

Regional Wall Motion from Radiopaque Markers After Intravenous and Intracoronary Injections of Nifedipine

P. W. SERRUYS, M.D., R. W. BROWER, PH.D., H. J. TEN KATEN,
A. H. BOM, B.Sc., AND P. G. HUGENHOLTZ, M.D.

SUMMARY In 11 patients, 1 mg of i.v. nifedipine was administered over 3 minutes and regional wall motion was studied during atrial pacing. The dominant effect of nifedipine at basal heart rate (HR) was a lowering of peak left ventricular pressure (152 to 128 mm Hg) with an increase in HR from 70 to 86 beats/min. During pacing, nifedipine produced ($p < 0.02$) a similar reduction in pressure at all rates, which is a mechanism reducing or sparing myocardial oxygen consumption. At the highest paced rate, the maximal velocity (V_{max}) of the contractile element was significantly ($p < 0.02$) increased from 61 to 68 sec^{-1} and the regional shortening fractions were increased over the entire pacing range: basal HR, 13.7% to 14.6% ($p < 0.025$); HR 120 beats/min, 11.6% to 13.5% ($p < 0.005$); maximal HR, 10.9% to 11.8% ($p < 0.05$). No evidence of a negative inotropic effect after i.v. administration of nifedipine was observed, myocardial oxygen consumption was probably reduced and there was an increase in regional function.

Nifedipine (0.1 mg within 10 seconds) was selectively injected into bypass grafts at a constant paced rate in 10 patients. Seventeen marker pair regions were directly supplied by bypasses selectively injected with nifedipine (group A), and nine were independently perfused (group B). The pressure-derived variables showed a direct negative inotropic effect and a slowed relaxation phase. Thirty seconds after injection, minimal marker separation in group A occurred 78 msec after end-systole (ES), whereas before injection, minimal marker separation occurred 39 msec before ES ($p < 0.0001$). At the same time, the relation between minimal marker separation and ES in group B was unaffected. In consequence, the regional shortening fraction in group A contributing to left ventricular ejection decreased significantly 30 seconds after injection (-32% , $p < 0.01$), while that calculated simply from minimal and maximal marker separation remained unchanged (-9% , NS). Active regional contraction starting after the beginning of ejection and ending after ES must be considered as asynchrony and can be considered responsible for the slowed isovolumic contraction and relaxation of the whole ventricle. The dominant effect of i.v. nifedipine at clinical dosage levels is a lowering of systemic blood pressure, possibly reducing oxygen demand. When regionally administered, nifedipine exerts a direct negative inotropic effect, but after i.v. injection, this effect is overridden by reflex increases in contractility and in heart rate as a result of lowered systemic arterial pressure.

NIFEDIPINE has been classified as a calcium antagonist that inhibits the electromechanical coupling process¹ and results in the relaxation of the muscle fiber. For the blood vessel, this means vasodilation and for the myocardium, a negative inotropic effect. Therefore, early investigations of the effects of nifedipine on myocardial contractility described primarily a reduction in contractility and oxygen consumption for the isolated papillary muscle and for the isolated heart preparation,² but this negative inotropic effect has not been found in the intact resting heart in man at therapeutic dosages.³⁻⁵ This may be due to reflex activation of the sympathetic system caused by decreased arterial pressure when the peripheral vascular resistance is reduced under the influence of nifedipine. This effect is most clearly demonstrated as reflex tachycardia.

To override this compensatory reaction, we first

studied 11 coronary patients during pacing-induced tachycardia after i.v. injection of nifedipine. Regional shortening in the bypassed regions was measured from pairs of radiopaque markers implanted during surgery.⁶ The aim of this work, in its first stage, was to investigate the effects of nifedipine on regional and overall left ventricular (LV) contractility at rest and with the reflex increase in heart rate eliminated by atrial pacing. To determine the direct effect of nifedipine on the myocardium, we also injected nifedipine into bypass grafts in 10 patients with implanted radiopaque markers and monitored beat-to-beat ventricular performance continuously. We thereby determined the regional and global LV responses to this medication.

Materials and Methods

Patients

We studied 21 patients, selected on the basis of normal postoperative recovery from coronary artery bypass graft surgery without recurrent disabling angina pectoris, in two related protocols.

The first group of 11 patients (all males) received i.v. injections of nifedipine 1 year after coronary artery bypass grafting. Nine were in New York Heart Association (NYHA) functional class I and two were in class II. There was no evidence of perioperative or

From the Thoraxcenter, Erasmus University, Rotterdam, The Netherlands.

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Address for correspondence: Dr. R.W. Brower, Cardiovascular Research Ee 2332, Erasmus University, POB 1738, 3000 DR Rotterdam, The Netherlands.

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postoperative myocardial infarction, but nine patients had ECG evidence of old preoperative infarctions. The median ejection fraction (EF) was 0.54 and the median end-diastolic volume was 72 ml/m². In these patients, 29 marker pairs had been implanted and 26 bypass grafts had been placed; 23 grafts were patent 1 year after surgery. Twenty-one marker pairs were implanted in these successfully grafted regions: six pairs near the proximal or middle left anterior descending coronary artery (LAD) including the first and second diagonal branches, seven pairs near the marginal and posterolateral branches of the left circumflex (CX) artery, and eight pairs near the posterior portion of the right coronary artery (RCA). Six pairs of markers were implanted in nongrafted regions near the base of the left ventricle and classified as controls because the preoperative and postoperative angiograms revealed no disease in the arteries perfusing these regions. Two marker pairs were located in regions with occluded bypasses. One of them (occluded graft and coronary artery, preoperative myocardial infarction) showed paradoxical systolic expansion and was not included in the measurements.

In the second group of patients, also recatheterized 1 year after bypass grafting, the clinical data did not differ from those in the first group. Nine were in NYHA class I and one was in NYHA class II. The median EF was 0.62 and the median EDV was 64 ml/m². In this second group of patients, a total of 20 bypass grafts were placed, of which 17 remained patent 1 year after surgery. Sixteen selective intrabypass injections of nifedipine were performed. Seventeen pairs of markers were placed in selectively injected regions (10 LAD, four CX and three RCA) and nine pairs were placed in independently perfused regions (six control regions and three regions with occluded bypasses, but patent coronary arteries).

Intravenous Injection of Nifedipine

Catheterization was performed without premedication. Beta blockade, digitalis, and all other medications were withdrawn at least 48 hours before catheterization. After right-heart catheterization, but before angiography, LV and aortic pressures were recorded by tip micromanometry. A bipolar pacing electrode was placed in the right atrium. After control determination of LV pressure and marker motion, pacing was started just above control heart rate. The pacing rate was incremented by 20 beats/min, with a 1-minute interval for stabilization after each step, and 20 seconds for measurement of LV pressure and marker motion. An on-line computer system^{7, 8} with manual datachecks for correct phasing of the isovolumic period was used for the determination of peak LV pressure, LV end-diastolic pressure (LVEDP), peak positive dP/dt, and dP/dt/P linearly extrapolated to P = 0 (Vmax). Pacing was continued to 180 beats/min or until atrioventricular block occurred. There was no occurrence of precordial pain during the control pacing and during the test after nifedipine. The heart rates terminating the atrial pacing stress tests were identical for each patient during

the control and nifedipine stress tests. After the control pacing test, we waited 15 minutes and monitored the pressure-derived variables until they returned to control values. An i.v. infusion of 1 mg of nifedipine was performed over 3 minutes; all tests and measurements were repeated starting 3 minutes after the infusion ended. The atrial pacing stress test after nifedipine was performed in the same way as during the control determinations.

Direct Intrabypass Injection of Nifedipine

Before administration of nifedipine, up to 3 ml of contrast material were injected in patent grafts to verify selective positioning of the Sones catheter, but no other angiographic investigation was done before the measurements. One milliliter of a solution containing 0.1 mg of nifedipine was first introduced into the catheter, of which the dead space is 1.2 ml. At the appropriate moment the catheter was flushed with 2 ml of physiologic saline within 10 seconds. It has been shown in pigs that the solvent for nifedipine (ethanolic solution) has no activity on the heart (Verdouw PD: personal communication).

The heart was paced at 90 beats/min. Biplane marker motion was recorded before injection and 30, 60, 120 and 180 seconds after injection. Pressure was recorded continuously over 4 minutes and analyzed beat by beat.⁸ In addition to the variables measured during i.v. infusion of nifedipine, we determined several isovolumic relaxation phase variables: peak negative dP/dt and the time constant of relaxation (T) by least-squares fit of $P = e^{At} + B$ ($T = -1/A$) from the moment of peak negative dP/dt to a pressure of 35 mm Hg.

Regional Marker Motion

Regional shortening was determined from radiopaque markers implanted during surgery on the epicardium in each bypassed region, in pairs 2 cm apart and located from 0–3 cm distal to the coronary anastomosis.^{6, 9, 10} Five consecutive beats were filmed at midexpiration using synchronized biplane cinefilms (50 frames/sec) at 30° right anterior oblique and 60° left anterior oblique. Correction for x-ray and optical distortion was performed to give true anatomic dimensions (see Appendix). Because the biplane technique was used, the small errors due to lateral and transverse rotation were eliminated.¹⁰ The position of the Roentgen apparatus was not changed during sequential recordings. As shown in figure 1, separation of marker pairs was plotted with regard to the phase of the cardiac cycle. Lmax and Lmin are defined as the maximal and minimal marker separation. The shortening fraction calculated between these two points is given by $SF_{max} = (L_{max} - L_{min})/L_{max}$ and expressed as a percentage. The mean shortening rate is defined by $SR = SF_{max}/T_s$, where T_s is the time interval between Lmax and Lmin. Lej is the marker separation at beginning of ejection, defined as the onset of the upstroke of aortic pressure, and Les is the marker separation at end-systole, defined as the

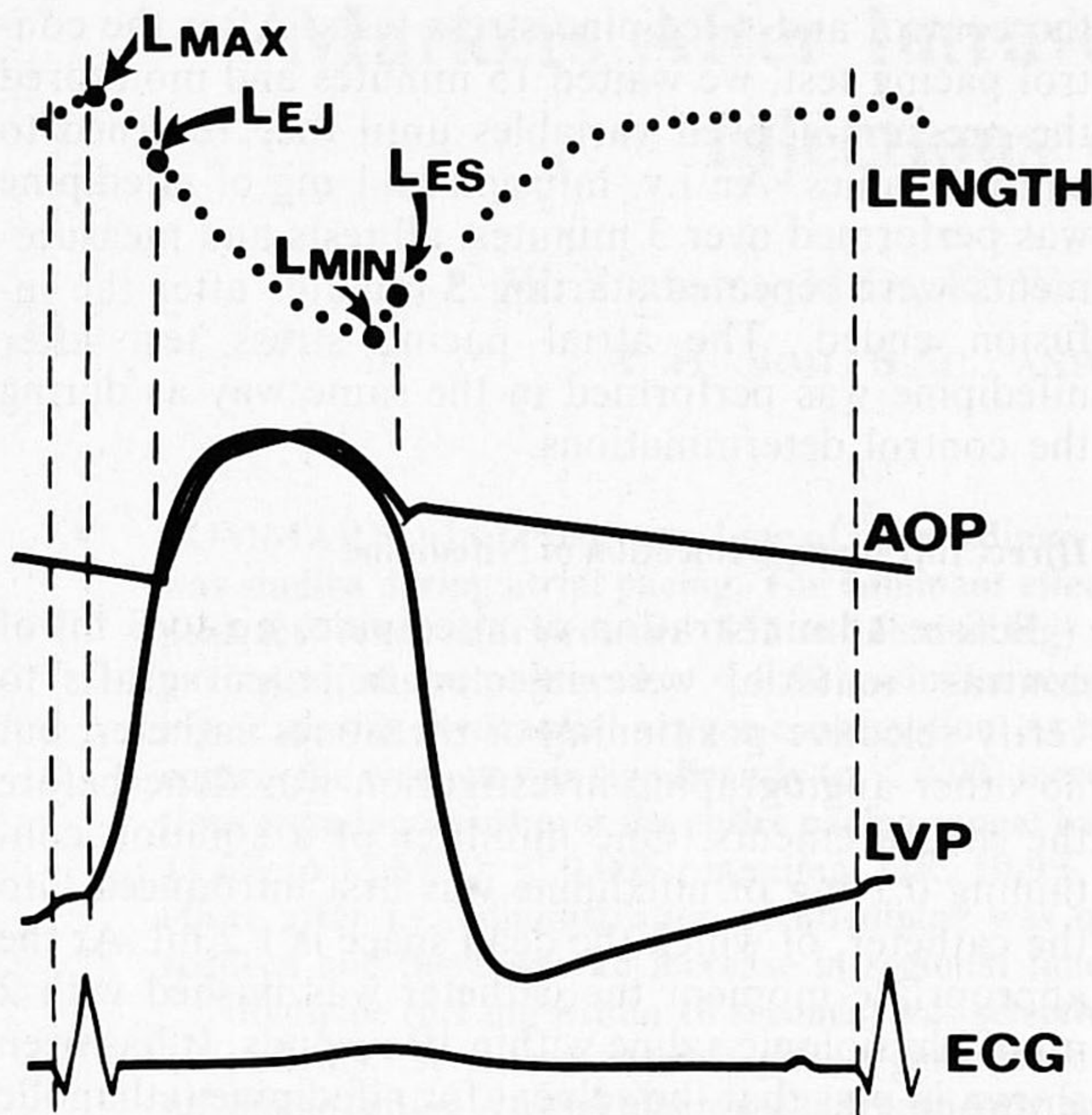


FIGURE 1. Relationship between cardiac cycle and regional length. L = marker separation; max = maximal value; min = minimal value; EJ = beginning of ejection; ES = end-systole; AOP = aortic pressure; LVP = left ventricular pressure.

occurrence of the incisura of the central aortic pressure. The shortening fraction contributing to LV ejection is calculated as: $SF_{ej} = (L_{ej} - L_{es})/L_{ej}$, and expressed as a percentage. The time intervals from onset of the Q wave (ECG lead II) to L_{max} , from L_{max} to L_{ej} , and from L_{es} to L_{min} were determined. The accuracy of these time interval measurements is limited by the sampling rate (20 msec/frame). However, a change of 40 msec between sequential measurements can be detected with 95% confidence.⁶ Each variable is expressed as the average of five consecutive beats. All data are reported as the mean \pm SEM. The paired *t* test was used where appropriate.

Because cinefilms were performed without repositioning the equipment or patient during data acquisition, the measurement error is primarily due to the beat-to-beat variability, which is defined as the pooled standard deviation in L_{max} divided by L_{max} and expressed as a percentage.⁶ For biplane recordings this averaged 0.66%. Given an L_{max} of 20 mm, a change of more than 0.26 mm for any one heart beat can be measured with 95% confidence. As we averaged the results of five beats, the 95% confidence band of the mean is less than 0.13 mm.

Results

Hemodynamics

Intravenous Injection

Intravenous nifedipine led to a significant ($p < 0.0001$) decrease in LV systolic pressure, from 152 to

128 mm Hg at basal heart rate. Simultaneously, there was an increase in the spontaneous heart rate, from 71 to 87 beats/min ($p < 0.0005$). The pressure-rate product remained unchanged (10,700 vs 11,200 mm Hg/min), as the drop in LV pressure was overridden by the increase in heart rate. End-diastolic pressure was unchanged after nifedipine (17 ± 1 to 18 ± 1 mm Hg). The pressure-derived variable V_{max} tended to increase (48 ± 3 to 53 ± 4 sec⁻¹), but this small change was not significant. The mean slope of V_{max} vs heart rate was 0.20 sec⁻¹/beats/min before nifedipine and 0.27 sec⁻¹/beats/min after nifedipine. Thus, an increase in heart rate of 16 beats/min would respectively induce an increment of 3.5 sec⁻¹ and 4.5 sec⁻¹ in V_{max} , showing that the change in V_{max} was secondary to the heart rate change.

During pacing-induced tachycardia, peak LV pressure remained 10 mm Hg below control values at both a heart rate of 120 beats/min and at the highest rate (147 beats/min during control, 148 beats/min with nifedipine). V_{max} at a heart rate of 120 beats/min was unchanged; however, at the highest paced rate, the tendency of V_{max} to increase (61 sec⁻¹ to 68 sec⁻¹) after nifedipine became significant at the 0.02 level (fig. 2). This observation confirms that nifedipine at therapeutic dosage appears to have no negative inotropic effect; indeed, nifedipine may have a slight positive inotropic effect. After i.v. nifedipine the peak LV pressure was reduced at all heart rates,

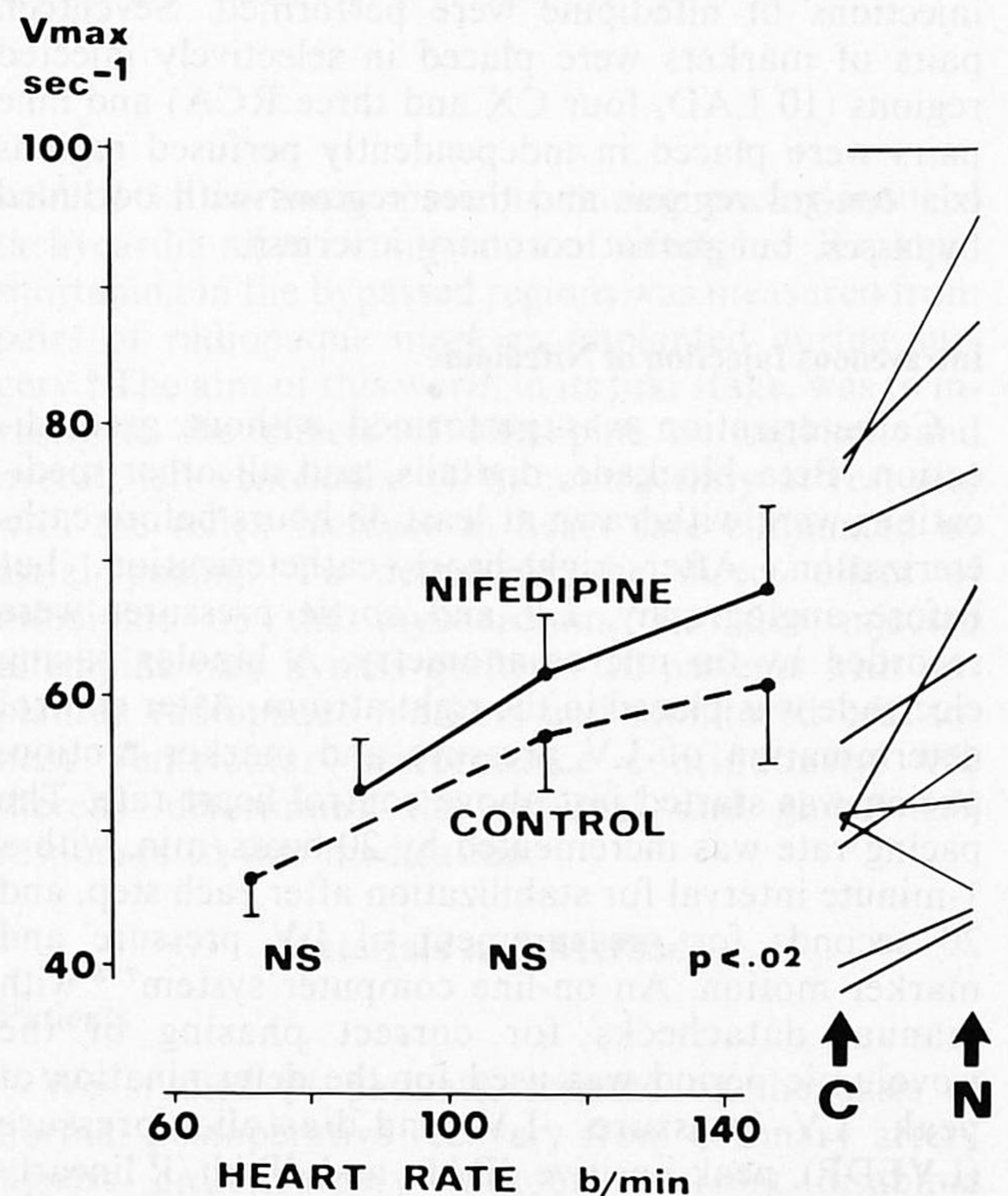


FIGURE 2. V_{max} from total pressure, control (C) vs nifedipine (N) (mean \pm SEM), at basal heart rate and during pacing-induced tachycardia. On the right side of the figure, V_{max} at the highest paced heart rate is plotted for individual patients.

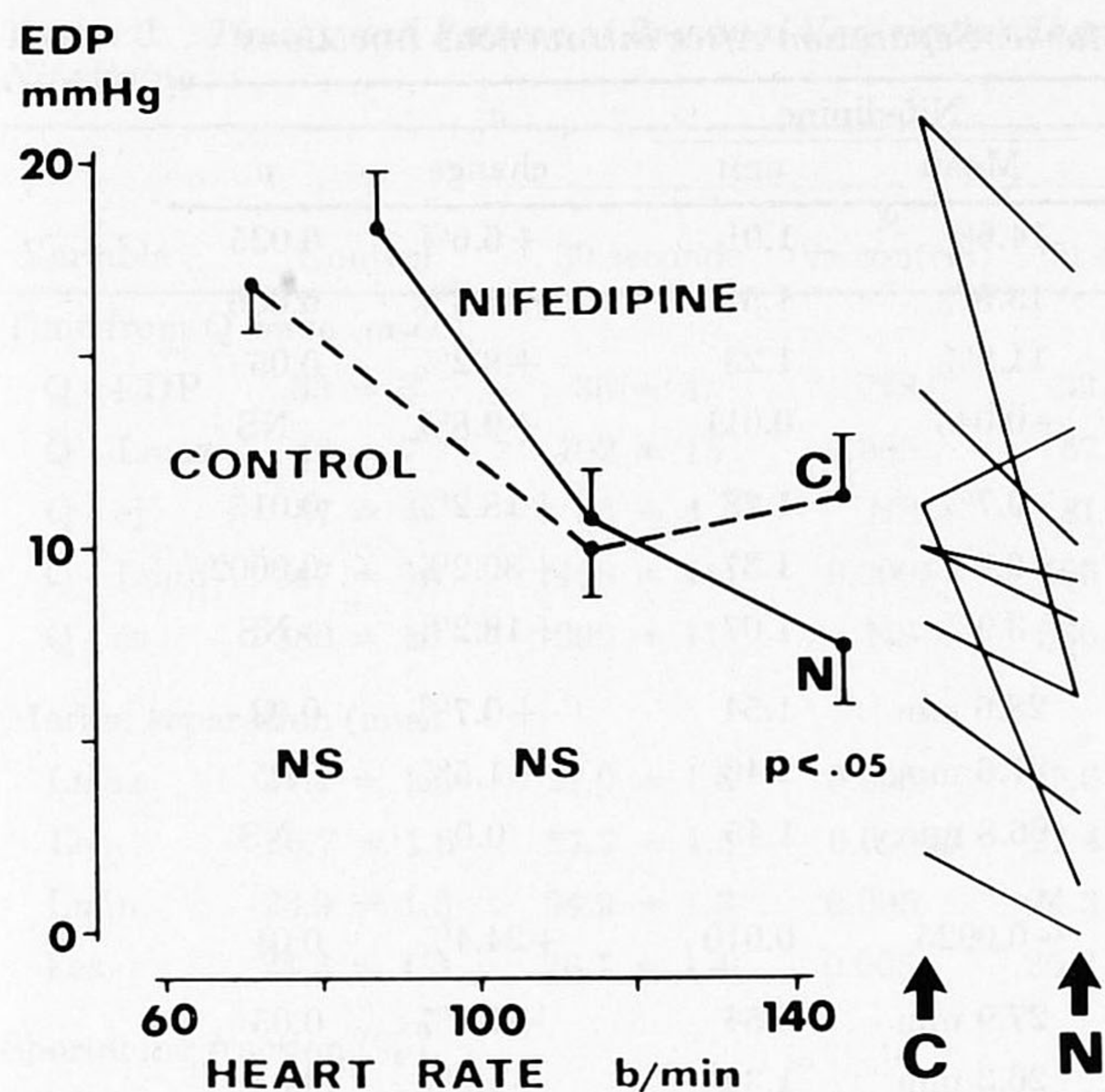


FIGURE 3. Left ventricular end-diastolic pressure (EDP) control (C) vs nifedipine (N) (mean \pm SEM) at basal heart rate and during pacing-induced tachycardia. On the right side of the figure, EDP at the highest paced heart rate is plotted for individual patients.

possibly reducing oxygen consumption, and contractility was unchanged or slightly increased.¹¹

End-diastolic pressure (EDP) showed no significant change at a heart rate of 120 beats/min (10 vs 10.5 mm Hg), but during the control pacing there was an increase at the highest pacing rate (fig. 3), which represents a compromised response.¹² After nifedipine, this increase disappeared, and the normal decrease in EDP was observed. Nevertheless, this response cannot be considered as completely normal because of the slightly elevated basal values, but rather as an improved response. After nifedipine, EDP decreased at the highest paced rate, from 11.2 to 7.4 mm Hg ($p < 0.05$), so that the negative slope of EDP vs heart rate increased from 0.095 to 0.190 mm Hg/beats/min ($p < 0.02$).

Intrabypass Injection

The changes in LV pressure produced by intrabypass injection of nifedipine at constant paced heart rate are shown in table 1. There was a decrease of 17 mm Hg in LV pressure 17 seconds after injection. Simultaneously, peak dP/dt and V_{max} decreased by 18% and 22%, respectively. Ten seconds after the peak effect on LV pressure, EDP increased by an average of 10 mm Hg. Peak negative dP/dt decreased by 26% and the time constant of relaxation increased by 38%, showing impaired relaxation simultaneously with the drop in LV pressure. These changes were transient and returned to control values within 5 minutes. As these measurements were performed at a constant paced heart rate (mean RR interval of 734 msec), a direct slowing of the contractile process and mechanism involved in relaxation must be inferred.

Myocardial Shortening

Intravenous Injection

The changes in myocardial shortening after i.v. nifedipine are shown in table 2. There is an increase in the shortening fraction over the entire pacing range, the greatest increment occurring at a common rate of 120 beats/min (fig. 4). The slope of the regression line of shortening fraction vs heart rate for control and nifedipine are virtually identical (table 2). The timing between the regional shortening and the cardiac cycle was also recorded. At spontaneous heart rate, the time of occurrence of L_{max} remains unchanged after i.v. nifedipine — 32 ± 7 msec after Q wave onset (ECG lead II) and 53 ± 7 msec before opening of the aortic valve. L_{min} occurs 6 ± 10 msec before closure of the aortic valve. Hence, the shortening fraction contributing to the ventricular ejection (SF_{ej}) was also increased over the entire pacing range. At spontaneous heart rate, there was a consistent but small increase in L_{max} of 0.2 mm (table 2) after nifedipine, although a decrease of 0.3 mm would be expected from the increase in spontaneous heart rate alone (71 vs 87 beats/min) (table 2, slope L_{max}). Indeed, at the paced rate of 120 beats/min, L_{max} increased by 0.4 mm. At

TABLE 1. Pressure-derived Variables After Intrabypass Injection of Nifedipine

	Control	Nifedipine peak effect	<i>p</i> (control vs peak effect)	Time to peak effect (seconds)
Peak LVP (mm Hg)	141 \pm 8	124 \pm 7	0.0001	17 \pm 3
EDP (mm Hg)	16 \pm 2	26 \pm 3	0.0001	27 \pm 4
Peak positive dP/dt (mm Hg \times sec ⁻¹)	1855 \pm 118	1521 \pm 72	0.001	19 \pm 3
V_{max} (sec ⁻¹)	55 \pm 3	43 \pm 2	0.0001	23 \pm 3
Peak negative dP/dt (mm Hg \times sec ⁻¹)	2133 \pm 135	1575 \pm 86	0.0001	20 \pm 2
Time constant of relaxation (msec)	39 \pm 2	54 \pm 3	0.0001	21 \pm 3

Values are for 16 injections, mean \pm SEM. Basal hemodynamics were recorded at a fixed heart rate (mean RR interval 734 msec).

Abbreviations: LVP = left ventricular pressure; EDP = end-diastolic pressure; V_{max} = maximal velocity.

TABLE 2. Measurement of Shortening Fraction and Marker Separation After Intravenous Injections

Variable	Control		Nifedipine		% change	p
	Mean	SEM	Mean	SEM		
SFmax (basal HR)	13.7%	0.88	14.6%	1.01	+6.6%	0.025
SFmax (110-120 beats/min)	11.6%	1.13	13.5%	1.51	+16.4%	0.005
SFmax (HP HR)	10.9%	1.11	11.8%	1.23	+8.2%	0.05
Slope SFmax vs HR	-0.041	0.009	-0.045	0.011	+9.8%	NS
SFej (basal HR)	8.2%	1.11	9.7%	1.28	+18.2%	0.015
SFej (110-120 beats/min)	5.3%	1.29	6.9%	1.37	+30.2%	0.0002
SFej (HP HR)	3.3%	1.01	3.9%	1.07	+18.2%	NS
Lmax (basal HR)	28.4 mm	1.53	28.6 mm	1.54	+0.7%	0.02
Lmax (110-120 beats/min)	27.2 mm	1.45	27.6 mm	1.46	+1.5%	0.05
Lmax (HP HR)	26.8 mm	1.45	26.8 mm	1.45	0.0	NS
Slope Lmax/Lmax (120) vs HR (10 ⁻² /beats/min)	-0.0745	0.010	-0.0925	0.010	+24.4%	0.01
Lej (basal HR)	27.6 mm	1.48	27.9 mm	1.54	+1.0%	0.05
Lej (110-120 beats/min)	26.0 mm	1.32	26.3 mm	1.30	+1.2%	0.05
Lej (HP HR)	25.5 mm	1.36	25.4 mm	1.33	-0.4%	NS
Lmin (basal HR)	24.4 mm	1.27	24.4 mm	1.29	0.0	NS
Lmin (110-120 beats/min)	23.9 mm	1.28	23.9 mm	1.28	0.0	NS
Lmin (HP HR)	23.9 mm	1.29	23.6 mm	1.28	-0.8%	0.025
Les (basal HR)	25.3 mm	1.33	25.0 mm	1.30	-1.2%	0.05
Les (110-120 beats/min)	24.6 mm	1.36	24.5 mm	1.34	-0.4%	NS
Les (HP HR)	24.5 mm	1.28	24.4 mm	1.28	-0.4%	0.05

Abbreviations: max = maximal value; min = minimal value; SF = shortening fraction; ej = beginning of ejection; es = end-systole; L = absolute marker separation; HP = highest paced; HR = heart rate.

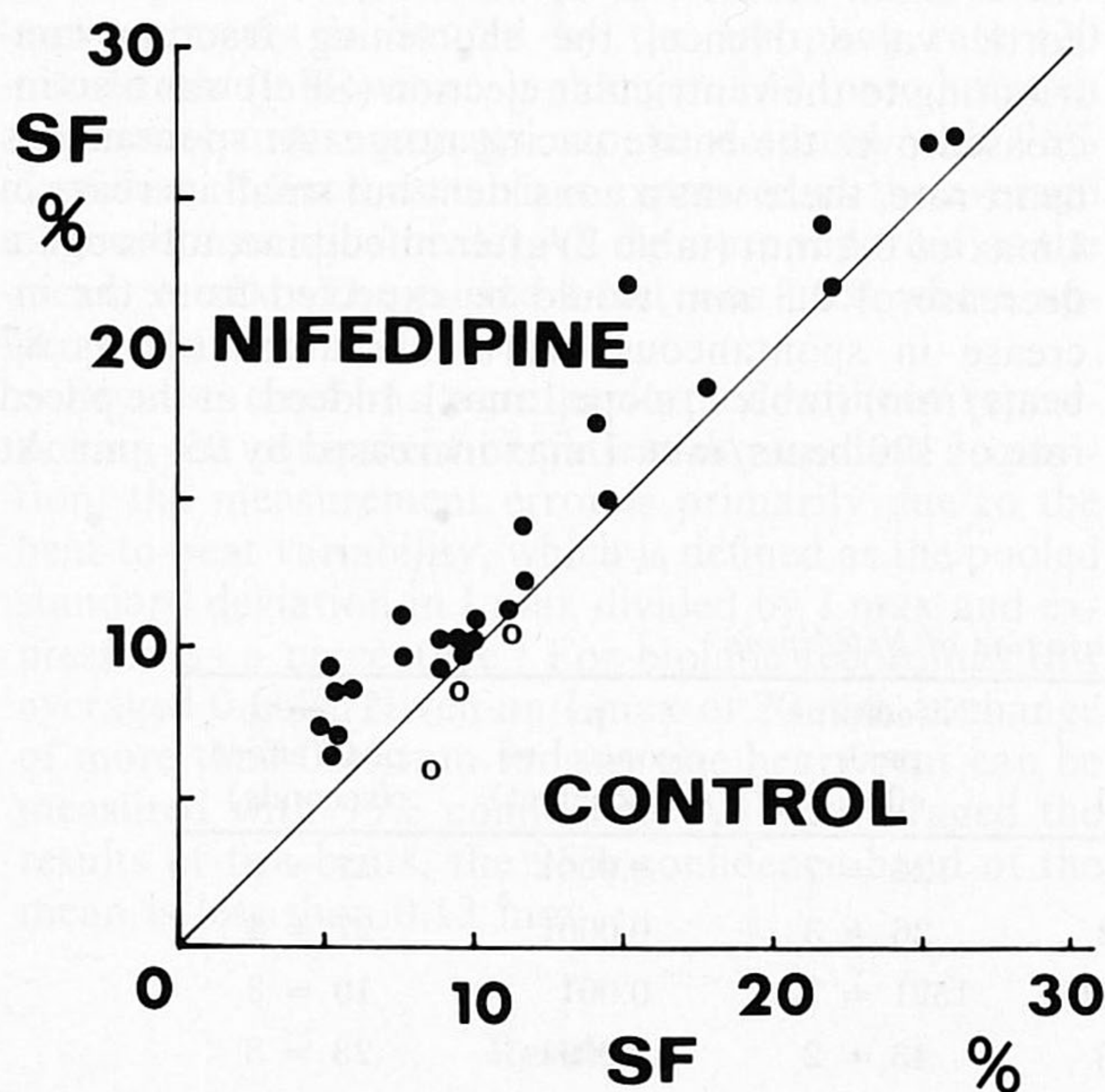


FIGURE 4. Maximal shortening fraction (SF) at a heart rate of 110 beats/min, control (C) vs nifedipine (N). The open dots below the identity line are data points that indicate decreased SF after i.v. nifedipine.

a heart rate of 120 beats/min, the minimal marker separation was unchanged. Thus, with the increase in end-diastolic dimensions, shortening fraction also increased, so that during contraction the same end-systolic dimension was reached. It might be inferred that the increase in shortening fraction was related to a regional preload effect.

At a heart rate of 120 beats/min, the increase in shortening fraction correlated weakly ($r = 0.47$, $p < 0.02$) with the change in Lmax, but not with the change in peak LV pressure ($r = 0.01$, NS). The increase in regional shortening fraction after nifedipine seems to be more strongly influenced by preload than by afterload. On the other hand, at the highest paced rate, statistical analysis failed to demonstrate any relationships between the above variables.

Intrabypass Injection (table 3)

Regional shortening in the 17 selectively injected marker pair regions (group A) and in the nine independently perfused regions (group B) is shown in figure 5. During the control period, the marker separation was maximal 46 ± 7 msec after the onset of the Q wave in group A and 35 ± 14 msec in group B, and 41 msec before ejection in group A and 51 msec in group

TABLE 3. *Timing and Pattern of Regional Ventricular Shortening in 17 Marker Pair Regions After Intrabypass Injection of Nifedipine*

Variable	Control	Time after nifedipine injection						
		30 seconds	<i>p</i> (vs control)	60 seconds	<i>p</i> (vs control)	120 seconds	180 seconds	300 seconds
Time from Q wave (msec)								
Q - EDP	33 ± 3	36 ± 4	NS	33 ± 5	NS	32 ± 4	27 ± 5	30 ± 5
Q - Lmax	46 ± 7	102 ± 15	0.005	67 ± 10	NS	44 ± 8	48 ± 8	46 ± 9
Q - ej	87 ± 4	86 ± 4	NS	81 ± 5	NS	83 ± 5	83 ± 4	91 ± 5
Q - Lmin	347 ± 14	468 ± 11	0.0005	406 ± 21	0.005	321 ± 18	328 ± 17	347 ± 17
Q - es	386 ± 10	390 ± 11	NS	386 ± 10	NS	381 ± 7	377 ± 7	379 ± 7
Marker separation (mm)								
Lmax	27.1 ± 1.5	28.0 ± 1.6	0.005	27.6 ± 1.5	0.05	27.3 ± 1.5	27.3 ± 1.5	27.2 ± 1.5
Lej	26.7 ± 1.6	27.7 ± 1.5	0.00005	27.4 ± 1.5	0.005	26.9 ± 1.5	27.0 ± 1.5	26.7 ± 1.5
Lmin	23.9 ± 1.3	24.9 ± 1.3	0.005	24.5 ± 1.3	0.005	24.2 ± 1.3	24.0 ± 1.3	24.0 ± 1.3
Les	24.3 ± 1.3	26.1 ± 1.4	0.005	25.2 ± 1.3	0.005	24.6 ± 1.3	24.6 ± 1.2	24.5 ± 1.3
Shortening fraction (%)								
SF max	11.7 ± 0.9	10.7 ± 1.1	NS	11.2 ± 1.2	NS	11.4 ± 1.0	11.7 ± 1.0	11.4 ± 1.0
SFej	8.1 ± 1.2	5.5 ± 0.9	0.05	7.8 ± 1.0	NS	8.0 ± 1.2	8.5 ± 1.3	7.9 ± 1.2
Shortening rate (sec ⁻¹)								
SFmax/ Ts	0.41 ± 0.04	0.30 ± 0.03	0.005	0.32 ± 0.04	0.05	0.41 ± 0.03	0.39 ± 0.03	0.40 ± 0.04

Values are mean ± SEM.

Abbreviations: EDP = end-diastolic pressure; L = marker separation; max = maximal; min = minimal; ej = at beginning of ejection; es = end-systole; SF = shortening fraction; Ts = time interval between Lmax and Lmin.

B. Minimal marker separation occurred 39 ± 14 msec before end-systole in group A and 7 ± 11 msec before end-systole in group B. Thirty seconds after injection, three major changes in wall motion were observed in group A. (1) Lmax increased (27.1 vs 28.0 mm, $p < 0.001$) and reached its peak value 16 msec after opening of the aortic valve while ejection had already begun. (2) The shortening rate diminished (0.41 vs 0.30 sec⁻¹, $p < 0.005$), as indicated by the change in the slope of the curve in figure 5. (3) The marker separation reached its minimum early in diastole, 78 msec

after closure of the aortic valve instead of 39 msec before closure. In other words, the onset of shortening was delayed, the shortening rate was diminished and Lmin was shifted from end-systole to early diastole so that 38% of the regional shortening occurred during the early diastole of the ventricle. There was a gradual return to the normal wave form of myocardial shortening at 120 seconds, with all timing relationships restored to normal. Conversely, the wall motion of independently perfused regions (group B) remained unchanged. The net effect of the regional

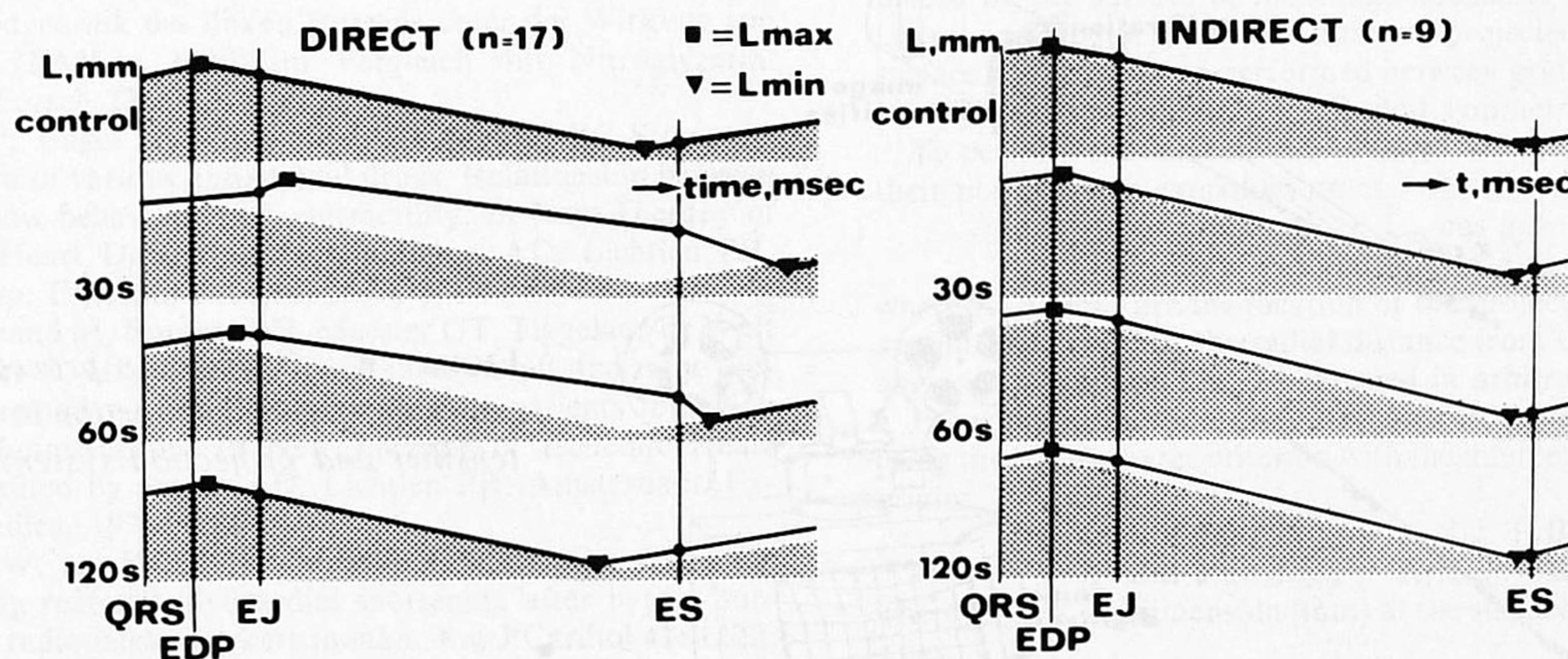


FIGURE 5. *Regional shortening in selectively injected marker pair regions (direct, n = 17) and independently perfused marker pair regions (indirect, n = 9). From top to bottom, control period, 30 seconds, 60 and 120 seconds after intrabypass injection of nifedipine. For abbreviations, see figure 1. The shaded area represents the shortening pattern of the control period.*

asynchrony after selective injection of nifedipine is that the regional shortening during ventricular ejection is decreased to 67% of its control value and the independent regions are unaffected.

Discussion

Previous studies on the isolated papillary muscle¹ and isolated heart² have shown that nifedipine has a negative inotropic effect, whereas studies in intact man³⁻⁵ have shown either no change or a possible increase in contractility. Our results with i.v. nifedipine confirm these latter findings. The vasodilation and subsequent hypotension caused by nifedipine necessarily induces reflex baroreceptor activation and it is possible that β -adrenergic stimulation could easily abolish the expected negative inotropic action of a calcium antagonist. Indeed, the dominant effect of i.v. nifedipine at spontaneous heart rate was a lowering of peak LV pressure with an increase in heart rate. During pacing, nifedipine reduced the pressure at all common rates, suggesting a mechanism sparing myocardial oxygen consumption.¹¹ At the highest paced rate, V_{max} was greater than control values at the same rate, while regional shortening was increased over the entire pacing range. The increase in regional shortening can be attributed largely to the reduction in afterload, despite the poor correlation between change in shortening and change in pressure.

At this stage, it was unclear whether we had measured the effects of loading changes or whether we had measured a direct action of nifedipine on the heart. To separate the direct effect from other systemic effects, selective intrabypass injections of nifedipine were performed. After intrabypass injection, the pattern of myocardial wall motion changed its configuration completely in the regions directly supplied by the selectively injected bypasses. Within seconds, the onset of shortening was delayed, the shortening rate was diminished, and minimal marker

separation was shifted from end-systole to early diastole. The entire relaxation phase was slowed.

There is a striking similarity in the timing of alterations in regional shortening and wall thickening in human and in animal experiments after intracoronary injection of nifedipine (Verdouw PD: personal communication). Our results show that nifedipine delays and prolongs segmental contraction in the region selectively influenced by nifedipine, as in the animal experiments. Changes in the rate of pressure relaxation can reflect either altered myocardial relaxation or heterogeneity in activation and performance within the "sarcomere population." In other words, impaired relaxation of the ventricle as a whole must not be automatically equated with impaired relaxation on a cellular level. If the independently perfused areas of the myocardium maintain their pattern and rate of contraction and relaxation after nifedipine, then the only way by which overall relaxation variables can be affected is by a continuation of contraction and tension development extending into the isovolumic period in the areas directly influenced by nifedipine.

Our results with intrabypass injection show the negative inotropic properties of nifedipine when regionally administered. The difference in effects of i.v. vs intrabypass injection is partially due to the fact that the regulatory mechanism of the blood pressure is practically not solicited, or very transiently. This latter point has been confirmed by Kaltenbach et al.,¹⁴ who did not observe any peripheral or central hemodynamic changes after i.v. injection of 0.1 mg, the dosage we used for intrabypass injection. Therefore, the transient drop in peak systolic pressure, lasting less than 3 minutes, after intrabypass injection must be interpreted as the result of a negative inotropic effect on the myocardium, whereas the decrease in blood pressure, lasting more than 20 minutes, after i.v. injection of 1.0 mg is the result of a persistent decrease in peripheral resistance as well.

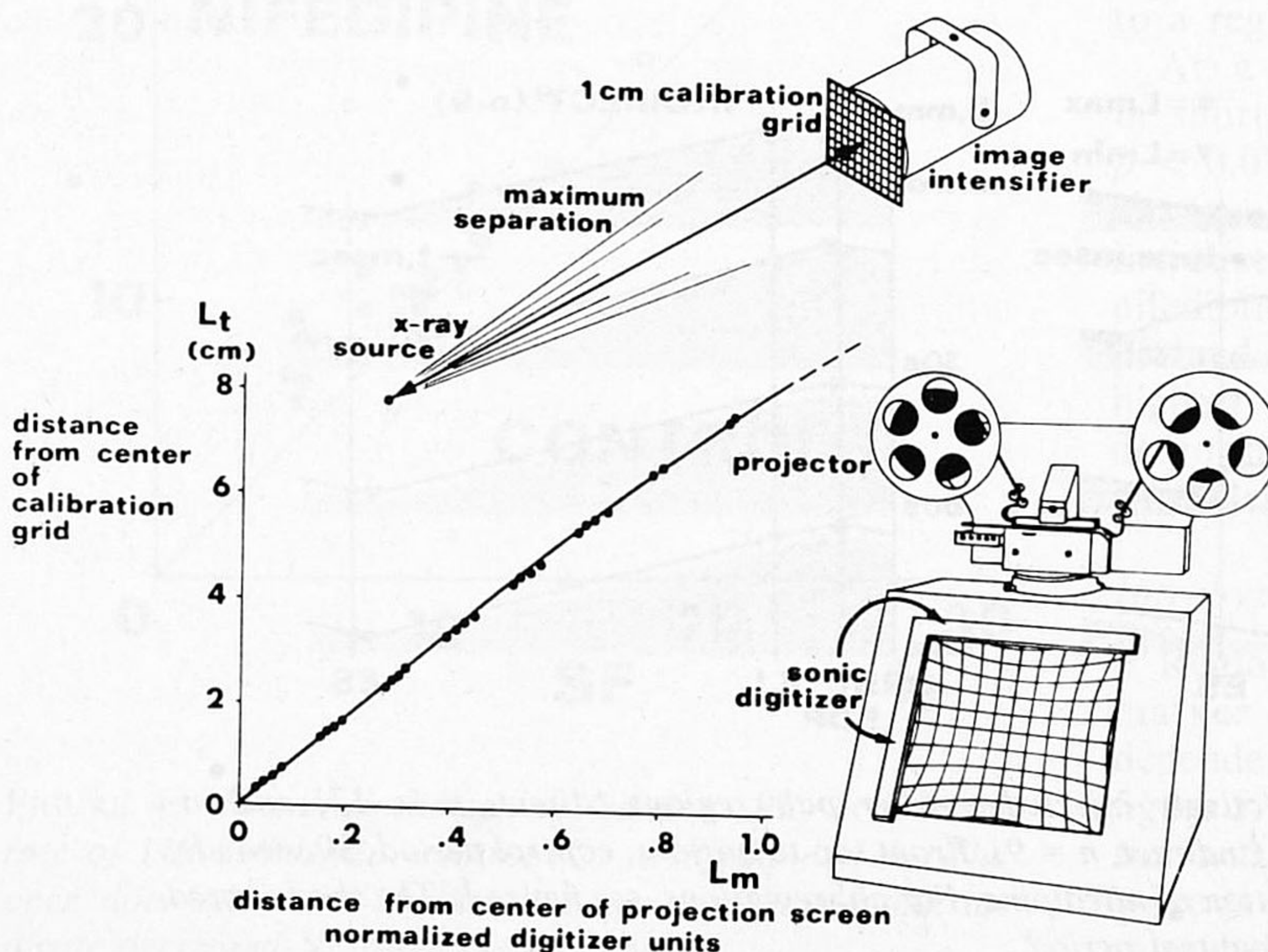


FIGURE 6. Calibration procedure for correction for optical distortion in the image intensifier and projection system.

It has been shown that intracoronary injection of nifedipine (1–3 $\mu\text{g}/\text{kg}$ in 20 seconds) in dogs decreases dose-dependent myocardial oxygen consumption (25% and 42%) in the region supplied, with a slight decrease in blood pressure (7% and 8%).¹⁵ In view of the similar response in man and dog to nifedipine, it may be assumed that a similar effect occurs in the human heart after intracoronary injection of a comparable amount of nifedipine (1.4–2 $\mu\text{g}/\text{kg}$ within 10 seconds). To what extent the decrease in oxygen consumption is due to the decrease in blood pressure or to a direct action of the drug on cardiac metabolism or the contractility of the muscle was not investigated. However, Fleckenstein et al.¹ indicated that electromechanical decoupling occurs, which leads to a decrease in contraction and may be the cause of the decrease in regional myocardial oxygen consumption. The negative inotropic effect on the heart that we recorded is probably an expression of that fundamental biochemical effect: Nifedipine interrupts the normal process by which calcium is transported to the cell and therefore inhibits contraction of the myocardial wall, although oxygen supply is not depressed. In intact man, the negative inotropic effect of nifedipine is masked or even inhibited by the systemic effects when administered intravenously.

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References

1. Fleckenstein A, Tritthart H, Döring HJ, Byon KY: BAY a 1040: ein hochaktiver Ca^{++} -antagonistischer Inhibitor des elektromechanischen Koppelungsprozess in Warmblüter Myokard. *Arzneim Forsch* **22**: 22, 1972
2. Raff KH, Kosche F, Lochner W: Untersuchungen mit Nifedipin, einer coronargefässerweiterenden Substanz mit schneller sublingualer Wirkung. *Arzneim Forsch* **22**: 33, 1972
3. Kaltenbach M, Becker HJ, Kober G, Loos A: Veränderungen der Hämodynamik des linken Herzens unter der Wirkung von Nifedipin (BAY a 1040) im Vergleich mit Nitroglyzerin. *Arzneim Forsch* **22**: 362, 1972
4. Lichtlen P, Engel HJ, Amende I, Rafflenbeul W, Simon R: Mechanism of various antianginal drugs. Relationship between regional flow behaviour and contractility. *In New Therapy of Ischemic Heart Disease*, edited by Jatene AD, Lichtlen PR. Amsterdam, Excerpta Medica, 1976, p 14
5. van den Brand M, Remme WJ, Meester GT, Tiggelaar-de Widt I, de Ruitter R, Hugenholtz PG: Changes in left and right ventricular haemodynamics in angina pectoris patients following Adalat administration. *In New Therapy of Ischemic Heart Disease*, edited by Jatene AD, Lichtlen PR. Amsterdam, Excerpta Medica, 1976, p 69
6. Brower RW, ten Katen HJ, Meester GT: Direct method for determining regional myocardial shortening after bypass surgery from radiopaque markers in man. *Am J Cardiol* **41**: 1222, 1978
7. Meester GT, Bernard N, Zeelenberg C, Brower RW, Hugenholtz PG: A computer system for real time analysis of cardiac catheterization data. *Cathet Cardiovasc Diagn* **1**: 113, 1975
8. Meester GT, Zeelenberg C, Gorter S, Miller AC, Hugenholtz PG: Beat-to-beat analysis of left ventricular function parameters. *Eur J Cardiol* **1**: 279, 1974
9. Brower RW, Serruys PW, Bos E, Nauta J: Regional myocardial shortening in relation to graft reactive hyperemia and flow after coronary bypass surgery. *J Thorac Cardiovasc Surg* **7**: 92, 1979
10. Brower RW, ten Katen HJ: A new method for the post-operative measurement of regional shortening in three dimensions. *In Transactions of the European Society of Cardiology*. Rotterdam, European Society of Cardiology, 1978, p 25
11. Mérillon JP, Morgant C, Zygelman M, Beaufile J, Patart O, Chapuy JY, Gourgon R: Comparaison des effets hémodynamiques et coronariens de deux drogues vasodilatatrices anti-angineuses: la nifédipine et la trinitrine. *Arch Mal Coeur* **71**: 913, 1978
12. Brower RW, Remme WJ, ten Katen HJ, van den Brand M: Quantification of the atrial pacing stress test: normal values and limits between normal and abnormal for coronary artery disease in man. *In Computers in Cardiology*. Long Beach, California, IEEE Computer Society, 1977, p 591
13. Tyberg JV, Forrester JS, Parmley WW: Altered segmental function and compliance in acute myocardial ischemia. *Eur J Cardiol* **1**: 307, 1974
14. Kaltenbach M, Schulz W, Kober G, Bamberg E: Cardiac and peripheral action of a calcium inhibitive antianginal drug. *In Transactions of the European Society of Cardiology*. Rotterdam, European Society of Cardiology, 1978, p 22
15. Vater W: Myocardial oxygen consumption under the influence of nifedipine (Adalat) in the anaesthetized dog. *In New Therapy of Ischemic Heart Disease*, edited by Lochner W, Kronenberg G. Berlin, Springer Verlag, 1975, p 77
16. Dodge HT, Sandler H, Ballew DW, Lord JD: The use of biplane angiocardiology for the measurement of left ventricular volume in man. *Am Heart J* **60**: 762, 1960

Appendix

The monoplane filming of marker pair motion has been described.⁶ This procedure required sequentially positioning of each marker pair in the center of the image intensifier, and aligning the image intensifier to minimize the effect of myocardial rotation. However, this study required simultaneous filming of all marker pairs necessitating biplane fluoroscopy. Marker pair separation in true anatomic dimensions requires determining the absolute positioning of all markers. As normal marker shortening is 1–2 mm for a pair separated by 20 mm, correction for all optical distortion was necessary because markers could be filmed on the periphery of the image intensifier.

Optical distortion at the image intensifier, camera and projection system were corrected to obtain true absolute marker position, as is necessary for accurate biplane measurements. A centimeter grid, placed on the surface of the image intensifier was filmed for both lateral and frontal units. The film was projected onto the digitizing surface and calibration performed between grid coordinates and arbitrary digitizer units (fig. 6). Radial symmetry was confirmed.

To perform the correction of a set of measured coordinates (x,y), their position was expressed as:

$$\begin{aligned}x &= X_c + L_m \cos \theta \\y &= Y_c + L_m \sin \theta\end{aligned}$$

where X_c and Y_c are the location of the projected center of the image intensifier, L_m is the radial distance from the center, and θ the angular coordinate. L_m is expressed in arbitrary digitizer units.

From the calibration grid, a second-order polynomial was fitted using the least-squares criterion with the intercept constrained to the origin:

$$\begin{aligned}\text{lateral unit: } L_{\text{true}} &= A_l L_m + B_l L_m^2 \\ \text{frontal unit: } L_{\text{true}} &= A_f L_m + B_f L_m^2\end{aligned}$$

where L_{true} is the dimension (mm) at the surface of the image intensifier.

Image intensifier coordinates were then expressed in rectangular coordinates from the image intensifier center:

$$\begin{aligned}x &= L_t \cos \theta \\y &= L_t \sin \theta\end{aligned}$$

Further correction for nonparallel beam distortion followed conventional techniques described by Dodge.¹⁶