45.5 ± 11.0 to 41.8 ± 12.0 mm, $p < 0.05$). After the administration of nifedipine, this decrease in pressure was not associated with a reduction in internal dimension (Table 2).

The mechanism of the decrease in left ventricular end-diastolic pressure was further analyzed by examination of plots of the left ventricular pressure-internal dimension relation. Figure 2 shows complete left ventricular pressure-internal dimension loops obtained in control conditions, during the infusion of nitroprusside and after the administration of nifedipine (Case 2). After nifedipine, the area enclosed by the pressure-internal dimension loop is larger than that during nitroprusside infusion or control conditions, suggesting an effect of nifedipine on both diastolic compliance and systolic loading conditions.

Table 1. Left Ventricular and Systemic Hemodynamics in 10 Patients With Nonobstructive Hypertrophic Cardiomyopathy

Case	Age (yr) & Sex	HR (beats/min)			LVPSP (mm Hg)			MAP (mm Hg)			LVEDP (mm Hg)			MRAP (mm Hg)			CI (liters/min per m^2)			SVR (dynes·s·cm^{-5})			T (ms)			ΔP/IVRT (mm Hg/ms)		
		C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif
1	17M	73	97	82	100	88	96	86	73	82	11	7	11	5	2	4	3.3	3.1	4.7	1080	997	726	61	48	47	0.43	0.50	0.58
2	64F	96	82	90	160	103	139	115	75	98	15	7	11	5	5	8	2.7	2.6	3.0	2316	1555	1714	38	27	30	1.11	0.77	1.14
3	82F	76	77	80	161	149	147	105	97	93	17	9	10	7	5	5	1.7	1.7	2.3	3267	2967	2200	75	59	48	0.62	0.58	0.79
4	48F	105	115	111	184	160	166	140	128	130	37	30	32	11	7	8	4.7	5.5	5.5	1323	1060	1069	50	48	45	1.79	1.67	2.08
5	68F	57	58	59	219	209	176	130	115	108	37	33	30	15	10	12	1.7	1.9	2.3	3407	2625	2021	65	56	57	1.40	1.37	1.33
6	34F	71	89	73	106	93	95	87	80	82	21	12	12	2	2	2	3.4	4.4	3.9	1193	992	1143	59	31	27	1.28	1.03	1.20
7	55F	67	71	71	121	98	103	87	70	81	39	36	35	17	17	16	2.6	2.8	3.2	1142	785	861	72	65	63	—	—	—
8	32M	78	87	83	157	126	163	128	109	130	11	15	18	1	1	2	5.6	3.8	6.0	1814	2273	1706	32	33	36	1.50	1.18	1.50
9	38M	81	96	89	163	146	141	139	120	120	17	10	15	3	2	3	5.5	4.9	7.5	1978	1927	1248	40	35	39	0.75	0.95	0.87
10	45F	114	129	126	219	144	95	175	115	76	18	10	6	2	2	3	3.3	3.1	3.5	2506	1739	1024	50	40	35	1.78	0.95	0.66
Mean		82	90	86	158	132	132	119	98	100	22	17	18	7	5	6	3.5	3.4	4.2	1993	1692	1371	54	44	42	1.2	1.0	1.1
± 1 SD		18	20	20	42	38	32	29	22	21	11	11	10	6	5	5	1.4	1.2	1.7	861	753	505	15	13	12	0.5	0.4	0.5
(n = 10)																												

*$p < 0.05$. C = control; CI = cardiac index; F = female; Δ P/IVRT = mean isovolumic pressure decay rate; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVPSP = left ventricular peak systolic pressure; M = male; MAP = mean arterial pressure; MRAP = mean right atrial pressure; Nif = 20 minutes after nifedipine administration; Nit = during nitroprusside administration; SD = standard deviation; SVR = systemic vascular resistance; T = time constant of left ventricular pressure decay.

Table 2. Echocardiographic Evaluation of Left Ventricular Systolic and Diastolic Function in 10 Patients With Nonobstructive Hypertrophic Cardiomyopathy

Case	IVRT (ms)			dPW/dt (mm/s)			ΔPW (mm)			dD_{LV}/dt (mm)			ΔD_{LV} (mm)			EDD (mm)			ESD (mm)			%FS		
	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif	C	Nit	Nif
1	145	112	110	46	55	65	11.0	8.3	10.3	56	81	79	20.4	14.4	19.5	46.3	34.9	47.8	25.9	20.3	28.3	44	42	41
2	111	105	87	87	32	146	8.2	6.0	11.0	49	56	81	15.7	13.7	22.7	27.1	24.1	32.6	11.3	10.3	11.0	58	57	69
3	159	118	96	33	34	44	4.8	3.6	7.0	39	35	45	9.1	7.0	11.5	46.7	36.8	38.8	37.6	39.8	27.3	20	19	30
4	57	61	50	106	163	209	10.1	12.4	13.6	159	197	210	15.1	17.7	18.0	46.8	45.6	47.5	31.7	27.9	29.5	32	39	38
5	80	70	57	37	39	41	7.5	7.0	9.0	82	84	88	17.9	16.4	18.5	54.8	53.7	53.3	36.9	37.3	34.8	33	31	35
6	60	65	59	39	90	93	8.3	9.4	12.8	60	110	104	14.0	17.2	20.5	50.6	49.2	52.7	36.6	32.0	32.2	28	35	39
7	—	—	—	66	75	105	9.6	9.1	9.6	85	102	114	18.0	19.0	20.7	68.3	66.0	70.4	50.3	47.0	49.7	26	28	29
8	84	82	80	20	41	47	5.9	4.5	5.7	43	55	71	11.4	10.6	13.8	39.3	35.9	42.0	27.9	25.1	28.3	29	30	33
9	158	130	126	61	74	99	8.8	9.1	12.7	95	111	175	19.6	20.3	26.6	37.5	37.4	44.5	17.9	17.1	17.9	52	54	66
10	92	110	95	37	32	52	5.0	3.5	4.6	71	60	88	9.4	12.8	12.0	36.4	34.8	33.1	27.0	22.0	21.1	26	37	36
Mean	105	95	84	53	64	90	7.9	7.3	9.6	74	89	106	15.1	14.9	18.4	45.4	41.8	46.3	30.3	27.9	28.0	35	37	42
± 1 SD	40	26	25	27	41	54	2.1	2.9	3.1	35	46	50	4.1	4.1	4.8	11.0	12.0	11.1	11.0	11.3	10.4	12	12	15
(n = 10)																								

*$p < 0.05$. dD_{LV}/dt = peak posterior wall thinning rate; ΔD_{LV} = left ventricular internal dimension change during diastole; ΔPW and ΔPW/dt = left ventricular posterior wall diastolic thickness change and its first derivative; EDD = left ventricular end-diastolic internal dimension; ESD = left ventricular end-systolic internal dimension; IVRT = isovolumic relaxation time; %FS = percent fractional shortening of the left ventricular internal dimension; other abbreviations as in Table 1.

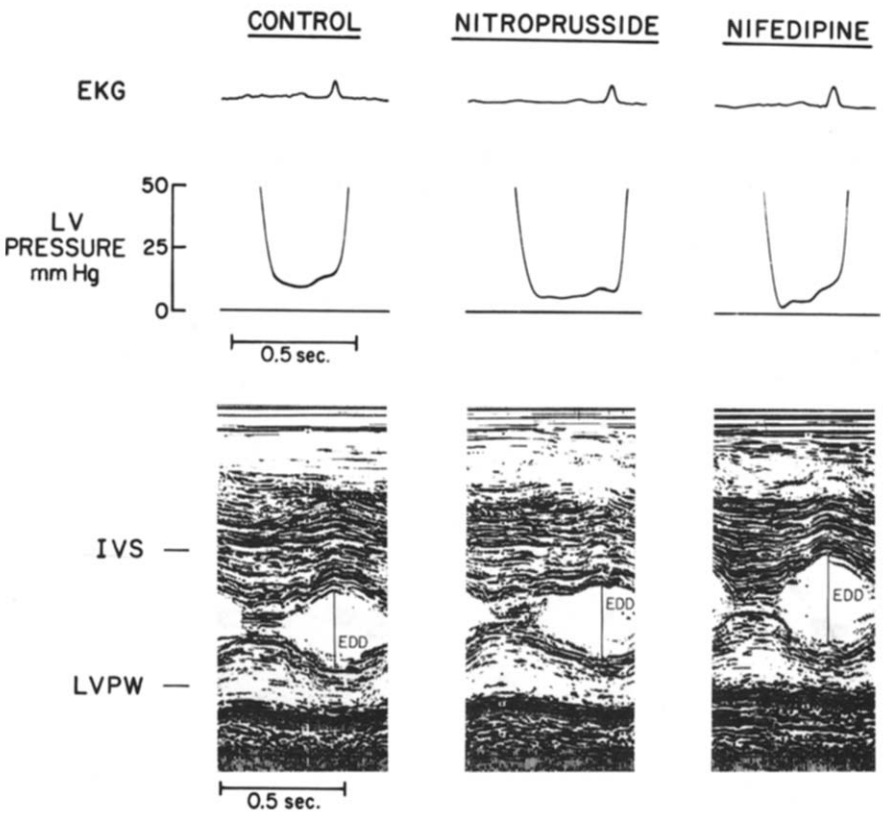

Figure 1. Case 2. A representative example of simultaneously recorded electrocardiogram (EKG), left ventricular (LV) micromanometer diastolic pressure and left ventricular cavity echocardiogram in the control state, during the administration of nitroprusside and after the administration of nifedipine. EDD = end-diastolic dimension; IVS = interventricular septum; LVPW = left ventricular posterior wall.

Discussion

Effect of nitroprusside and nifedipine on left ventricular diastolic properties. Calcium channel blocking agents have been shown to favorably modify abnormal left ventricular diastolic properties in patients with hypertrophic cardiomyopathy (1–5), but it has been unclear whether the mechanism of these effects can be entirely ascribed to diminished left ventricular systolic loading via systemic vasodilation or is, in part, related to improved cardiac muscle inactivation. In our study, nitroprusside and nifedipine caused similar reductions in left ventricular loading as assessed by peak left ventricular systolic pressure in patients with nonobstructive hypertrophic cardiomyopathy. However, nifedipine caused greater modification of abnormal left ventricular relaxation and diastolic filling patterns than that induced by the vasodilator nitroprusside. In these patients, in comparison with nitroprusside, nifedipine caused greater improvement of prolonged left ventricular relaxation as assessed by shortening of the isovolumic relaxation time and modification of abnormal left ventricular diastolic waveforms. Nifedipine also was associated with significant improvement of the depressed peak left ventricular posterior wall thinning rate and peak left ventricular internal dimension filling rate. In contrast to nitroprusside, after nifedipine the decrease in left ventricular end-diastolic pressure occurred with left ventricular end-diastolic dimension unchanged, or in some cases actually increased (Fig. 2), suggesting improved left ventricular distensibility.

Effects on isovolumic relaxation time. The prolongation of the left ventricular isovolumic relaxation time and the time constant T of relaxation observed in this study and their modification by the calcium channel blocking agents have been previously recognized (2,6–8). Care must be taken in the interpretation of the values of the time constants obtained because the isovolumic pressure decay in these patients is not adequately approximated by a monoexponential function (8,27). In this study, the time constants obtained from a polynomial model reflect only gross abnormalities in the rate of isovolumic muscle relaxation, which appears to improve during intervention with nitroprusside and nifedipine. The presence of profound slowing of left ventricular muscle inactivation extending beyond mitral valve opening is supported by the observation of an abnormal left ventricular waveform, with a continuous pressure decrease into mid-diastole that was restored to normal by the administration of nifedipine. The decrease in time constant T during both nitroprusside infusion and after nifedipine administration may reflect predominant load-dependent effects on early isovolumic relaxation (24,28). A mean isovolumic left ventricular pressure decay rate ($\triangle P/IVRT$) was obtained by dividing the decrease in isovolumic left ventricular pressure by the isovolumic left ventricular relaxation

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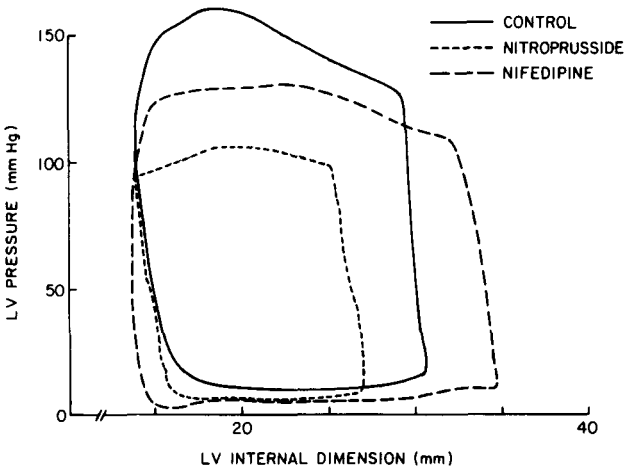

Figure 2. Total left ventricular (LV) pressure-internal dimension relations obtained in control conditions, during the infusion of nitroprusside and after the administration of nifedipine.

time. This index of relaxation was unaffected by either nitroprusside or nifedipine, illustrating the counterbalancing effects of lowered aortic valve closure pressure, lowered mitral valve opening pressure and changed intrinsic isovolumic left ventricular pressure decay rate after nitroprusside and nifedipine administration.

Effects on ventricular wall thinning and internal dimension. After nifedipine administration, peak left ventricular posterior wall thinning and internal dimension filling rates improved with respect to both control conditions and nitroprusside infusion. It has been previously shown that cardiac muscle peak lengthening velocity in physiologically loaded papillary muscles (29) is, in part, determined by the end-diastolic muscle length and the instantaneous load during muscle lengthening (30). When muscle inactivation is impaired by hypoxia or caffeine administration (31), peak muscle lengthening velocity is depressed for the same extent of muscle shortening (14). As there were no significant changes in end-systolic left ventricular internal dimension after nifedipine administration, the improvement of left ventricular filling after nifedipine supports the hypothesis that muscle inactivation was improved.

During nitroprusside infusion, left ventricular diastolic pressure decreased to the same extent as that after nifedipine. However, left ventricular end-diastolic dimension and right atrial pressure were significantly reduced, associated with a slight downward shift of the diastolic pressure-internal dimension relation after nitroprusside. These actions of nitroprusside suggest an effect of systemic venous vasodilation and, consequently, a reduction of left and right ventricular preload. These findings are consistent with prior observations (16,32) which have shown that downward displacement of the left ventricular diastolic pressure-volume relation occurs during vasodilator therapy and may be dependent on multiple variables, including reduction of right ventricular filling pressure and reduced coronary vascular turgor. After nifedipine, left ventricular end-diastolic pressure decreased at an unchanged left ventricular end-diastolic dimension, which is consistent with an increase in left ventricular distensibility. A smaller change in right atrial pressure was observed after nifedipine, in comparison with nitroprusside, which argues against a predominant effect of altered external constraints such as the pericardium or the right ventricle on left ventricular compliance during nifedipine administration.

Mechanisms of nifedipine's beneficial effects. These observations indicate that the increase in left ventricular distensibility after nifedipine in hypertrophic cardiomyopathy is unlikely to be solely due to either left ventricular systolic or diastolic unloading. At least three mechanisms could theoretically explain nifedipine's beneficial action on abnormal left ventricular properties in hypertrophic cardiomyopathy.

First, coronary vasodilation (especially at the level of the coronary microvasculature) might alleviate subendocardial ischemia, thereby improving ischemia-induced changes in cardiac muscle inactivation and compliance (19,33–37).

Second, nifedipine might directly alter intracellular calcium availability, thereby restoring normal muscle tone (38). With regard to the latter possibility, increased intracellular calcium availability has been hypothesized to occur in hypertrophic cardiomyopathy in human patients (11) and in Syrian hamsters (39). A prolonged plateau phase of the action potential of hypertrophied myocardium (40,41) and a consequent increase in slow channel calcium influx might also promote such a state of intracellular calcium overload. However, recent studies (42) on papillary muscles isolated from hypertrophic rat hearts have shown unaltered load dependency of muscle relaxation, which implies the presence of a normal muscle inactivation rate in isolated well oxygenated hypertrophied myocardium. This finding argues against a primary aberration of intracellular calcium availability in secondary myocardial hypertrophy.

Third, nifedipine administration could induce a combination of afterload reduction and diminished contractility. These actions could explain a decrease in left ventricular filling pressure at an unreduced end-diastolic dimension. However, the reduction in end-systolic dimension, the increase in percent fractional shortening and the increase in cardiac index argue against depressed contractility after nifedipine administration in these patients.

Conclusions. We compared the effects of nifedipine and nitroprusside on left ventricular relaxation, diastolic filling and distensibility in 10 patients with nonobstructive hypertrophic cardiomyopathy. Despite equal decreases in left ventricular peak systolic pressure after both nitroprusside and nifedipine, nifedipine administration caused significantly more improvement of left ventricular isovolumic relaxation time, left ventricular filling rates and left ventricular diastolic dis-

tensibility. Therefore, the improvement in diastolic function observed after nifedipine is unlikely to be entirely due to left ventricular systolic unloading. Both relief of subendocardial ischemia related to coronary vasodilation or the correction of an intracellular calcium overload, or both, may contribute to the beneficial effects of nifedipine on left ventricular relaxation and compliance in hypertrophic cardiomyopathy.

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