JACC Vol. 14, No. 2
August 1989:515–22

REPORTS ON HYPERTENSION

Comparative Effects of Verapamil and Nitroprusside on Left Ventricular Function in Patients With Hypertension

JOHN E. BRUSH, JR, MD, FACC, JAMES E. UDELSON, MD, STEPHEN L. BACHARACH, PHD, RICHARD O. CANNON, III, MD, FACC, MARTIN B. LEON, MD, FACC, TERRI F. RUMBLE, RN, ROBERT O. BONOW, MD, FACC

Bethesda, Maryland

The effects of verapamil were compared with those of nitroprusside at matched mean arterial pressures and heart rates in 10 symptomatic hypertensive patients during cardiac catheterization. Simultaneous radionuclide angiography and micromanometer pressure measurements were obtained to assess left ventricular pressure-volume relations. Compared with control conditions, verapamil increased left ventricular end-diastolic volume index from 57 ± 16 to 70 ± 28 ml/m^2 ($p = 0.05$) without a significant increase in left ventricular end-diastolic pressure (from 10 ± 4 to 13 ± 6 mm Hg). Despite a downward and rightward shift in the end-systolic pressure-volume relation indicating negative inotropic effects, ejection fraction did not decrease significantly (from 52 ± 9% to 46 ± 9%); cardiac index and stroke volume index remained unchanged. The change in stroke volume index with verapamil was directly related to the magnitude of change in end-diastolic volume index ($r = 0.82$, $p < 0.005$), suggesting that the increase in end-diastolic volume did not arise purely from negative inotropic effects. Systemic vascular resistance index decreased from 42 ± 8 to 34 ± 7 mm Hg·min·m^2/liter ($p < 0.05$).

In contrast, nitroprusside decreased left ventricular end-diastolic volume index from 57 ± 16 to 41 ± 10 ml/m^2 ($p < 0.05$), cardiac index from 3.2 ± 0.7 to 2.8 ± 0.6 liters/min per m^2 ($p < 0.05$) and stroke volume index from 28 ± 6 to 24 ± 5 ml/m^2 ($p < 0.01$), with no change in systemic vascular resistance index (40 ± 10 mm Hg·min·m^2). The end-systolic pressure-volume relation shifted downward and leftward in all patients, stemming from altered left ventricular loading.

Thus, in equihypotensive doses, verapamil and nitroprusside have markedly different effects on left ventricular function. The peripheral vasodilation and apparent improvement in left ventricular filling during verapamil balanced the negative inotropic effects, resulting in maintenance of stroke volume and cardiac index. The primary hypotensive effect of verapamil was a decrease in systemic vascular resistance, whereas that of nitroprusside was a decrease in cardiac index stemming from reduced left ventricular preload.

(J Am Coll Cardiol 1989:14:515–22)

Congestive heart failure is a common complication of chronic systemic hypertension (1), and left ventricular systolic dysfunction is the usual underlying cause (2). However, left ventricular diastolic dysfunction occurs in patients with systemic hypertension (3,4), and frank congestive heart failure can occur in patients with preserved systolic function (5,6).

Antihypertensive drugs alter left ventricular function by a variety of mechanisms, predominantly by affecting left ventricular loading conditions. Calcium channel antagonists may also affect left ventricular function directly through negative inotropic actions. The effects of calcium channel antagonists on diastolic function in hypertensive patients have not been investigated intensively. Verapamil, nifedipine and diltiazem have been shown to improve left ventricular relaxation and filling in patients with other cardiac disorders including hypertrophic cardiomyopathy (7–13) and coronary artery disease (14–16). The purpose of this investigation was to study the acute effects of the calcium channel antagonist verapamil on systolic and diastolic left ventricular function in patients with systemic hypertension. To evaluate the pharmacologic effects that were independent of changes in blood pressure or heart rate, verapamil was

From the Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Manuscript received August 15, 1988; revised manuscript received February 1, 1989, accepted February 14, 1989.

Address for reprints: John E. Brush, Jr., MD, Cardiology Section, University Hospital, Boston University School of Medicine, 75 East Newton Street, Boston, Massachusetts 02118.

0735-1097/89/$3.50

compared with nitroprusside at equihypotensive doses during atrial pacing.

Methods

Patient selection. We studied 10 patients with systemic hypertension who had symptoms of angina pectoris or dyspnea but no evidence of coronary artery disease. There were seven men and three women, ranging in age from 43 to 62 years (mean 51). Each patient had a history of hypertension requiring therapy, persistent hypertension during hospitalization and a mean arterial pressure of >110 mm Hg at cardiac catheterization.

Noninvasive evaluation. Each patient was hospitalized and underwent routine admission evaluation. Antihypertensive and cardioactive medications were discontinued ≥48 h before study except for one patient who received a single dose of hydralazine 3 h before study. Patients underwent M-mode and two-dimensional echocardiography, and measurements of chamber size and wall thickness were made according to previously described methods (17). Radionuclide angiography was performed, and left ventricular ejection fraction and indexes of left ventricular diastolic filling were calculated as previously described (18). No patient had evidence of coexistent valvular heart disease or dilated or hypertrophic cardiomyopathy. For the group, the mean ventricular septal dimension was 14 ± 3 mm, left ventricular free wall dimension was 12 ± 4 mm and left ventricular end-systolic cavity dimension was 34 ± 5 mm. The rest ejection fraction by radionuclide angiography was 54 ± 10% as compared with our lower normal limit of 45% (18). All patients had evidence of impaired left ventricular diastolic filling at rest, with reduced peak filling rate (<2.5 end-diastolic vol/s), prolonged time to peak filling rate (≥180 ms) or both.

Cardiac catheterization protocol. The study protocol was approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute, and all patients gave informed consent before cardiac catheterization. Patients were premedicated 1 h before study with diazepam (10 mg orally). During cardiac catheterization, arterial pressure was monitored with use of an indwelling 20 gauge catheter in the brachial artery. Pulmonary artery pressure and cardiac output were measured with a balloon-tipped thermodilution catheter, and cardiac output was recorded as the mean of at least three measurements that were within 10% agreement.

A thermodilution coronary sinus catheter (Elecath Corporation) was positioned with the catheter tip at the junction of the great cardiac vein and anterior interventricular vein by using manual injection of contrast medium to confirm catheter position. The catheter was maintained in stable position by repeatedly assessing the relation of the catheter to bone landmarks by using fluoroscopy. Coronary blood flow was measured by the thermodilution technique according to previously described methods (19).

At the beginning of the procedure, red blood cells were labeled in vivo with 20 to 25 mCi of technetium-99m. Ten minutes after administration of technetium-99m, heparin sulfate (5,000 U, intravenously) was administered for anticoagulation. Coronary arteriography was performed with use of multiple angulated views to confirm the absence of significant coronary artery disease (defined as >50% narrowing of the lumen of a major coronary artery). A micromanometer-tipped catheter (Millar Instruments) was then positioned in the left ventricle for pressure monitoring, and a portable gamma camera was positioned over the left thorax for acquisition of scintigraphic data.

Study sequence and pharmacologic interventions. Baseline hemodynamic and scintigraphic studies were initiated ≥15 min after any administration of contrast medium (20). Baseline data obtained included heart rate, systemic blood pressure, left ventricular pressure, cardiac output, great cardiac vein flow and scintigraphic data. In anticipation of nitroprusside and verapamil causing reflex tachycardia, the patient was then atrially paced using the coronary sinus catheter at heart rates of 100 and 130 beats/min for 3 min at each pacing rate to enable subsequent comparison of drug effects at similar heart rates. At each pacing rate, the hemodynamic and scintigraphic data were again obtained. Patients who developed atrioventricular (AV) block during pacing were given atropine (0.5 mg intravenously).

Nitroprusside and verapamil were sequentially administered and titrated to achieve a 20% reduction in mean arterial pressure to enable measurement of drug effects at comparable systemic arterial pressure. Nitroprusside was administered intravenously at an initial infusion rate of 0.5 μg/kg per min, and the infusion rate was increased by 0.5 μg/kg per min every 2 min until an approximate 20% reduction in mean arterial pressure was achieved. The hemodynamic and scintigraphic data were recorded at the spontaneous heart rate and during atrial pacing at 100 and 130 beats/min. The nitroprusside infusion was discontinued and, when heart rate and systemic pressure returned to baseline, verapamil was administered as an intravenous bolus of 0.1 mg/kg followed by an intravenous infusion of 0.005 mg/kg per min. The infusion was increased by 0.005 mg/kg per min every 2 min until an approximate 20% reduction in mean arterial pressure was achieved, and hemodynamic and scintigraphic data were recorded at the spontaneous heart rate and during atrial pacing at 100 and 130 beats/min.

Pressure-volume analysis. Scintigraphic data were collected with use of a mobile gamma camera equipped with a high sensitivity parallel hole collimator positioned over the left thorax in a modified left anterior oblique position for optimal separation of the left from the right ventricle. Electrocardiogram (ECG)-gated equilibrium scintillation

Table 1. Hemodynamic Effects of Nitroprusside and Verapamil at Spontaneous Heart Rates in 10 Patients

Patient No.	Heart Rate (beats/min)			Mean Arterial Pressure (mm Hg)			Cardiac Index (liters/min per m^2)			SVRI (mm Hg·min·m^2/liter)			Stroke Volume Index (ml/m^2)			LV End-Diastolic Pressure (mm Hg)			LV Ejection Fraction (%)		
	C	N	V	C	N	V	C	N	V	C	N	V	C	N	V	C	N	V	C	N	V
1	80	125	105	108	90	100	3.8	3.3	3.9	28	27	26	48	26	37	9	9	11	47	55	44
2	88	108	101	128	120	120	2.4	2.4	2.4	53	50	50	27	22	24	6	4	17	57	70	54
3	110	130	132	120	98	100	2.6	—	3.1	46	—	32	24	—	23	8	6	5	37	39	37
4	72	124	90	122	104	104	2.7	2.7	3.3	45	39	32	38	22	37	12	5	14	55	59	46
5	88	110	97	124	90	108	3.4	2.9	4.8	36	31	23	39	26	49	16	8	20	52	45	40
6	74	90	86	138	120	118	2.4	—	2.9	58	—	41	32	—	34	25	10	20	38	36	32
7	68	100	87	118	95	92	2.7	2.6	2.2	44	37	42	40	26	25	21	15	—	69	60	62
8	95	125	110	140	125	130	5.0	4.1	3.7	28	30	35	53	33	34	22	15	12	65	68	60
9	77	105	98	115	108	98	2.7	2.2	3.3	43	49	30	35	21	34	6	2	4	56	56	48
10	63	115	81	116	100	105	2.4	2.9	3.0	48	34	35	38	25	37	16	10	8	51	64	53
Mean	82	113	99	123	105	108	3.1	2.9	3.3	41	37	34	40	25	35	13	8	12	53	55	48
SD	14	13	15	10	13	12	0.9	0.6	0.8	9	9	9	8	4	8	7	4	6	10	12	10
p values	<0.001	<0.005		<0.001	NS		NS	NS		NS	NS		<0.001	<0.02		0.005	0.06		NS	<0.005	
	<0.001			<0.001			NS			NS			NS			NS			<0.005		

C = control; LV = left ventricular; N = nitroprusside; SVRI = systemic vascular resistance index; V = verapamil.

data were collected in LIST mode to a preset count limit of 10 million counts for each baseline study and to a preset time comprising the middle 2 min of each 3 min study period during pacing. High temporal resolution (20 ms/frame) left ventricular time-activity curves representing relative changes in left ventricular volume during the average cardiac cycle were generated from the cardiac image sequence after background correction and exclusion of extrasystolic and postextrasystolic cycles. End-diastolic counts, end-systolic counts, stroke counts and ejection fraction were computed for each study after correction for physical decay of the isotope. Simultaneous determination of thermodilution cardiac output permitted calculation of absolute left ventricular volumes.

Left ventricular pressure data obtained simultaneously with the scintigraphic data were also collected in LIST mode with use of ECG gating and cycles identical to those used in constructing the time-activity curves. The pressure data were obtained at an acquisition rate of 200/s (4 ms/point) and were then condensed to 20 ms/point to correspond to the scintigraphic volume data. The resulting left ventricular pressure-time curve and time-activity curve were then combined automatically to create loops representing high temporal resolution (20 ms) pressure-volume relations throughout the average cardiac cycle.

Data analysis. The hemodynamic effects of nitroprusside and verapamil were compared with each other and with control conditions by choosing the rest or pacing sequences that allowed comparisons at the lowest, most closely matched heart rates in each patient. It was not feasible to choose arbitrarily a uniform paced heart rate for all patients with which to compare the effects of the drugs because nitroprusside caused reflex tachycardia in some patients and verapamil caused AV block at higher paced heart rates in others. In each patient, however, it was possible to select a condition either at the spontaneous heart rate or during pacing that allowed close matching of heart rate during control conditions and during infusion of each drug.

Mean arterial pressure was calculated electronically from the arterial pressure recording. Cardiac index was calculated as cardiac output divided by body surface area. Systemic vascular resistance index was calculated as mean arterial pressure divided by cardiac index. Stroke volume index was calculated as cardiac index divided by heart rate; end-diastolic volume index was calculated as stroke volume index divided by ejection fraction; and end-systolic volume index was calculated as end-diastolic volume index minus stroke volume index. Coronary resistance was calculated as mean arterial pressure divided by coronary blood flow.

To assess left ventricular pressure decline during isovolumic relaxation, the high temporal resolution (4 ms/point) left ventricular pressure-time data were analyzed. The time constant (T) was computed from the equation $P = Po^{e^{-t/T}} + C$, where Po = pressure at the time of maximal negative dP/dt, t = time, C = the baseline asymptote to which the exponential would decay (21). We also computed the half-time (T-1/2) of pressure decay during isovolumic relaxation. T-1/2 was computed according to the method of Mirsky (22) as the time required for the left ventricular pressure to decline to one-half of the pressure at peak negative first derivative of left ventricular pressure (dP/dt).

Statistical methods. Data are represented as mean values ± SD. The effects of verapamil and nitroprusside relative to each other and to baseline conditions were analyzed with

Table 2. Effects of Nitroprusside and Verapamil at Comparable Heart Rate in 10 Patients

Patient No.	Heart Rate (beats/min)			Mean Arterial Pressure (mm Hg)			Cardac Index (liters/min per m^2)			SVRI (mm Hg·min·m^2/liter)			Stroke Volume Index (ml/m^2)		
	C	N	V	C	N	V	C	N	V	C	N	V	C	N	V
1	100	125	105	110	90	100	2.9	3.3	3.9	38	27	26	29	26	37
2	100	108	101	135	120	120	2.4	2.4	2.4	56	50	50	24	22	24
3	130	130	130	115	98	95	2.6	1.9	3.1	44	52	31	20	15	24
4	130	124	120	120	104	100	3.4	2.7	3.0	36	39	33	26	22	25
5	100	110	97	128	90	108	3.8	2.9	4.8	34	31	23	38	26	50
6	79	90	86	139	120	118	2.5	2.3	2.9	56	52	41	32	26	34
7	130	130	130	140	92	96	3.5	2.8	3.2	40	33	30	27	21	25
8	130	125	130	135	125	130	4.7	4.1	3.6	29	30	36	36	33	28
9	130	119	130	124	108	108	2.8	2.2	3.1	44	49	35	22	19	24
10	100	115	100	128	100	118	3.0	2.9	3.2	43	34	37	30	25	32
Mean	113	118	113	127	105	109	3.2	2.8	3.3	42	40	34	28	24	30
SD	18	12	16	10	13	12	0.7	0.6	0.7	8	10	7	6	5	8
	NS	NS		<0.05	NS		<0.05	<0.005		NS	<0.05		<0.01	<0.0005	
p values	NS			<0.05			NS			<0.005			NS		

T = time constant of isovolumic relaxation; T-1/2 = half time of isovolumic relaxation; other abbreviations as in Table 1.

analysis of variance of repeated measures. A p value of <0.05 was considered to be statistically significant.

Results

Effects on blood pressure and heart rate. Hemodynamic data at baseline and during verapamil and nitroprusside infusions at spontaneous heart rates are shown in Table 1. The average mean arterial pressure was 123 ± 9 mm Hg (range 110 to 140). Left ventricular end-diastolic pressure at baseline was elevated in 5 of the 10 patients. Reflecting the study design, each drug reduced systemic blood pressure by approximately 20%. This reduction was associated with reflex tachycardia, which was more marked during nitroprusside infusion.

Hemodynamic data during control conditions and during nitroprusside and verapamil infusions (with atrial pacing to attain comparable heart rates) are shown in Table 2. Heart rates during control conditions and during nitroprusside and verapamil infusions were similar (113 ± 18, 118 ± 12 and 113 ± 16 beats/min, respectively). Mean arterial pressures were similar during nitroprusside and verapamil infusions (105 ± 13 versus 109 ± 12 mm Hg).

Hemodynamic indexes (Table 2). Nitroprusside and verapamil had distinctly different effects on cardiac index and stroke volume index (Fig. 1). Nitroprusside significantly decreased cardiac index from 3.2 ± 0.7 to 2.8 ± 0.6 liters/min per m^2. In contrast, verapamil resulted in no significant change in cardiac index from control conditions (3.3 ± 0.7 versus 3.2 ± 0.7 liters / min per m^2). The cardiac index, however, was significantly higher with verapamil than with nitroprusside. Similarly, stroke volume index was 28 ± 6 ml/m^2 during control conditions, decreased with nitroprusside to 24 ± 5 ml/m^2 and was maintained with verapamil at 30 ± 8 ml/m^2. Stroke volume index with verapamil was not significantly different from that in control conditions, but was significantly higher than the stroke volume index during nitroprusside infusion. Systemic vascular resistance index was 42 ± 8 mm Hg·min·m^2/liter during control conditions and was not significantly changed with nitroprusside (40 ± 10). In contrast, systemic vascular resistance index significantly decreased to 34 ± 7 mm Hg·min·m^2/liter with verapamil.

Left ventricular systolic function (Table 2). Nitroprusside and verapamil also had distinctly different effects on ejection fraction (Fig. 2). Ejection fraction increased significantly with nitroprusside from 52 ± 9% to 60 ± 14% even though systemic vascular resistance was unchanged and stroke volume index was decreased with nitroprusside. With verapamil, ejection fraction decreased in 7 of 10 patients; however, important decreases (≥5%) occurred in only 3 patients, and the mean ejection fraction with verapamil (46 ± 9%) was not significantly different from that during control conditions. End-systolic volume increased in 8 of 10 patients with verapamil (Fig. 2), and the end-systolic pressure-volume relation was displaced downward and rightward with verapamil in these 8 patients (Fig. 3), indicating a negative inotropic effect (23). No such effect was apparent with nitroprusside; nitroprusside infusion decreased the end-systolic volume in all patients (Fig. 2), resulting in a downward and leftward shift in the end-systolic pressure-volume relation in all 10 patients that was compatible with altered left ventricular loading conditions.

Left ventricular diastolic indexes (Table 2). Nitroprusside and verapamil had opposite effects on left ventricular end-diastolic volume and pressure (Fig. 4). During control con-

Table 2. *Continued*

LV End-Diastolic Volume Index (ml/m²)			LV End-Diastolic Pressure (mm Hg)			LV End-Systolic Volume Index (ml/m²)			LV Ejection Fraction (%)			T (ms)			T-1/2 (ms)		
C	N	V	C	N	V	C	N	V	C	N	V	C	N	V	C	N	V
63	48	84	5	9	11	34	22	47	46	55	44	66	84	61	38	41	39
39	32	40	6	4	12	15	10	16	62	70	60	42	80	67	29	39	37
51	37	65	8	6	5	31	23	41	39	39	37	56	55	62	33	31	33
44	37	64	12	5	14	18	15	39	59	59	39	76	82	79	40	37	41
75	48	141	10	3	20	37	22	92	51	55	35	—	—	—	—	—	—
89	62	91	14	6	22	36	37	57	36	41	37	104	82	98	43	39	43
43	25	55	12	15	12	16	4	30	63	85	46	70	79	80	39	35	39
64	48	47	12	14	12	28	15	19	56	68	59	60	91	163	39	35	51
39	30	44	6	2	4	17	12	20	56	61	54	110	41	101	39	35	39
64	39	64	16	10	20	34	14	32	47	64	50	152	77	118	43	35	43
57	41	70	10	7	13	29	17	39	52	60	46	82	75	92	38	36	41
16	10	28	4	4	6	12	9	21	9	14	9	34	16	33	5	3	4
<0.05	<0.0005		NS	<0.005		<0.05	<0.0005		<0.05	<0.0005		NS	NS		NS	<0.05	
<0.05			NS			<0.05			NS			NS			NS		

ditions, left ventricular end-diastolic volume index was 57 ± 16 ml/m², significantly decreasing with nitroprusside to 41 ± 10 ml/m². In contrast, left ventricular end-diastolic volume index increased significantly with verapamil to 70 ± 28 ml/m². The change in end-diastolic volume index with verapamil correlated positively with the change in stroke volume index ($r = 0.82$, $p < 0.005$) (Fig. 5). The change in end-diastolic volume did not correlate with the change in end-diastolic pressure during either verapamil or nitroprusside infusion.

Although left ventricular end-diastolic pressure was not altered significantly from control by either nitroprusside or verapamil (Table 2), the end-diastolic pressure was significantly less during nitroprusside compared with verapamil ($p < 0.005$) (Fig. 4). The end-diastolic pressure-volume relation shifted downward and leftward in 7 of the 10 patients during nitroprusside infusion. In contrast, during verapamil infusion, it shifted downward and rightward in two patients, rightward with no vertical change in two and upward and rightward in six.

The time constant of isovolumic relaxation was not significantly different during control conditions (82 ± 34 ms), with nitroprusside (75 ± 16 ms) or with verapamil (92 ± 33 ms). The half-time of isovolumic pressure decline (T-1/2) was 38 ± 5 ms during control conditions and was not significantly changed during either nitroprusside (36 ± 3 ms) or verapamil (41 ± 4 ms) infusion. The T-1/2 was significantly less during nitroprusside compared with verapamil ($p < 0.05$).

Coronary blood flow was 96 ml/min and coronary resistance was 1.6 mm Hg·min/ml during control conditions. Coronary blood flow and coronary resistance were not

Figure 1. Cardiac index and stroke volume index during control conditions and during nitroprusside and verapamil infusion.

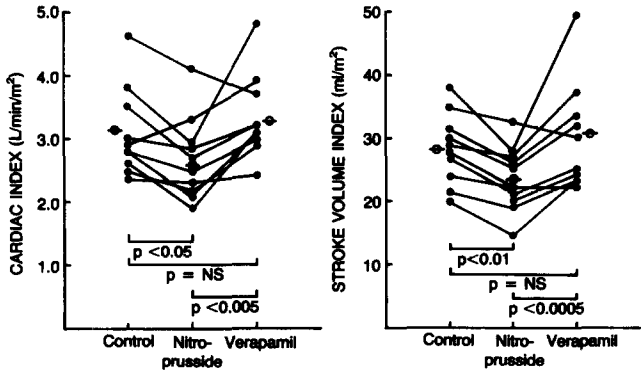
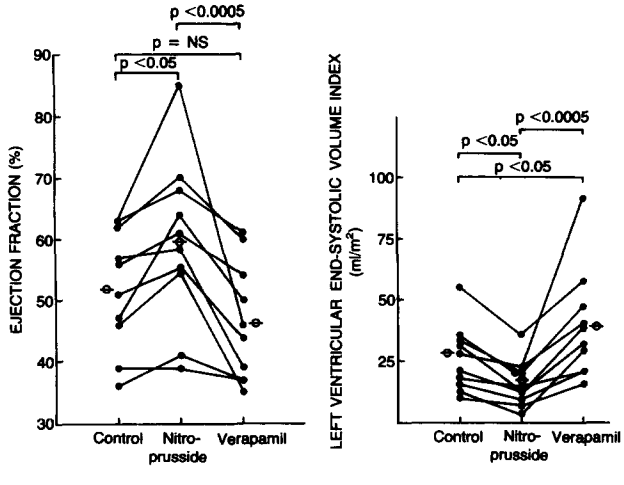


Figure 2. Left ventricular ejection fraction and left ventricular end-systolic volume index during control conditions and during nitroprusside and verapamil infusion.



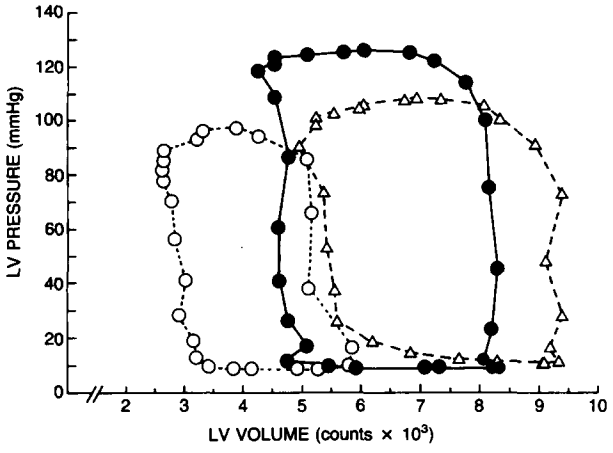


Figure 3. Left ventricular (LV) pressure-volume relations during control conditions (**solid circles**) and during nitroprusside (**open circles**) and verapamil (**triangles**) infusion.

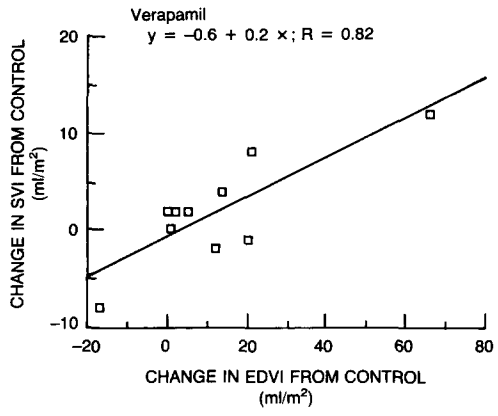


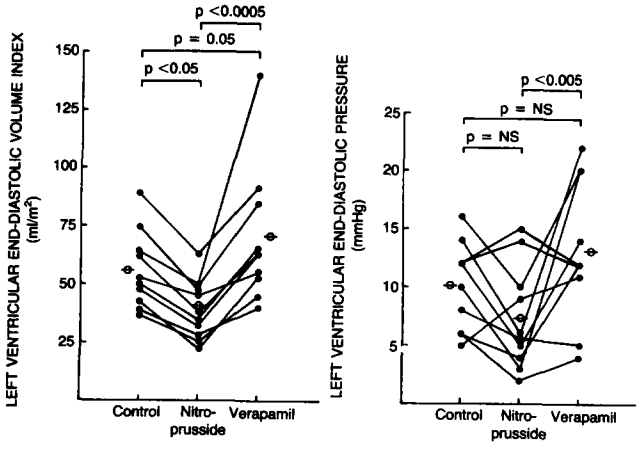
Figure 5. Change in stroke volume index (SVI) with verapamil plotted as a function of the change in end-diastolic volume index (EDVI) with verapamil.

significantly altered by either nitroprusside (85 ml/min and 1.4 mm Hg·min/ml) or verapamil (94 ml/min, 1.5 mm Hg·min/ml).

Discussion

In this study of 10 symptomatic patients with systemic hypertension, nitroprusside and verapamil were administered sequentially, and patients were paced atrially before and during drug infusions to allow a direct comparison of the drug effects on cardiac function at matched mean aterial pressures and heart rates. The findings of this study indicate that, under these acute study conditions, the two drugs have markedly different effects on cardiac index, systemic vascular resistance and left ventricular volume indices.

Figure 4. Left ventricular end-diastolic volume index and pressure during control conditions and during nitroprusside and verapamil infusion.



Cardiac effects of verapamil. Verapamil infusion resulted in a negative inotropic effect as evidenced by a downward and rightward shift in the pressure-volume relation in 8 of the 10 patients (23). Despite the negative inotropic effect, cardiac index and stroke volume index were maintained during verapamil infusion. These findings indicate that the negative inotropic action of verapamil was balanced by two additional drug effects. First, verapamil reduced systemic arterial resistance, and diminished arterial impedance served to augment stroke volume despite reduced contractile state. Second, our data suggest that left ventricular filling was enhanced by verapamil. The significant increase in end-diastolic volume in the absence of a significant increase in end-diastolic pressure and the significant correlation between increased end-diastolic volume and augmented stroke volume (Fig. 5) both argue strongly that the increase in end-diastolic volume did not result merely from negative inotropic mechanisms.

From our data it is not possible to draw firm conclusions concerning the mechanism responsible for the increase in left ventricular end-diastolic volume induced by verapamil. It is possible that verapamil directly enhanced left ventricular relaxation by reducing calcium influx through its calcium channel-blocking properties. However, the time constant of isovolumic relaxation and the half-time of isovolumic pressure decline were not decreased significantly during verapamil infusion. Therefore, the beneficial effect of verapamil on left ventricular diastolic filling is not reflected by these indexes of left ventricular relaxation. The apparent improvement in left ventricular filling during verapamil infusion is also not related to changes in coronary blood flow, which was not affected by verapamil, nor is it likely that verapamil affected sympathetic activation more than nitroprusside to secondarily affect left ventricular filling. Nevertheless, it appears that verapamil had an overall favorable effect on the

complex interplay of factors that affect ventricular filling (24–26), resulting in increased left ventricular volume. In this regard, the effect of verapamil on ventricular filling and diastolic pressure-volume relations in hypertensive patients is similar to the effect of calcium channel blocking agents previously demonstrated in patients with hypertrophic cardiomyopathy (8–10,12) and coronary artery disease (14,16).

Cardiac effects of nitroprusside. Under rest conditions, nitroprusside caused significant reflex tachycardia that maintained cardiac output. When compared with verapamil at matched heart rates, however, it was apparent that the two drugs had markedly different effects. Nitroprusside caused a significant decrease in cardiac index and stroke volume index related to a significant decrease in left ventricular end-diastolic volume index (Fig. 5). Nitroprusside did not alter systemic arterial resistance. Thus, the principal effect of nitroprusside was a reduction in left ventricular preload. The decrease in cardiac index with nitroprusside indicates a dependence of the hypertensive ventricle on adequate left ventricular preload to maintain cardiac output. Ejection fraction increased with nitroprusside but, considering the effects on systemic vascular resistance and stroke volume, this appeared to reflect merely the short-term alteration in relative end-diastolic and end-systolic volumes arising from reduced preload rather than from a peripheral unloading effect.

The half-time of pressure decay during isovolumic relaxation (T-1/2) was significantly less, and the time constant of exponential isovolumic pressure decline tended to be less during nitroprusside infusion as compared with verapamil infusion. Because isovolumic relaxation can be affected by the extent of end-systolic fiber shortening (22,27,28) and because end-systolic volume index was significantly reduced during nitroprusside infusion, it is likely that the degree of end-systolic fiber shortening accounted for the significant decline in both T-1/2 and the time constant (T). Moreover, the lack of reduction in these time constants during verapamil could reflect the reduced end-systolic fiber shortening and increased end-systolic volumes stemming from the negative inotropic effects.

The reduction in cardiac index associated with a decrease in left ventricular end-diastolic volume with nitroprusside was opposite to the effect of nitroprusside reported previously in patients with left ventricular systolic dysfunction and chronic volume overload (28), but similar to the effect previously reported in hypertensive patients (29). In the present study, there was no decrease in systemic vascular resistance during nitroprusside infusion, and the decrease in mean arterial pressure resulted mainly from reduced cardiac index. In contrast, verapamil caused a 19% reduction in systemic vascular resistance. Thus, the mechanisms for the reduction in blood pressure by the two drugs were clearly different. Nitroprusside reduced blood pressure principally by diminishing cardiac index stemming from decreased preload. Because cardiac index was maintained with verapamil, blood pressure reduction with verapamil was accomplished to a similar degree through a predominant effect on arterial resistance.

Clinical implications. These data have practical implications concerning treatment of hypertensive patients. Because diastolic dysfunction is not uncommon in patients with hypertension and left ventricular hypertrophy (5,6), an optimal antihypertensive agent would lower systemic blood pressure while favorably affecting left ventricular diastolic filling. Our data indicate that verapamil has such properties after acute administration in symptomatic patients, although the negative inotropic effect might limit its use in patients with impaired left ventricular systolic function.

Our data concerning the short-term hemodynamic effects of nitroprusside in hypertension also have possible implications regarding the effects of other vasodilating agents with venodilating effects that are used for long-term treatment of hypertension. Although compensatory hemodynamic changes are likely to occur with long-term therapy, it is also likely that antihypertensive agents that have purely vasodilating actions may have deleterious effects on left ventricular filling in hypertensive patients. In patients with severe left ventricular hypertrophy, antihypertensive therapy with such vasodilating agents has been associated with severe adverse consequences (30). Our data provide a hemodynamic mechanism that could explain the previously reported clinical findings and suggest that deleterious hemodynamic effects can occur in hypertensive patients with impaired left ventricular filling even in the absence of severe left ventricular hypertrophy.

We gratefully acknowledge the technical assistance of Beverly Barber, Cecilia Bergamo, Anne Danforth, Greg Johnson, Carl Newman, William Schenke, Annette Stine, Timothy Stockdale, Gale White and Judith Winkler, as well as the editorial assistance of Maude Atcheson.

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