

Direct Cardiac and Peripheral Vascular Effects of Intracoronary and Intravenous Nifedipine

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The hemodynamic effects of a new parenteral formulation of nifedipine administered by the intravenous (1 mg) and intracoronary (IC) (0.1 and 0.2 mg) routes were studied in 10 patients with symptomatic coronary artery disease undergoing diagnostic right- and left-sided cardiac catheterization. Intravenous nifedipine (1 mg) reduced systemic vascular resistance by 34% ($p < 0.01$), increased cardiac output by 28% ($p < 0.01$) and decreased mean arterial pressure by 10% ($p < 0.01$). It had less effect on peak positive dP/dt (-8% $p < 0.025$) and on peak negative dP/dt (-15% $p < 0.01$). Coronary blood flow increased 20% ($p < 0.025$). In contrast, IC nifedipine (0.2 mg) increased coronary blood flow 46% ($p < 0.025$),

depressed contractility as assessed by peak positive dP/dt (-26% $p < 0.01$) and prolonged diastolic relaxation time. The effect of 0.1 mg was similar but less pronounced. These data suggest that the primary therapeutic effect of nifedipine administered systemically to patients at rest results from an increase in coronary blood flow and, to a lesser extent, from afterload reduction; its myocardial depressant effects are small, transient and masked by reflex catecholamine release. IC nifedipine increases coronary blood flow, has a transient negative inotropic effect and prolongs relaxation. The relative importance of these myocardial effects in preventing myocardial ischemia is not known.

(Am J Cardiol 1986;58:25-30)

Nifedipine, a calcium-channel blocking drug, has negative inotropic and vasodilatory effects in vitro, but acts primarily as a vasodilator in vivo.^{1,2} It is effective in the treatment of angina pectoris due to coronary vasospasm³⁻⁵ or after exertion.⁶⁻⁸ Administered systemically, its efficacy in ameliorating pacing- and exercise-induced angina has been attributed to afterload reduction,^{6,7,9,10} to increased coronary blood flow^{9,11}—via a direct vasodilatory effect or by reducing extrinsic coronary vascular compressive forces in diastole^{8,10}—and to a direct myocardial effect.¹² Administered by the intracoronary (IC) route, nifedipine increases coronary sinus flow,¹¹⁻¹³ decreases myocardial oxygen consumption,^{13,14} relieves spontaneous or ergonovine-induced coronary artery spasm⁴ and prolongs regional shortening,¹⁵ thereby prolonging relaxation time.¹⁶ Kaltenbach et al¹² observed that the antianginal effect

of IC nifedipine persisted for 10 minutes longer than its effect on hemodynamics and on coronary flow and, on that basis, suggested that intracoronary nifedipine has a direct myocardial effect. This study relates the direct myocardial effects of the drug administered by the IC route to changes in coronary blood flow in patients with ischemic disease, and compares these effects with those of nifedipine administered by the intravenous (IV) route.

Methods

Patients: Ten patients (8 men, 2 women), 38 to 59 years old, who underwent diagnostic cardiac catheterization for symptomatic coronary artery disease were studied (Table I). Mean ejection fraction was 63%. None had valvular or congenital heart disease, unstable angina, second- or third-degree heart block, major systemic disorders or diabetes mellitus.

Protocol: Topical nitrate and β -blocker therapy were stopped 48 hours, and calcium-channel blocker therapy 72 hours before catheterization. After routine right- and left-sided cardiac catheterization and coronary arteriography, the baseline hemodynamic values were measured. They included heart rate, blood pressure, left ventricular pressure (4Fr or 5Fr Millar micro-

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TABLE I Clinical Characteristics

Pt	Age (yr) & Sex	EF (%)	LV (s/d) (mm Hg)	% Diameter Stenosis at CA			
				LM	LAD	LC	R
1	38M	71	126/20	60	...
2	63F	63	146/11	70	...
3	63M	50	134/12	50
4	59M	54	140/6	...	40
5	55M	78	114/9	...	60
6	49M	76	115/8	...	90	70	...
7	46M	67	103/14	90	...
8	50M	55	106/6	...	70	...	80
9	50M	45	124/11	...	90	...	90
10	57M	68	107/12	...	50	...	90

CA = coronary arteriography; EF = ejection fraction; LAD = left anterior descending artery; LC = left circumflex artery; LM = left main artery; LV (s/d) = left ventricular systolic/end-diastolic pressure; R = right coronary artery.

manometer-tip catheter), electronically differentiated left ventricular dP/dt, pulmonary capillary wedge, pulmonary artery and right atrial pressures, cardiac output (thermodilution, Swan-Ganz catheter) and coronary sinus flow (thermodilution, Wilton-Webster catheter through the left antecubital vein). Measurement of coronary blood flow remained stable: coronary flows measured before infusion of different doses were the same, and coronary flows at the end of a period of observation were the same as at the beginning (Tables II, III and IV). After 2 successive measurements were stable, nifedipine (0.1 mg/10 ml of vehicle) was infused over 30 seconds with an infusion pump (Harvard model 2803) into the left coronary artery. Pressures, cardiac output and coronary sinus flow were measured at baseline, after the infusion was stopped (time 0) and at 1, 3, 5 and 10 minutes. After restabilization of measurements, 0.2 mg/10 ml of vehicle was infused over 60 seconds and measurements

were repeated. Then, 1 mg was infused by the IV route over 3 minutes; measurements were made at the end of infusion, at 1, 3, 5 minutes and every 5 minutes thereafter for 30 minutes.

Evaluation of data: All phasic pressures were determined as the mean of 5 successive sinus beats over 1 respiratory cycle. Cardiac outputs represent the mean of 3 measurements. The value of a hemodynamic parameter was calculated as the absolute or percent difference between the baseline value and each subsequent value. The time constant of relaxation, τ , was derived from the best fit of a monoexponential to the time course of isovolumic left ventricular pressure decay.^{17,18} The correlation coefficients for these experimental fits were never less than 0.97. Statistical significance was determined using a Student *t* test on paired differences between the value of a hemodynamic variable at any time during the infusion and its baseline value.

Results

Systemic effects of nifedipine (Tables II, III and IV, Fig. 1 and 2): After IV administration, left ventricular systolic pressure decreased by 22 ± 12 mm Hg ($p < 0.01$), mean arterial pressure by 10 ± 6 mm Hg ($p < 0.01$) and systemic vascular resistance by 422 ± 228 dynes s cm^{-5} ($p < 0.01$). These effects lasted for only 5 to 10 minutes. Heart rate increased transiently and cardiac index rose by 0.8 ± 0.6 liters/min/m² ($p < 0.01$). As assessed by systolic pressure-rate product, external cardiac work was reduced for at least 15 minutes after drug administration. Left ventricular end-diastolic pressure, peak positive and negative dP/dt and τ changed little. In contrast, the systemic effects of IC nifedipine were small and short-lived.

Direct effects of nifedipine (Tables II, III and IV, Fig. 1 and 2): Cardiac: IC nifedipine (0.1 mg) depressed

TABLE II Hemodynamic Effects of Intracoronary Nifedipine (0.1 mg)

	Baseline	Time (minutes)				
		0	1	3	5	10
PCW (mm Hg)	7 ± 2(9)	+7 ± 1(2) [‡]	+0.8 ± 2.5(6)	+0.9 ± 2.2(7)	+1.0 ± 2.0(8)	+2.4 ± 2.2(8) [†]
LVEDP (mm Hg)	10 ± 5	+2 ± 6	+1 ± 5	0 ± 4(9)	+1 ± 3	+1.4 ± 4
+dP/dt (mm Hg/s)	1,067 ± 171	-223 ± 118*	-110 ± 113 [†]	-4 ± 73	-4 ± 73	
-dP/dt (mm Hg/s)	1,231 ± 203	-360 ± 216*	-221 ± 83*	-88 ± 113(9)	-72 ± 126	-55 ± 86
τ (s ⁻¹)	45.0 ± 6.9	+6.2 ± 32	+4.2 ± 20.0	+0.6 ± 14.5	—	+0.5 ± 9.6
CBF (ml/min)	162 ± 27(6)		+62 ± 49(6) [‡]	+16 ± 22(2)	+4 ± 8(6)	+2 ± 26(6)
CVR (mm Hg/ml/min)	0.56 ± 0.14(6)		-0.18 ± 0.15(5)	+0.08 ± 0.11(6)	+0.03 ± 0.19(5)	-0.01 ± 0.15(5)
HR (beats/min)	73 ± 10	+7 ± 7*	+4 ± 6	0 ± 6(9)	0 ± 6	+2 ± 7
MAP (mm Hg)	94 ± 11	-11 ± 4(5)	-6 ± 7(7)	-1 ± 7(7)	-4 ± 7(8)	0 ± 14(9)
LVSP (mm Hg)	122 ± 15	-16 ± 12*	-8 ± 13	-4 ± 6(9)	+4 ± 6 [‡]	+3 ± 12
CO (liters/min)	5.6 ± 0.7		+0.4 ± 0.4(6)	+0.4 ± 0.4(7)*	0.2 ± 0.3(9)	0.3 ± 0.5
CI (liters/min/m ²)	2.8 ± 0.3		0.2 ± 0.2(6)	+0.3 ± 0.2(7)*	-0.1 ± 0.1(9) [†]	+0.2 ± 0.2 [†]
SVR (dynes s cm^{-5})	1,296 ± 236		-201 ± 253(5)	-106 ± 116(6)	-33 ± 124(9)	-93 ± 221
DP (% of baseline)	100		99 ± 10		100 ± 10	110 ± 15

Data are expressed as the mean change from baseline ± standard deviation. The number of patients evaluated is in parentheses unless the number is 10.

* $p < 0.01$; [†] $p < 0.025$; [‡] $p < 0.05$ by paired *t* test.

CBF = coronary blood flow; CI = cardiac index; CO = cardiac output; CVR = coronary vascular resistance; DP = double product; +dP/dt = peak positive dP/dt; -dP/dt = peak negative dP/dt; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; MAP = mean arterial pressure; PCW = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; τ = time constant of relaxation.

TABLE III Hemodynamic Effects of Intracoronary Nifedipine (0.2 mg)

	Baseline	Time (minutes)				
		0	1	3	5	10
PCW	8 ± 3	+3 ± 3(6)	-2 ± 6(9)	0 ± 3	0 ± 2	0 ± 2(8)
LVEDP	11 ± 3	+6 ± 4*	+3 ± 3 [‡]	+1 ± 4(9)	+1 ± 2	-2 ± 2(8) [†]
+dP/dt	1,068 ± 169	-273 ± 116*	-174 ± 93*	-25 ± 85(9)	-2 ± 48(10)	-16 ± 90(8)
-dP/dt	1,169 ± 164	-327 ± 173*	-176 ± 142*	-113 ± 292(9)	-7 ± 65(9)	+32 ± 87(8)
τ	48.6 ± 9.3	+13.1 ± 8.0*	+7.1 ± 10.8(8)	-5.7 ± 9.4(7)	-5.7 ± 9.4(7)	+0.2 ± 7.9
CBF	172 ± 30(6)		+79 ± 71(6) [‡]	+1 ± 10(4)	-9 ± 37(6)	-2 ± 31(6)
CVR	0.51 ± 0.12(6)		-0.16 ± 0.12(6) [†]	-0.09 ± 0.07(4)	+0.08 ± 0.14(6)	+0.05 ± 0.11(6)
HR	71 ± 8	+11 ± 8*	+8 ± 11	+2 ± 7	-1 ± 6	+1 ± 7
MAP	92 ± 9	-6 ± 3(5)	-5 ± 11(9)	+1 ± 12	+6 ± 13	+4 ± 15(8)
LVSP	123 ± 14	-19 ± 7*	-12 ± 12 [†]	-2 ± 7	-1 ± 8	+1 ± 10(8)
CO	5.8 ± 0.5		+0.7 ± 0.8(8) [‡]	+0.5 ± 1.0(4)	0.0 ± 0.7	+0.1 ± 0.7(8)
CI	2.9 ± 0.3		0.2 ± 0.4	+0.2 ± 0.4(4)	+0.0 ± 0.5	+0.0 ± 0.4
SVR	1,197 ± 169		-130 ± 165(9) [‡]	-91 ± 166(4)	+110 ± 190	+48 ± 159
DP	100	96.5 ± 15.4	96.0 ± 19.0		102 ± 0	103 ± 17

Data are expressed as the mean change from baseline ± standard deviation. The number of patients evaluated is in parentheses unless the number is 10.

* p < 0.01; [†] p < 0.025; [‡] p < 0.05 by paired t test.

Abbreviations as in Table I.

peak positive dP/dt by 223 ± 118 mm Hg/s (p < 0.01) and 0.2 mg of nifedipine by 273 ± 116 mm Hg/s (p < 0.01), significantly more than did IV nifedipine (87 ± 90 mm Hg/s p < 0.025). These effects were transient. Nifedipine (0.2 mg IC) significantly depressed early diastolic relaxation: τ was prolonged by 30% (p < 0.01). It also reduced compliance, as reflected by the increase in left ventricular end-diastolic pressure. Although IV nifedipine significantly reduced peak negative dP/dt, the effect was not significant, since τ was unaffected.

Coronary vascular: Both IV and IC nifedipine reduced coronary vascular resistance by 30 to 40%. IC nifedipine, 0.1 mg, increased coronary blood flow by 39 ± 17% (p < 0.05), and 0.2 mg by 46 ± 17% (p < 0.05) without altering myocardial oxygen consumption as assessed by the systolic pressure-rate product. IV ni-

fedipine increased coronary blood flow by only 20%; nonetheless, this occurred without a significant reduction in systolic pressure-rate product.

Discussion

Our data suggest that the antianginal effect of IV nifedipine results more from an increase in myocardial oxygen supply than from a reduction in myocardial oxygen consumption or in myocardial contractility. Despite the marked decrease in systemic vascular resistance, the reduction of mean arterial pressure was small. Reflex tachycardia, reflecting catecholamine release, precluded a marked and sustained reduction of systolic pressure-rate product, an adequate index of myocardial oxygen consumption that takes catecholamine effects into account.¹⁹ Koch²⁰ observed higher catecholamine levels among patients undergoing su-

TABLE IV Hemodynamic Effects of Intravenous Nifedipine (1.0 mg)

	Baseline	Time (minutes)					
		0	1	3	5	10	30
PCW	8 ± 2	1 ± 2(8)	+1 ± 2(6)	+1.3 ± 2.4(8)	+1 ± 2	0 ± 2	0 ± 2
LVEDP	12 ± 4	+1 ± 4	0 ± 3	+1 ± 3	+1 ± 3	+1 ± 4	0 ± 3(9)
+dP/dt	1,081 ± 203	-87 ± 90 [†]	-53 ± 105	+29 ± 55	+18 ± 97	-20 ± 89	+11 ± 135
-dP/dt	1,192 ± 151	-172 ± 131*	-102 ± 199	-54 ± 123	-76 ± 86 [†]	-52 ± 79	-7 ± 133(9)
τ	48.3 ± 10.8	+5.8 ± 11.1	+2.1 ± 9.8(9)	+4.1 ± 9.4(9)	+4.1 ± 9.4(9)	+1.3 ± 9.2	-4.3 ± 10.8
CBF	162 ± 43(6)		+34 ± 28(6) [†]	+23 ± 23(5)	+27 ± 55(6)	+12 ± 19(6)	+22 ± 47(6)
CVR	0.55 ± 0.11(6)		-0.17 ± 0.05(5)*	-0.09 ± 0.07(5) [‡]	-0.02 ± 0.15(6)	-0.05 ± 0.07(6)	-0.05 ± 0.08(6)
HR	74 ± 9	+13 ± 12*	+10 ± 7 [†]	+6 ± 8	+2 ± 8	+1 ± 6	-1 ± 8
MAP	94 ± 7	-10 ± 6(9)*	-13 ± 5(8)*	-8 ± 6	-4 ± 7	-4 ± 4	0 ± 6
LVSP	123 ± 17	-22 ± 12*	-21 ± 12*	-14 ± 13*	-11 ± 13*	-11 ± 9*	+1 ± 13
CO	5.9 ± 0.9		+1.7 ± 1.1(9)*	+1.2 ± 0.6(9)*	+0.4 ± 1.0(8)*	0.4 ± 0.6 [‡]	-0.2 ± 1.0
CI	3.0 ± 0.5		+0.8 ± 0.6*	0.6 ± 0.3(9)*	0.5 ± 0.5(9)*	+0.2 ± 0.3	-0.1 ± 0.4
SVR	1,238 ± 262		-422 ± 228(8)*	-327 ± 161(8)*	-270 ± 229(9)*	-49 ± 400	-12 ± 188
DP	100	95 ± 8.8	94 ± 7		94 ± 10	92 ± 9	103 ± 14.6

Data are expressed as the mean change from baseline ± standard deviation. The number of patients evaluated is in parentheses unless the number is 10.

* p < 0.01; [†] p < 0.025; [‡] p < 0.05 by paired t test.

Abbreviations as in Table I.

pine bicycle exercise after administration of nifedipine than among control subjects.

Our data are in agreement with those of Schanzenbacher et al,¹³ who administered IV nifedipine to patients at rest, and with those of Specchia et al,¹¹ who reported that the antianginal potency of nifedipine administered systemically to patients with exercise-induced angina was attributable almost entirely to an increase in coronary blood flow. However, our data are at variance with other reports. Engel,⁹ Emanuelsen¹⁰ and their co-workers attributed the efficacy of nifedipine administered systemically to patients with pacing-induced angina both to afterload reduction and to increased myocardial perfusion. Moskowitz et al⁶ found that systemic nifedipine ameliorated exercise-induced angina by reducing the double product at a given workload; however, myocardial oxygen supply was not measured. Kaltenbach et al¹² reported that IV nifedipine reduced afterload and increased coronary

blood flow, but also invoked a "direct myocardial influence" to explain the drug's antianginal effect. These differences may be explained by different doses and routes of drug administration, by the different levels of activity of the subjects or by different degrees of myocardial dysfunction.

The direct myocardial and coronary vascular effects of IC nifedipine help to rationalize the drug's transient antianginal effect. IC nifedipine depressed contractility, as evidenced by the decrease in peak positive dP/dt, which occurred despite an increase in heart rate; this was not attributable to the decrease in mean arterial pressure, since a larger and more sustained decrease in arterial pressure after IV nifedipine was not accompanied by a reduction of peak positive dP/dt of a similar magnitude or duration.²¹ This observation is compatible with that of Serruys et al,¹⁵ who noted prolongation of systolic shortening in the distribution of vein grafts after injection of nifedipine. Relaxation was prolonged, as observed by Serruys,²² Rousseau¹⁶ and their co-workers, probably because of drug-induced asynchronous myocardial contraction¹⁶ or to a direct myocardial effect on relaxation. Coronary blood flow was markedly increased in the absence of a significant change in double product. Although these effects explain a short-term antianginal effect observed by others,^{13,15} they do not explain the prolonged antianginal efficacy of IC nifedipine in exercise-induced ischemia reported by Kaltenbach et al.¹² It is possible that autoregulatory mechanisms governing coronary blood flow mobilized by pacing- or exercise-induced ischemia may potentiate the effects of nifedipine, or that a direct biochemical effect of the drug not studied explicitly may persist for up to 15 minutes.

Nifedipine has been reported to normalize relaxation⁸ when it is prolonged by ischemia²³⁻²⁷; under non-ischemic conditions, it prolongs relaxation.^{16,22} IC nifedipine reduced peak negative dP/dt, although the effect may have been partially antagonized by catecholamine release.^{28,29} At the higher dose, τ was significantly prolonged; at the lower dose, the reduction of peak negative dP/dt was attributable to a fall in left ventricular peak systolic pressure.^{17,18} Prolongation of diastole may reflect drug-induced slowing of calcium release in the perfused region, asynchronous contraction and subsequent prolonged relaxation.^{16,22} Under the nonischemic and eucalcemic conditions of this study, it is less likely that nifedipine improves relaxation by preventing intracellular calcium overload during systole, as suggested by recent studies of the effect of verapamil on chick embryo ventricular cells.³⁰

The present study confirms that the use of a parenteral formulation of nifedipine is safe, that IC nifedipine may be useful in the treatment of coronary spasm and that IV nifedipine may be useful in the treatment of hypertensive crises. In addition, the ability of IV nifedipine to lower systemic vascular resistance and increase cardiac output without depressing contractility suggests that it may be useful in the treatment of cardiac failure, particularly cardiac failure due to coronary artery disease.

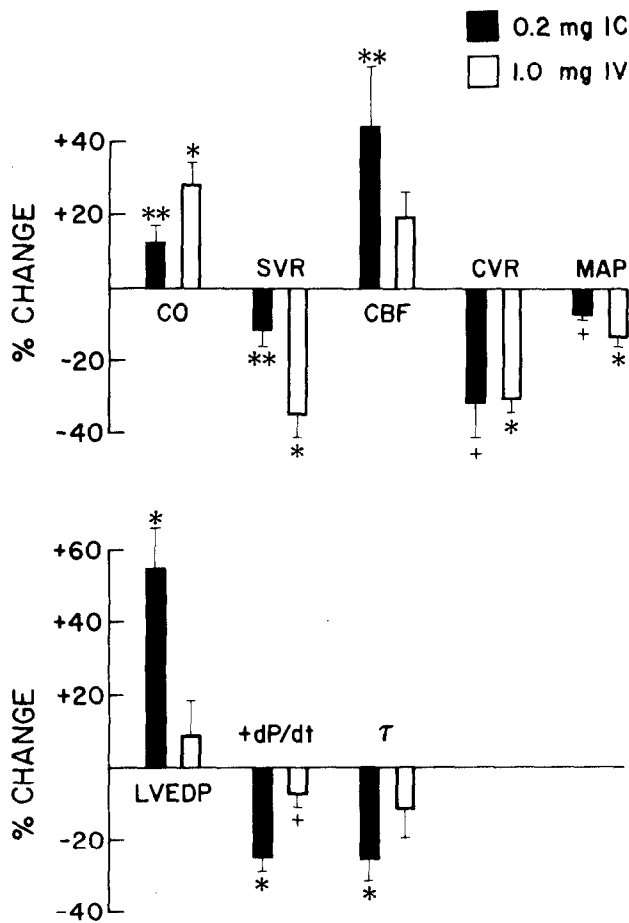


FIGURE 1. Peak hemodynamic effects of nifedipine infused by the intracoronary (IC) (0.2 mg) and intravenous (IV) (1.0 mg) routes. The difference between the baseline value and the peak value was calculated as a percentage of baseline value. The mean \pm standard error of the mean of the peak percentage change in all 10 patients is shown. * $p < 0.01$; † $p < 0.025$; ** $p < 0.05$ by paired t test. CBF = coronary blood flow; CO = cardiac output; CVR = coronary vascular resistance; +dP/dt = peak positive dP/dt; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; SVR = systemic vascular resistance; τ = time constant of relaxation.

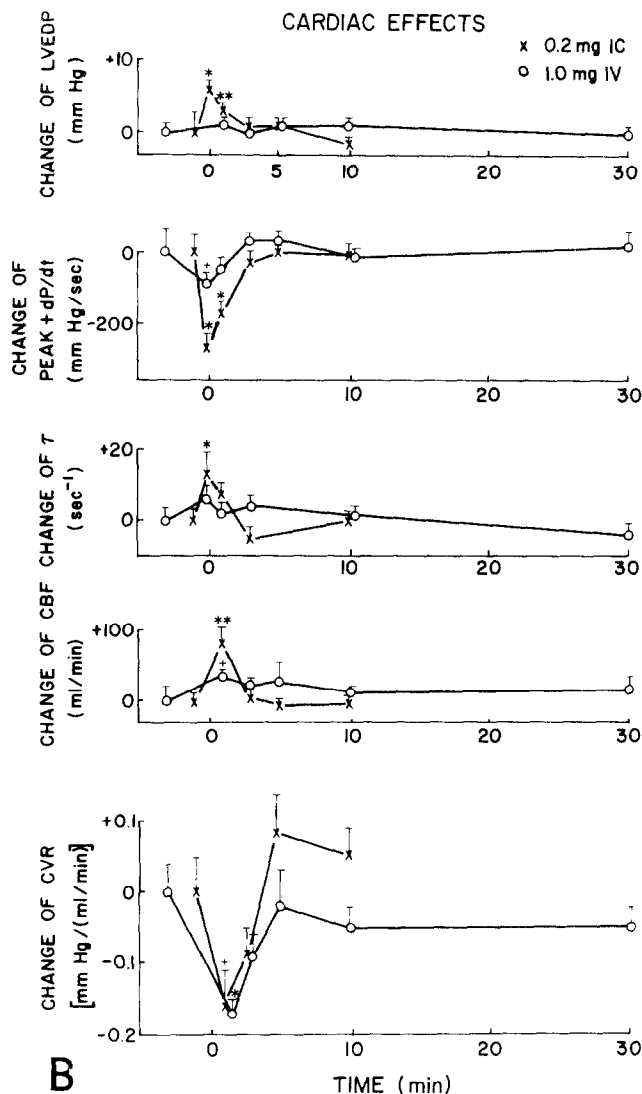
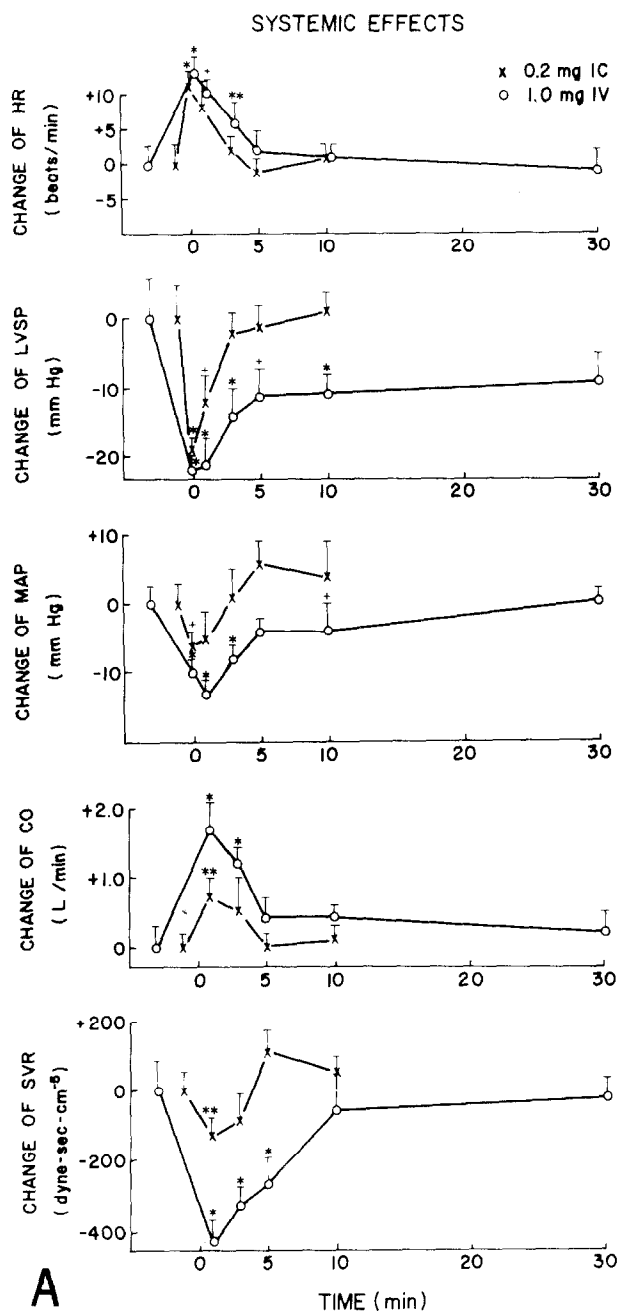


FIGURE 2. Time course of (A) systemic and (B) cardiac effects of 0.2 mg nifedipine infused by the intracoronary and 1.0 mg by the intravenous route. Data are expressed as absolute change from baseline value \pm standard error of the mean. * $p < 0.01$; † $p < 0.025$; ** $p < 0.05$ by paired *t* test. HR = heart rate; LVSP = left ventricular systolic pressure; other abbreviations as in Figure 1.

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