Acute Effects of Intravenous Nisoldipine on Left Ventricular Function and Coronary Hemodynamics

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The hemodynamic effects of nisoldipine were investigated in 16 patients with suspected coronary artery disease who underwent routine cardiac catheterization. Nisoldipine was given intravenously in a dose of 6 μg/kg over 3 minutes and measurements made before and after drug administration during spontaneous and matched atrial paced heart rate. During sinus rhythm, nisoldipine produced a significant increase in heart rate (19%, $p < 10^{-5}$). Left ventricular systolic pressure decreased 28% ($p < 10^{-6}$) and left ventricular end-diastolic pressure did not change significantly (5%, difference not significant). Coronary sinus and great cardiac vein blood flow increased by 21% ($p < 0.02$) and 25% ($p < 0.005$), respectively, after nisoldipine administration. Simultaneously, mean aortic pressure decreased 33% ($p < 10^{-6}$); consequently, the global and regional coronary vascular resistances decreased by 50% ($p < 10^{-4}$). The decreases in global (−8%) and regional (−4%) myocardial oxygen consumption did not reach statistical significance. A 6% (not significant) increase in end-diastolic volume and an 11% ($p < 0.002$) decrease in end-systolic volume resulted in an increase of 21% in stroke volume ($p < 10^{-4}$) with a consistent increase in ejection fraction (+16%, $p < 10^{-5}$). Total systemic vascular resistance was reduced by 30% ($p < 0.0002$). During spontaneous heart rate and matched atrial pacing, the time constant of isovolumic relaxation as assessed by a biexponential model, was significantly shortened. The maximal velocity of isovolumic contraction after nisoldipine was administered remained higher (+12%, $p < 0.02$) at an identical paced heart rate. Thus, nisoldipine is a potent coronary and peripheral vasodilator. No negative inotropic effects were observed in the dosage used.

(Am J Cardiol 1985;56:140–146)

Nisoldipine is a new dihydropyridine derivative, chemically similar to nifedipine and other related dihydropyridines.[1–4] Despite its chemical similarity, its pharmacologic properties differ substantially from nifedipine. Although less potent in the inhibition of contraction of isolated heart muscle, nisoldipine is 4 to 10 times more potent in the inhibition of vascular smooth muscle contraction.[5] The main in vivo pharmacologic action of nisoldipine appears to be its inhibitory effect on vascular smooth muscle, particularly that of the coronary vasculature.[5] The electrophysiologic effects at concentrations producing such vascular changes are minimal.[6]

The selectivity of nisoldipine for the coronary vascular bed may be of great significance in patients with coronary artery disease when imbalance in myocardial oxygen supply and demand is caused by increased tone of coronary vasculature. The present study was undertaken to investigate the effects of nisoldipine on peripheral and coronary vasculature and left ventricular (LV) function.

Methods

Sixteen patients who underwent investigation for chest pain and who were suspected of having coronary artery disease were studied at the time of cardiac catheterization. Eleven patients were men and mean age of the patients was 57 years (range 44 to 69). Significant coronary artery disease was defined as at least 50% luminal diameter narrowing in at least 1 major artery. Four patients had no significant coronary artery disease, and of these, 2 were subsequently diagnosed as having dilated

From the Thoraxcenter, Erasmus University, Rotterdam, the Netherlands. Dr. Jaski was supported by National Institutes of Health Training Grant 5-T32-HLO-7049, Bethesda, Maryland. Manuscript received November 19, 1984; revised manuscript received March 11, 1985, accepted March 19, 1985.

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cardiomyopathy. No patient had clinical evidence of cardiac failure and only 2 patients had LV ejection fraction of less than 40%. Seven patients had had a previous myocardial infarction. Patient data are summarized in Table I.

Protocol: Beta blockers, nitrates, calcium antagonists and digitalis were discontinued 36 hours before the study. Cardiac catheterization was performed with the patients fasting and without premedication. A Baim coronary sinus and great cardiac vein[7] flow catheter or a Ganz coronary sinus flow thermodilution catheter was inserted into the coronary sinus through a right antecubital vein. Aortic or LV pressures were recorded with manometers mounted on a pigtail catheter. Heart rate, aortic and LV pressures, pressure-derived indexes of isovolumic contraction and relaxation (see later), thermodilution coronary sinus and great cardiac vein flows, and oxygen saturations obtained simultaneously from the aorta and coronary sinus could thus be measured. To assess hemodynamic changes independent of changes in heart rate, measurements were made during spontaneous heart rate and at matched atrial paced rates.

After establishing a control state the following protocol was followed:

(1) LV cineangiography at a paced heart rate 15 beats more than the spontaneous heart rate was performed at 50 frames/s in a 30° right anterior oblique view with the injection of a nonionic contrast medium, which has been shown to have no effect on hemodynamic status.[8] Care was taken to avoid a Valsalva maneuver. Stroke volume was calculated as the difference between end-diastolic and end-systolic volumes. Simultaneous LV pressures recordings were made.

(2) At least 10 minutes after angiography and when spontaneous heart rate and pressure values had returned to control, the pressure measurements were repeated during the same paced rate as used for angiography. Immediately after, the pressures, oxygen saturations and coronary venous flow measurements were performed during spontaneous heart rate.

(3) Nisoldipine, 2 μg/kg/min, was then infused intravenously over 3 minutes.

(4) Two minutes after nisoldipine was administered the measurements outlined in protocol 2 were repeated during the same atrial paced rate and during spontaneous heart rate.

(5) The LV cineangiography at the matched atrial paced rate was then repeated with simultaneous LV pressure recording.

(6) Coronary angiography was performed.

Analysis of pressure-derived indexes during systole and diastole: Pressure measurements suitable for analysis before and after nisoldipine were obtained in 14 patients during spontaneous heart rate and 9 patients during paced heart rate. Pressure measurements during angiography were obtainable in each of the 15 patients with LV angiograms suitable for regional wall motion analysis. LV pressure was digitized at 250 samples/s. Peak LV pressure, LV end-diastolic pressure, peak positive dP/dt, peak negative dP/dt and the relation between dP/dt pressure and total pressure linearly extrapolated to pressure = 0 (Vmax) were computed on line after data acquisition of 20 seconds.

Determination of relaxation parameters: For off-line analysis of LV pressure relaxation, an updated version of the beat-to-beat program described previously[9,10] was used with the following definitions: Pressure at the beginning of isovolumic relaxation (P_b) is the pressure at the point at which dP/dt is minimal (maximal negative dP/dt), and pressure at the end of isovolumetric relaxation (P_e) is the pressure less than or equal to the previous end-diastolic pressure, but not less than 1 mm Hg. Although the latter definition may result in P_e being measured just after mitral valve opening, estimation of the time constants by more stringent criteria, such as end-diastolic pressure + 10 mm Hg, did not result in a significantly better estimation, and failed to measure pressure during increased heart rates. The semilogarithmic model used for the off-line beat-to-beat calculation of the relaxation parameters was: $P(t) = P_o e^{-t/T}$, where P is pressure; P_o is equivalent to P_b when a true exponential decay is present starting from the time of peak negative dP/dt. The P_o and T parameters were estimated from a linear least squares fit on $\ln P = -t/T + \ln P_o$. In addition, a biexponential fit for isovolumic relaxation was determined characterized by 2 exponential time constants; the fit for the first 40 ms (n = 8), T_1, and the fit after the first 40 ms, T_2 (n ≥3).[11]

TABLE I Clinical Data

Pt	Age (yr) & Sex	Coronary Artery Stenosed 50% in Diameter LM	LAD	LC	R	Previous MI
1	48M	—	—	+	+	+
2	49M	—	—	—	—	0
3	68F	+	+	—	+	+
4	52M	—	+	+	—	0
5	68F	—	+	—	+	0
6	57M	+	+	+	+	+
7	73F	+	+	+	—	0
8	55M	—	+	+	+	+
9	47M	—	—	—	—	0
10	45M	—	+	+	+	0
11	69M	—	+	—	—	+
12	59M	—	+	—	—	+
13	50M	—	—	—	—	0
14	44F	—	+	—	+	0
15	66F	—	+	+	+	+
16	63M	—	—	—	—	0

LAD = left anterior descending coronary artery; LC = left circumflex artery; LM = left main stem; MI = myocardial infarction; R = right coronary artery; + = present; 0 = absent; — = no.

Coronary blood flow measurements and myocardial oxygen consumption: In 11 patients coronary sinus flow and in 10 of these 11 great cardiac vein in flows were measured by the continuous thermodilution method of Ganz. Arterial, coronary sinus and great cardiac vein blood samples were simultaneously withdrawn to determine blood oxygen content. Global and regional myocardial oxygen consumption were calculated as the product of coronary blood flow and arteriocoronary venous oxygen content differences.

Regional and global coronary vascular resistances were derived from the ratio of mean aortic pressure to great cardiac vein or coronary sinus blood flows.

Analysis of global and regional left ventricular function: Global and regional LV function was studied from the LV angiogram with an automated hard-wired endocardial contour detector linked to a minicomputer.[12] For each analyzed cine frame, LV volume was computed according to Simpson's rule. After the end-diastolic and end-systolic frames were identified, stroke volume, global ejection fraction and total cardiac index were determined. Figure 1A illustrates the end-diastolic and end-systolic contours as displayed by the analysis system. Analysis of LV systolic function included both isovolumic and ejection phases indexes (ejection fraction and mean circumferential fiber shortening rate). Systolic regional wall displacement is determined along a system of 20 coordinates based on the pattern of actual endocardial wall motion in normal persons[13] and generalized as a mathematic expression amenable to automatic data processing.[14,15]

For each segment, segmental volume is computed from the local radius (R) and the height of each segment (1/10 of LV long-axis length) (L) according to the formula: $1/20\pi\ R^2L$.

TABLE II Isovolumic Contraction and Relaxation Before and After Nisoldipine

		Before Nisoldipine	After Nisoldipine	Δ%	p Value
RR (ms)	P	741 ± 27	741 ± 28	0	NS
	NP	868 ± 140	769 ± 97	−11	<0.003
Peak LVP (mm Hg)	P	160 ± 35	120 ± 23	−25	<0.00005
	NP	154 ± 30	117 ± 21	−24	$<10^{-5}$
−dP/dt (mm Hg s^{-1})	P	1,852 ± 324	1,552 ± 238	−16	<0.0005
	NP	1,661 ± 306	1,471 ± 289	−11	<0.005
+ dP/dt (mm Hg s^{-1})	P	1,515 ± 407	1,393 ± 355	−8	<0.005
	NP	1,470 ± 329	1,485 ± 437	+1	NS
Vmax (s^{-1})	P	41 ± 4	46 ± 8	+12	<0.02
	NP	40 ± 8	50 ± 12	+25	<0.0005
T (ms)	P	47 ± 6	43 ± 8	−9	NS
	NP	49 ± 7	44 ± 9	−10	<0.02
T_1 (ms)	P	52 ± 7	45 ± 6	−13	<0.005
	NP	55 ± 9	46 ± 8	−16	<0.0005
T_2 (ms)	P	40 ± 6	41 ± 12	+2.5	NS
	NP	44 ± 5	42 ± 10	−5	NS

dP/dt = rate of change in left ventricular pressure; LVP = left ventricular pressure; NP = spontaneous heart rate (n = 14); NS = not significant; P = matched pacing (n = 9); RR = cycle length; T = global time constant from the "semilogarhythmic" model; T_1 and T_2 = biexponential fitting: T_1—fit of first 40 ms, T_2—fit after 40 ms; Vmax = maximal velocity of contractile element shortening.

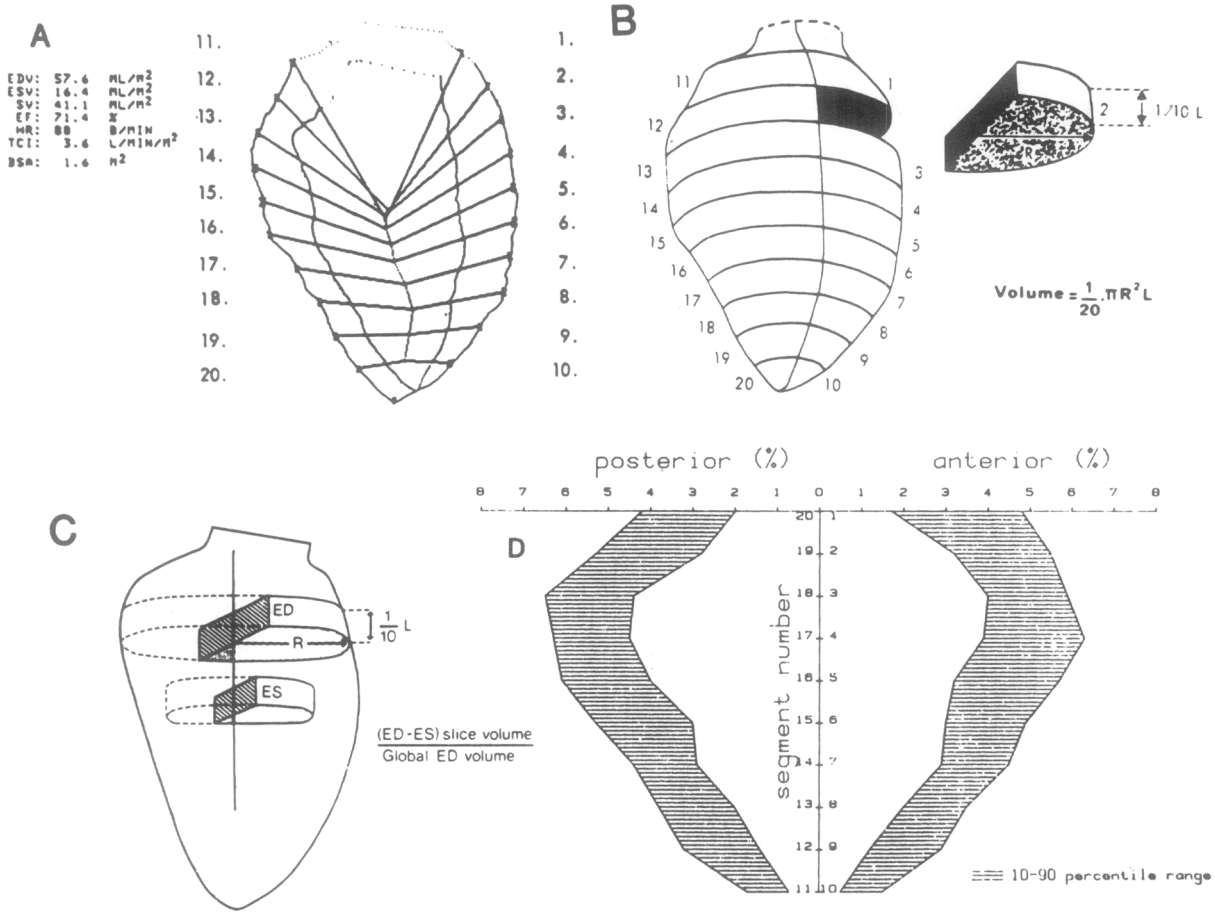

FIGURE 1. A, computer output showing the end-diastolic (EDV) and end-systolic (ESV) contours of the 30° right anterior oblique left ventriculogram and the system of coordinates along which left ventricular segmental wall displacement is determined. The corresponding volume data, ejection fraction (EF) and other parameters are shown in the **upper left corner. B,** left ventricular end-diastolic cavity is separated into 20 half-slices. The volume of each half-slice is computed according to the given formula: $1/20 \cdot \pi R^2 L$. **C,** regional contribution to global ejection fraction is determined from the systolic decrease of volume of the half-slice that corresponds to a particular wall segment. The systolic volume change is mainly a consequence of the decrease of radius (R) of the half-slice. **D,** The **shaded zones** represent the tenth to the ninetieth percentiles area of the regional contribution to ejection fraction (CREF) values in normal persons. On the X axis, the CREF values of the anterior and inferoposterior wall areas are displayed (%), while on the Y axis the segment numbers of the anterior wall (1 to 10) and of the inferoposterior wall (11 to 20) are depicted. BSA = body surface area; HR = heart rate; L = left ventricular long-axis length.

When normalized for end-diastolic volume, the systolic segmental volume change can be considered a parameter of regional pump function (Fig. 1B). During systole this parameter expresses quantitatively the contribution of a region to ejection fraction (CREF)[14] (Fig. 1C). The sum of the CREF values for all 20 segments equals to the global ejection fraction.

The cross-hatched zones in Figure 1D represent the CREF values between the tenth and the ninetieth percentile, as determined in 20 normal persons. The segmental CREF values in the anterobasal (segments 1 to 5), anterolateral (segments 5 to 9), apical (segments 9, 10, 19 and 20), inferior (segments 15 to 19) and posterobasal (segments 11 to 15) wall regions were analyzed. Interpretable LV angiograms were available in 15 patients, and a total of 300 segments were analyzed in these patients; 1 patient had normal wall motion pattern, 7 patients had abnormal wall motion in the inferior region, 4 patients in the anterior region and 3 in both regions (Fig. 2).

Statistics: Results are expressed as mean ± standard deviation. Group data before and after nisoldipine were compared by a paired Student t test. A p value of 0.05 was considered statistically significant.

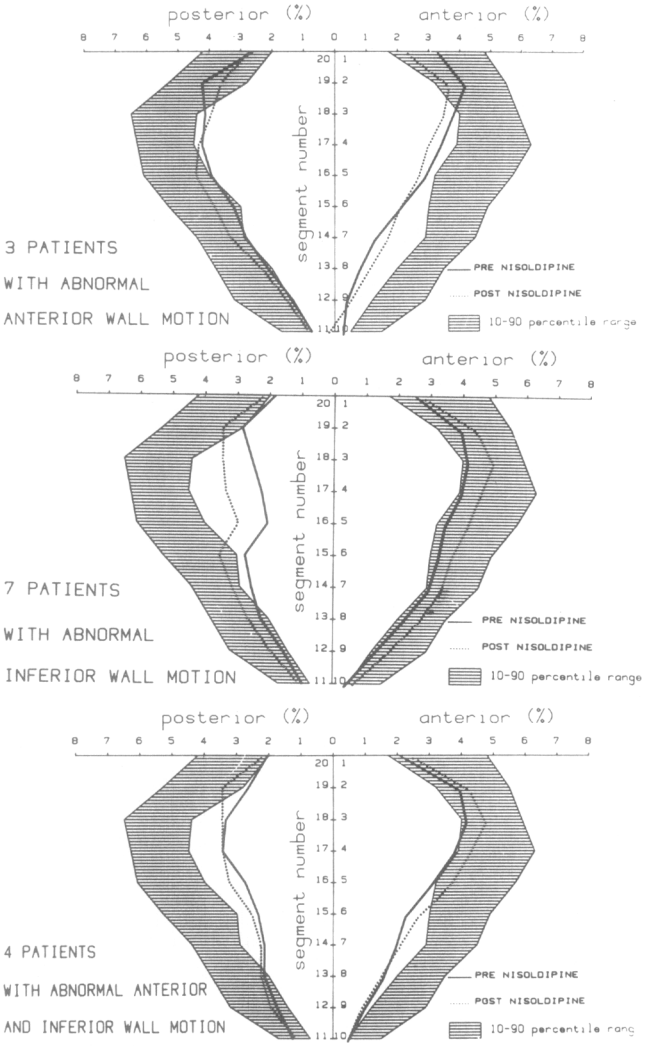

FIGURE 2. Left ventricular regional wall motion in 14 patients: 3 patients with abnormal anterior wall motion, 7 patients with abnormal inferior wall motion, and 4 patients with abnormal anterior and inferior wall motion.

Results

Measurements during spontaneous heart rate: During spontaneous heart rate nisoldipine produced a significant decrease in peak systolic pressure and an increase in heart rate (Fig. 3). At the end of the infusion the mean changes were 42 mm Hg for the peak systolic pressure (−28%, $p < 10^{-6}$) and 13 beats (+19%, $p < 10^{-5}$) for heart rate. Although peak Vce remained unchanged, Vmax was significantly increased, from 40 ± 8 to 47 ± 13 s^{-1} (+ 18%, $p < 0.005$). The end-diastolic pressure did not change (19 to 20 mm Hg).

Five minutes after administration of nisoldipine the pressure-derived indexes related to the isovolumic relaxation were studied at spontaneous heart rate in 14 patients (Table II). In this subset of patients, LV systolic pressure decreased 24% ($p < 10^{-5}$) and −dP/dt decreased 11% ($p < 0.005$). The time constant of relaxations was shortened.

Coronary sinus blood flow increased from 146 ± 40 to 176 ± 35 ml/min ($p < 0.02$) 3 minutes after completion of nisoldipine infusion while the great cardiac vein flow increased significantly after nisoldipine, from 87 ± 20 to 109 ± 24 ml/min ($p < 0.005$). Simultaneously, the mean aortic pressure decreased from 107 ± 20 to 72 ± 9 mm Hg (−33%, $p < 10^{-6}$); consequently the global and the regional coronary vascular resistance decreased,

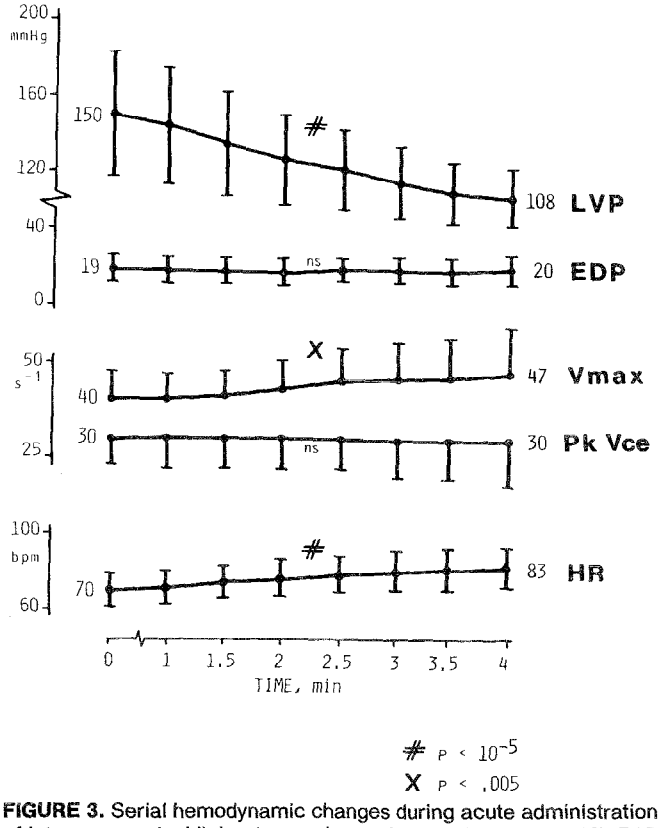

FIGURE 3. Serial hemodynamic changes during acute administration of intravenous nisoldipine (mean ± standard deviation, n = 16). EDP = left ventricular end-diastolic pressure; HR = heart rate; LVP = left ventricular peak systolic pressure; Pk Vce = peak velocity of contractile element; Vmax = maximal velocity of contractile element shortening.

TABLE III Myocardial Oxygen Consumption, Coronary Flow and Resistance Before and After Intravenous Nisoldipine

	Before Nisoldipine	After Nisoldipine	Δ%	p Value
CS flow (ml/min) n = 11	146 ± 40	176 ± 35	+21	<0.02
GCV flow (ml/min) n = 10	87 ± 20	109 ± 24	+25	<0.005
MVO_2 CS (ml/min) n = 11	15.1 ± 4.8	13.9 ± 3.2	−8	NS
MVO_2 GCV (ml/min) n = 10	9.2 ± 3.2	8.8 ± 2.5	−4	NS
(Art.-CS) O_2 diff—(ml%) n = 11	10 ± 2	8 ± 1	−20	<0.002
(Art.-GCV) O_2 diff (ml%) n = 10	10 ± 2	8 ± 1	−20	<0.005
Mean AoP (mm Hg) n = 11	107 ± 20	72 ± 9	−33	$<10^{-6}$
Resist. CS (mm Hg/ml/min) n = 11	0.8 ± 0.2	0.4 ± 0.1	−50	$<10^{-4}$
Resist. GCV (mm Hg/ml/min) n = 10	1.4 ± 0.2	0.7 ± 0.1	−50	$<10^{-4}$

AoP = aortic pressure; Art. = arteriocoronary; CS = coronary sinus; GCV = great cardiac vein; MVO_2 = global (CS) or regional (GCV) myocardial oxygen consumption; NS = not significant; O_2 diff = oxygen difference; Resist. = resistance.

TABLE IV Left Ventricular Performance at Matched Paced Heart Rate Before and After Nisoldipine Administration in 15 Patients

	Before Nisoldipine	After Nisoldipine	%	p Value
EDVI (ml/m²)	87 ± 30	92 ± 34	+6	<0.08
ESVI (ml/m²)	44 ± 23	39 ± 24	−11	<0.002
SVI (ml/m²)	43 ± 11	52 ± 13	+21	$<10^{-4}$
EF (%)	51 ± 8	59 ± 10	+16	$<10^{-5}$
CFSR (s^{-1})	0.7 ± 0.1	0.9 ± 0.2	+29	<0.0002
CI (liters min/m²)	3.4 ± 0.9	4.3 ± 1.2	+26	$<10^{-5}$
Ao mean (mm Hg)	107 ± 19	94 ± 13	−12	<0.001
SVR (dynes s cm^{-5})	1467 ± 493	1033 ± 362	−30	<0.0002
Peak LVP (mm Hg)	161 ± 29	127 ± 20	−21	<0.00005

Ao = aortic pressure; CFSR = mean circumferential fiber shortening rate; CI = cardiac index; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LVP = left ventricular pressure; SVI = stroke volume index; SVR = systemic vascular resistance.

respectively, from 0.8 ± 0.2 to 0.4 ± 0.1 mm Hg/ml/min ($p < 10^{-4}$) and from 1.4 ± 0.2 to 0.7 ± 0.1 mm Hg/ml/min ($p < 10^{-4}$) (Fig. 4, Table III).

Although the mean arteriocoronary sinus and great cardiac vein oxygen difference decreased from 10 ± 2 and 10 ± 2 to 8 ± 1 ($p < 0.002$) and 8 ± 1 ml/100 ml ($p < 0.005$), respectively, the decrease in global (from 15 ± 5 to 14 ± 3 ml/min) and regional (from 9 ± 3 to 9 ± 2 ml/min) myocardial oxygen consumption (Table III) did not reach statistical significance.

Measurements during matched paced heart rate: In a subset of 9 patients, 5 minutes after nisoldipine administration and at an identical paced heart rate (cycle length 741 ± 27 vs 741 ± 28 ms), the monoexponential time constant was not significantly shortened; however, T_1, the first biexponential time constant was significantly shortened (Table II). After nisoldipine, Vmax remained significantly higher (+12%, $p < 0.02$) at an identical paced heart rate. Table IV lists the change in LV volumes resulting from nisoldipine administration. A 6% (not significant) increase in end-diastolic volume and an 11% ($p < 0.002$) decrease in end-systolic volume resulted in a significant increase of 21% in systolic volume (from 43 ± 11 to 52 ± 13 ml/m², $p < 10^{-4}$) with a consistent increase in ejection fraction from 51 ± 8 to 59 ± 10% (+16%, $p < 10^{-5}$). Because of this increase in cardiac output and reduction in blood pressure, total systemic vascular resistance was significantly reduced by 30% (from 1,467 ± 493 to 1,033 ± 362 dynes cm^{-5}).

Ten minutes after the drug administration, at the time of the repeated LV angiogram, the peak LV pres-

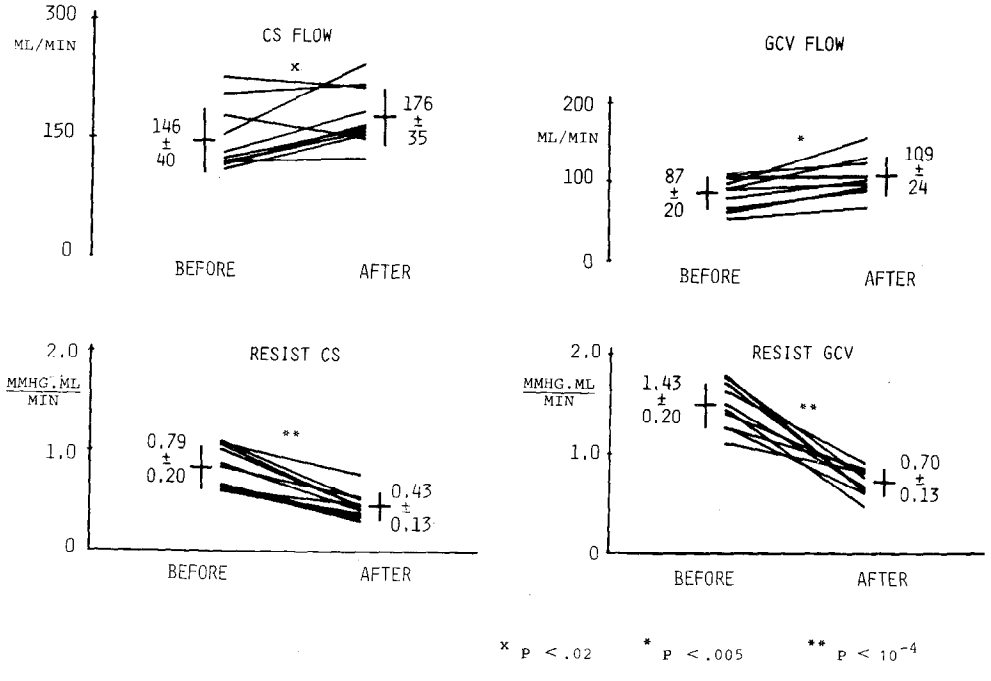

FIGURE 4. Individual and mean changes in global (CS) and regional (GCV) coronary vascular resistance and blood flow after intravenous administration of nisoldipine. Values represent mean ± standard deviation. RESIST CS = resistance calculated from coronary sinus blood flow; RESIST GCV = resistance calculated from great cardiac vein blood flow.

TABLE V Segments with Abnormal and Normal Contribution to Ejection Fraction (CREF)

Segments with Abnormal Contribution to Ejection Fraction				Segments with Normal Contribution to Ejection fraction			
No. of Segments		Sum of CREF*		No. of Segments		Sum of CREF†	
Before	After	Before	After	Before	After	Before	After
130	105	17 ± 8	21 ± 8	170	195	33 ± 13	36 ± 14

* $p < 0.02$; † $p < 0.05$.

sure had increased back from 108 to 127 mm Hg, and the different time constants measured during the second LV angiogram were no longer significantly shortened (Table IV).

From the regional wall displacement data, the CREF value was computed for each segment; 130 of 300 values were found abnormal, with a CREF value inferior to the tenth percentiles. Before administration of nisoldipine the sum of the CREF of these abnormal segments amounted to 17 ± 8% of the global ejection fraction, whereas the normal segments contributed 33 ± 13% to the ejection fraction (Table V). After nisoldipine therapy, 25 regions with functional impairment became normal and the sum of CREF values of these initially abnormal segments increased on average, from 17 ± 8% to 21 ± 8% ($p < 0.002$), whereas the sum of CREF of the normal segments ($n = 170$) increased relatively less, from 33 ± 13% to 36 ± 14% ($p < 0.05$). The regional functional improvement of patients with inferior and anterior wall dysfunction is shown in Figure 2.

Discussion

Effect on coronary blood flow: The present study confirms in humans that nisoldipine is a potent coronary vasodilator: Coronary blood flow and great cardiac vein flows increased significantly 3 minutes after administration of nisoldipine. With the decrease in mean aortic pressure, large calculated decreases in global (−50%) and regional (−50%) coronary vascular resistances were observed. These results are consistent with previously reported data from animal studies, in which measurable responses in coronary sinus blood flow were found with a dose as low as 0.3 to 0.5 μg/kg.[4,16]

This increase in the coronary sinus flow was associated with an increase in coronary sinus oxygen content, such that the calculated myocardial oxygen consumption did not decrease significantly. Of the main determinants of myocardial oxygen consumption, systolic and diastolic blood pressures were decreased while the isovolumic indexes of contractility, heart rate and stroke volume, were augmented, so that the myocardial oxygen consumption theoretically calculated according to the pressure work index of Rooke and Feigl[17] was only slightly reduced (−12%, $p < 0.02$).

The general profile of the response to this compound is similar to that of nifedipine. It can generally be interpreted as the result of afterload reduction associated with sympathetic counterregulation.[18] In conscious dogs, additional β blockade significantly diminished the tachycardic effects but not the vasodilating actions of nisoldipine.[5] The vasodilating action then is not a result of stimulation of vascular β adrenoreceptors, but must be a result of direct action on vascular smooth muscle. Nisoldipine has been shown to be 10 times more potent than nifedipine in dilating the coronary system.[4]

The decrease in total peripheral resistance (−30%) observed in our patients appears less pronounced than the vasodilating effect found in the coronary vasculature (−50%). This observation supports the hypothesis that the main vasodilating effect is on the coronary vasculature.

Effect on the inotropic state: Nisoldipine appears in vitro to be equipotent to nifedipine in inhibiting contractions of the isolated heart and thus behaves as a typical calcium antagonist. However, because of the high vascular specificity, very low doses of the drug are pharmacologically effective without a major negative inotropic effect.[5] Accompanying the decrease in afterload, the ejection as well as isovolumic indexes of contractility increased. This increase was not related to a change in heart rate since all the measurements were performed at a paced heart rate slightly above the spontaneous rhythm. This slight positive inotropic response may be explained by the sympathetic counterregulation that triggers not only an increase in heart rate, but also a release of catecholamines.[19] From the CREF values, our findings show that nisoldipine improves the function of hypokinetic segments at rest, because 25 of 130 chronically underperfused but noninfarcted areas demonstrated improvement in wall motion. It is doubtful that nisoldipine's coronary vasodilating action was the main reason for the improvement in ventricular function at rest. The improvement probably resulted from the LV afterload reduction.

Effect on isovolumic relaxation: Recent experimental studies have underscored the role of the calcium influx-efflux mechanism in regulating the relaxation of the myocardial cell.[20] LV isovolumic relaxation time is often abnormally prolonged in patients with coronary artery disease leading to regional asynergy.[8,11,21] According to previous reports,[21,22] this resting alteration in LV relaxation is probably due to the presence of fibrotic scar tissue within still viable myocardium in which the biochemical processes of activation-contraction-relaxation has been disturbed by chronic ischemia. Such increased stiffness is often seen after anginal attacks.

In the present study, the isovolumic relaxation period was evaluated by using a biexponential model. At a paced heart rate, the intravenous administration of nisoldipine shortened some of the most sensitive indexes of isovolumic relaxation time, such as the time constant for the first 40 ms of the relaxation phase. Because it was demonstrated that myocardial ischemia leads to asynergy of wall motion, which can play a major role in altering the time course of the isovolumic pressure decrease,[22,23] improvement of the asynergic zones may result in a more synchronous and rapid relaxation of the whole ventricle.

Nisoldipine in this study did not produce any overt untoward effects, but hemodynamic changes occurred that would seem beneficial in the treatment of coronary artery disease. The effects of nisoldipine in a continuous infusion remains to be determined in patients with both normal and impaired LV function. Oral nisoldipine has already been investigated in patients with congestive heart failure where it reduces LV filling pressure and increases stroke volume index by simultaneously reducing cardiac pre- and afterload.[24] The effect of nisoldipine on venous tone in this study is uncertain. There was no change in measured LV end-diastolic pressure; however, marked increases in cardiac output and thus venous return could have maintained LV end-diastolic pressure despite a decrease in venous tone. Direct assessment of venous tone (e.g., by forearm vascular capacitance) would be required to assess the relative venous vs arterial vasodilating effects of nisoldipine.

Acknowledgment: We thank A. J. Koster and A. P. van Huuksloot for preparing this manuscript.

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