European Heart Journal (1980) **1** (*Supplement B*), 71–85

Can unstable angina pectoris be due to increased coronary vasomotor tone?

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KEY WORDS: Unstable angina pectoris, nifedipine, coronary vasomotion, quantitative angiography.

In this study it is argued that the clinical manifestations of unstable angina pectoris, with at its extreme end impending myocardial infarction, may be due to increased coronary arterial vasomotion superimposed on a pre-existing obstruction in a coronary artery.

As nifedipine, a powerful calcium antagonist, has initially proven its efficacy in relieving the symptoms of Prinzmetal's angina, a condition in which severe spasm of the coronary artery is now proven to be the main cause, the drug was given to two groups of patients in whom abnormal vasomotion was suspected and its effects scrutinized.

Twelve patients with symptoms of coronary artery disease (CAD) were studied with repeated arteriograms after injection of 0·15 mg nifedipine in the left coronary artery. Two control cine-angiograms were made prior to drug administration and two cinefilms were repeated 30 s and 5 min after administration of nifedipine. The mean diameter of the normal, stenotic and poststenotic segments showed a statistically significant increase after drug administration. Vasodilation persisted after coronary O_2 saturation, and presumably coronary flow, had returned to normal.

In 52 other patients, who were seen in the coronary care unit for impending myocardial infarction and who had been treated with maximal beta-adrenergic blockade, nitrates and bedrest, but who remained symptomatic, nifedipine 60 mg orally for 24 h was added to the treatment. Within 2 h after administration 42 of the 52 became asymptomatic. In the 10 non-responders, all with extensive multi-vessel disease, two sustained a myocardial infarction and eight received urgent coronary artery bypass grafting in an effort to alleviate their symptoms. All had severe 3 vessel disease in contrast to the responders in whom 1 or 2 vessel disease was predominant.

These data show that increased coronary artery vasomotion can be influenced by nifedipine. The excellent clinical response to the drug in this group of patients with unstable angina pectoris indicates that nifedipine may become the preferred agent to be used particularly when the cause of the angina pectoris is suspected to be the result of abnormal coronary vasomotor tone.

Several studies in the literature[1–10] suggest that major coronary arteries can, under physiological conditions, approximately double their luminal diameter from their most constricted to their most dilated state. If, in contrast, a similar degree of vasoconstriction occurs around an already pre-existing fixed obstruction, a critical reduction in flow may take place which, under certain circumstances, will lead to irreversible ischemia. It then can be understood how the clinical manifestations of unstable angina and impending infarction may follow excessive coronary arterial vasomotion superimposed on an organically narrowed vessel. If this hypothesis is correct, it opens up new avenues of treatment, for if there was a truly long acting coronary vasodilator, then the process of impending infarction could be reversed in time and the patient returned to a more stable, or even asymptomatic, state. Nifedipine, a powerful calcium channel blocking agent, provides such vascular dilatation and its efficacy has been proved by many authors in the classical syndrome of Prinzmetal's angina[11–13], where complete spasm of the vascular wall has been shown.

Recently Previtali and coworkers[14] also reported a high degree of efficacy of nifedipine in patients with angina at rest where other causes were suspected. It is generally assumed that the effectiveness of nifedipine in angina at rest is mainly related to its pronounced

Received for publication 22 September 1980.

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Table 1 Clinical and hemodynamic features of the study group

	Age	Sex	NYHA classification	Coronary angiogram	Ejection fraction	EDV (ml/m^2)	Infarct location
1.	55	♂	II	normal	0·67	107	
2.	56	♂	II	three vessel disease	0·60	66	
3.	33	♂	II	three vessel disease	0·65	85	
4.	59	♂	II	single vessel disease	0·60	62	anterior
5.	47	♂	III	two vessel disease	0·58	98	anterior
6.	49	♂	II	normal	—	—	
7.	36	♂	III	three vessel disease	0·25	134	anterior
8.	58	♂	II	two vessel disease	0·32	91	anterior
9.	55	♂	III	two vessel disease	0·67	51	
10.	54	♂	II	two vessel disease	0·68	46	
11.	53	♂	I	two vessel disease	0·61	83	
12.	45	♂	III	three vessel disease	0·61	51	

Abbreviation: EDV = end-diastolic volume.

afterload reduction and to its direct blocking effect on the excitation-coupling mechanism inside the cardiac cells. However, efficacy may also be related to its capacity to decrease the calcium-dependent contractile tone of the cells in the epicardial coronary arterial wall[15, 16]. By reducing this tone these cells appear less sensitive to vasoconstricting stimuli, as indicated elsewhere in this symposium.

In order to unravel these often coincident actions, the effects of an intracoronary injection of nifedipine on coronary vasomotility and left ventricular hemodynamics were investigated in 12 patients with suspected coronary artery disease. Subsequently, the drug was also given to a group of 52 patients with unstable angina, whose pain persisted at rest, with continued ST-T wave changes, although therapy had been given over 8 h consisting of maximal beta-adrenergic blockade, nitrates (some intravenously) and bedrest.

Material and methods

For the first part of the study, data were collected from 12 patients catheterized for suspected coronary artery disease. Their clinical and hemodynamic data are summarized in Table 1. Two patients had normal coronary arteries, there was one patient with one vessel disease, six patients had two vessels obstructed, three patients had three vessel obstruction, all of 70% or more. The effects of an intracoronary injection of nifedipine on coronary vasomotility were studied in four consecutive coronary cine-angiograms. Before the angiographic study, a fiberoptic catheter* was inserted into the coronary sinus and the O_2 saturation continuously measured[17]. The left ventricular pressure was continuously recorded with a tipmanometer (Millar PC 471 or 481, PC 770 or 880†) and analyzed for changes in left ventricular contractility, reflected by peak dP/dt, peak VCE and V_{max}[18, 19].

A total of 41 segments were selected for quantitative angiographic analysis. Eight were stenotic in nature, 22 were poststenotic, and 11 were normal. Before the pharmacological intervention, two baseline coronary angiograms were performed with a 5 min interval. The second control angiogram was carried out to study the effect of the contrast agent itself on the artery.

Five minutes later, 0·15 mg of nifedipine was injected within 20 s, into the left main coronary artery[20], and an arteriogram was repeated as soon as the coronary sinus saturation reached its maximum value, usually within 30 s. The final coronary angiogram was obtained as soon as the coronary sinus saturation had returned to its control values, usually within 5 min.

All arteriograms were obtained via the Sones technic and recorded on Kodak 35 mm cinefilm (RAR

* American Optical Company, Southbridge, Massachusetts, U.S.A.
† Millar Instruments Inc., Houston, Texas, U.S.A.

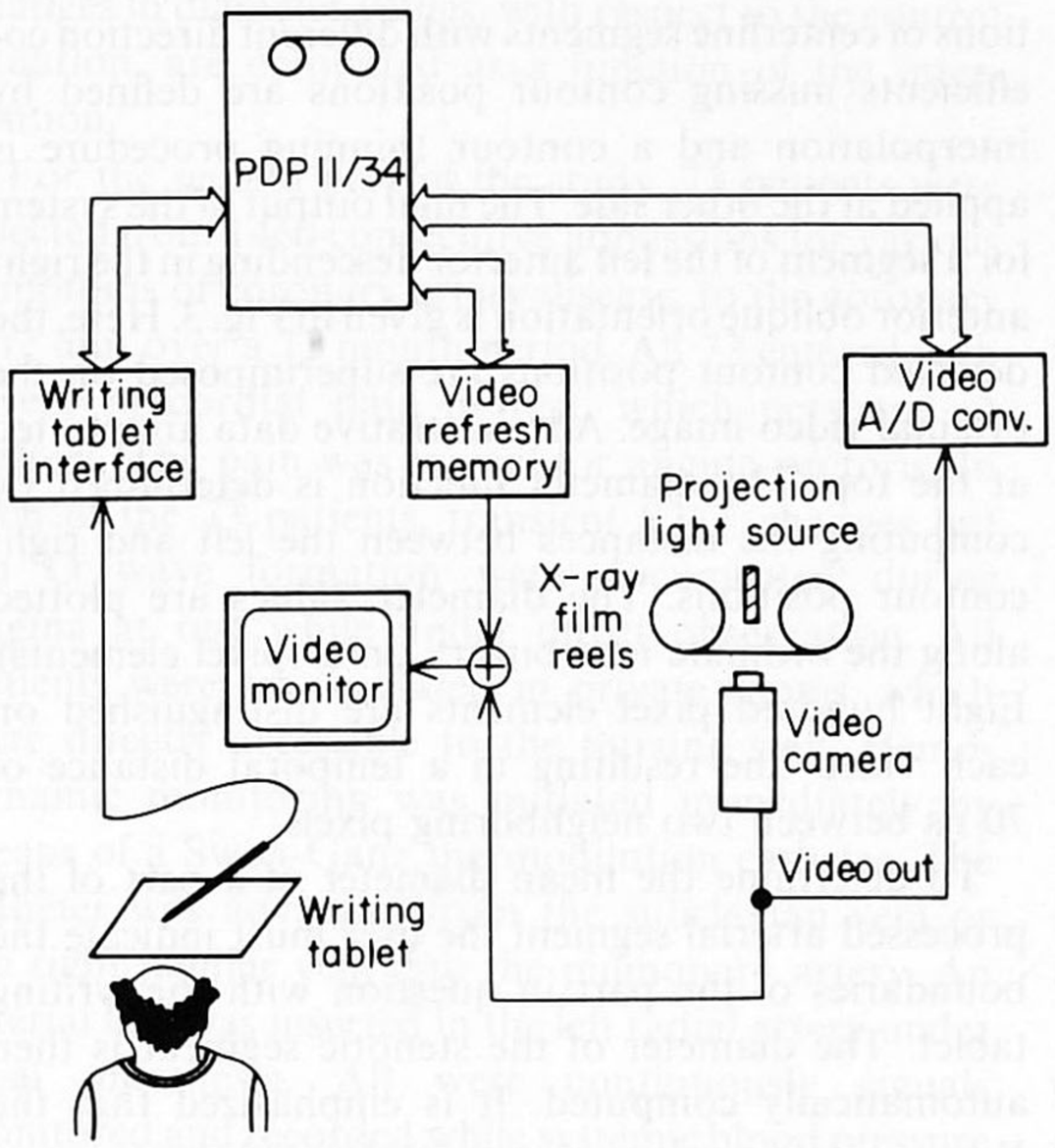
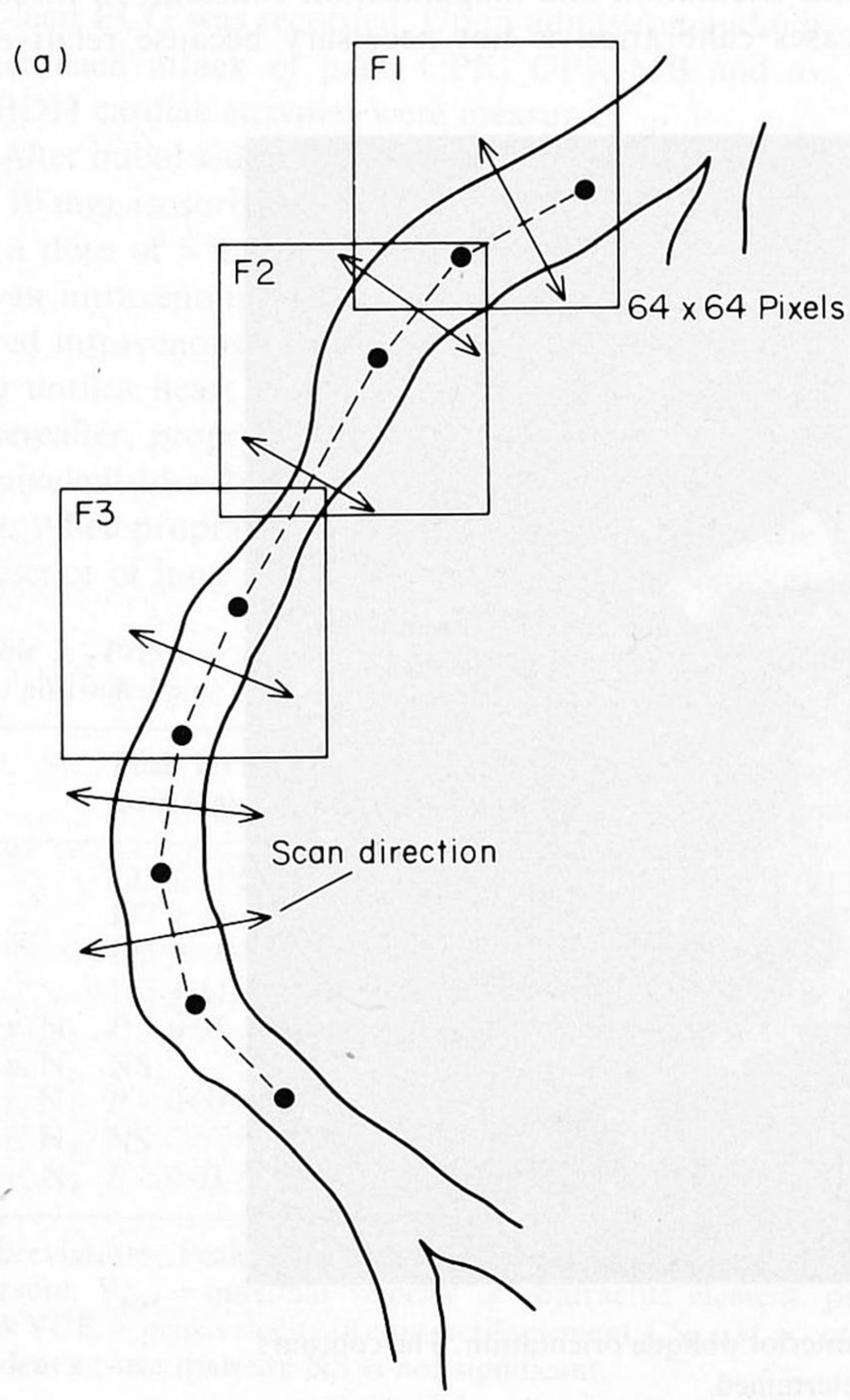


Figure 1 Block diagram of the coronary angiography analysis system.



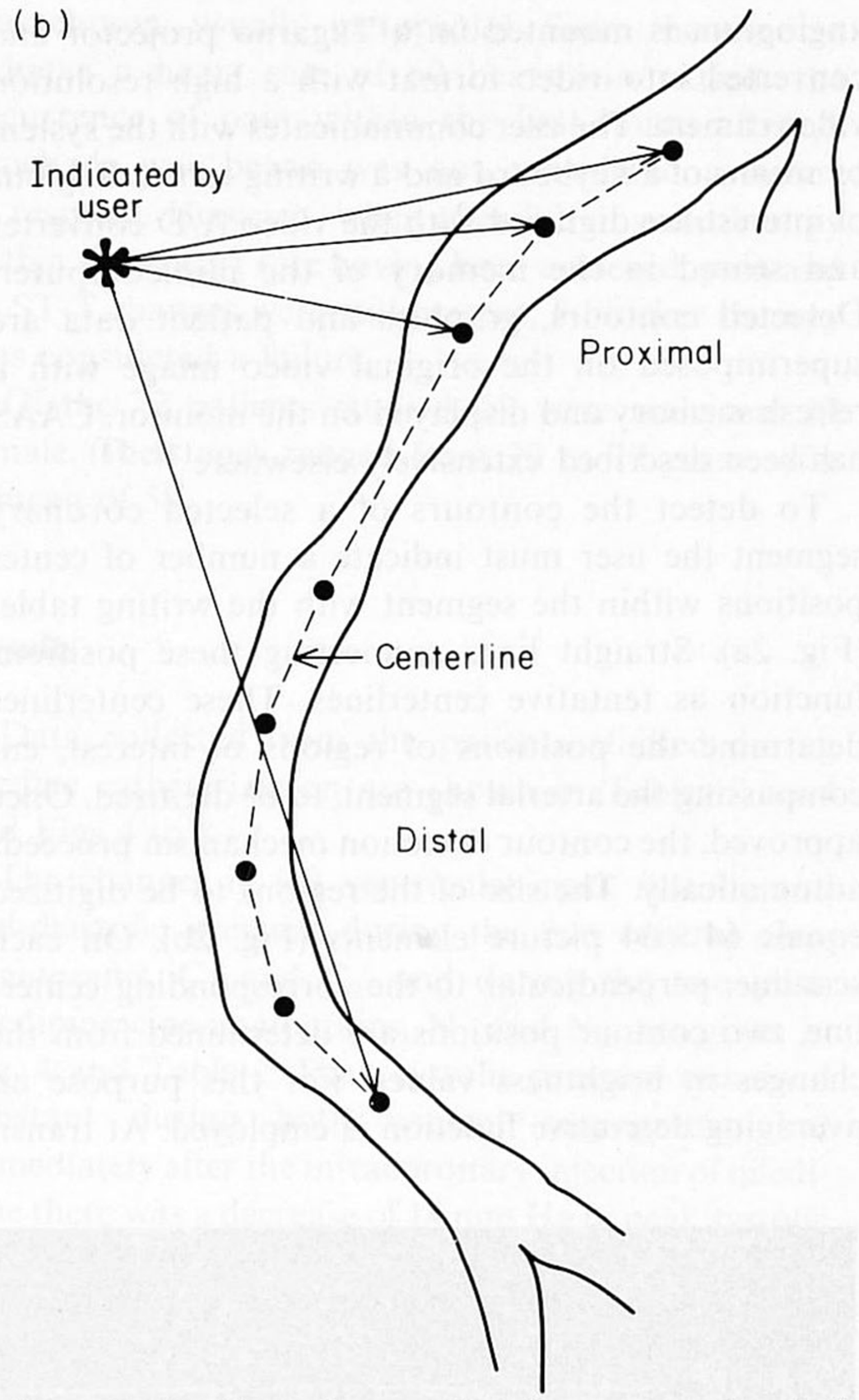


Figure 2 (a) To analyze a selected coronary artery lesion the user indicates a number of center positions. These inter-polated straight lines function as a tentative centerline. (b) For the schematic drawing of Fig. 2a the scan directions perpendicular to the corresponding centerline segments are given as well as the positions of the 64 × 64 matrices to be digitized.

film 2496) at the rate of 50 frames per s with the biplane Cardioskope U (Siemens*). As for the contrast medium, Urografin 76% (Schering†) was injected at a flow rate of 3 ml/s with a Medrad injector (Mark IV)‡.

CORONARY ANGIOGRAPHY ANALYSIS SYSTEM

The quantitative analysis of selected coronary segments was carried out with the help of a computer based Coronary Angiography Analysis System (CAAS), of which a block diagram is shown in Fig. 1. The central processor is a PDP 11/34 mini computer with 32k words of memory. A 35 mm frame of a cine-

* Siemens AG, Henkestrasse, Erlangen, G.B.R.
† Schering AG, Berlin, Bergkammen, G.B.R.
‡ Medrad Inc., Pittsburgh, Pennsylvania, U.S.A.

angiogram is mounted on a Tagarno projector and converted into video format with a high resolution video camera. The user communicates with the system by means of a keyboard and a writing tablet. Regions of interest are digitized with the video A/D converter and stored in the memory of the minicomputer. Detected contours, graphics and patient data are superimposed on the original video image with a refresh memory and displayed on the monitor. CAAS has been described extensively elsewhere[21–23].

To detect the contours of a selected coronary segment the user must indicate a number of center positions within the segment with the writing tablet (Fig. 2a). Straight lines connecting these positions function as tentative centerlines. These centerlines determine the positions of regions of interest, encompassing the arterial segment, to be digitized. Once approved, the contour detection mechanism proceeds automatically. The size of the regions to be digitized equals 64×64 picture elements (Fig. 2b). On each scanline, perpendicular to the corresponding centerline, two contour positions are determined from the changes in brightness values. For this purpose an averaging derivative function is employed. At transitions of centerline segments with different direction coefficients missing contour positions are defined by interpolation and a contour thinning procedure is applied at the other side. The final output of the system for a segment of the left anterior descending in the right anterior oblique orientation is given in Fig. 3. Here, the detected contour positions are superimposed on the original video image. Administrative data are plotted at the top. The diameter function is determined by computing the distances between the left and right contour positions. The diameter values are plotted along the ordinate in arbitrary units (pixel elements). Eight hundred pixel elements are distinguished on each video line resulting in a temporal distance of 70 ns between two neighboring pixels.

To determine the mean diameter of a part of the processed arterial segment the user must indicate the boundaries of the part in question with the writing tablet. The diameter of the stenotic segment is then automatically computed. It is emphasized that the X-ray system settings were not changed during consecutive filming after drug injection in order to hold the orientation and magnification constant. In these cases calibration is not necessary because relative

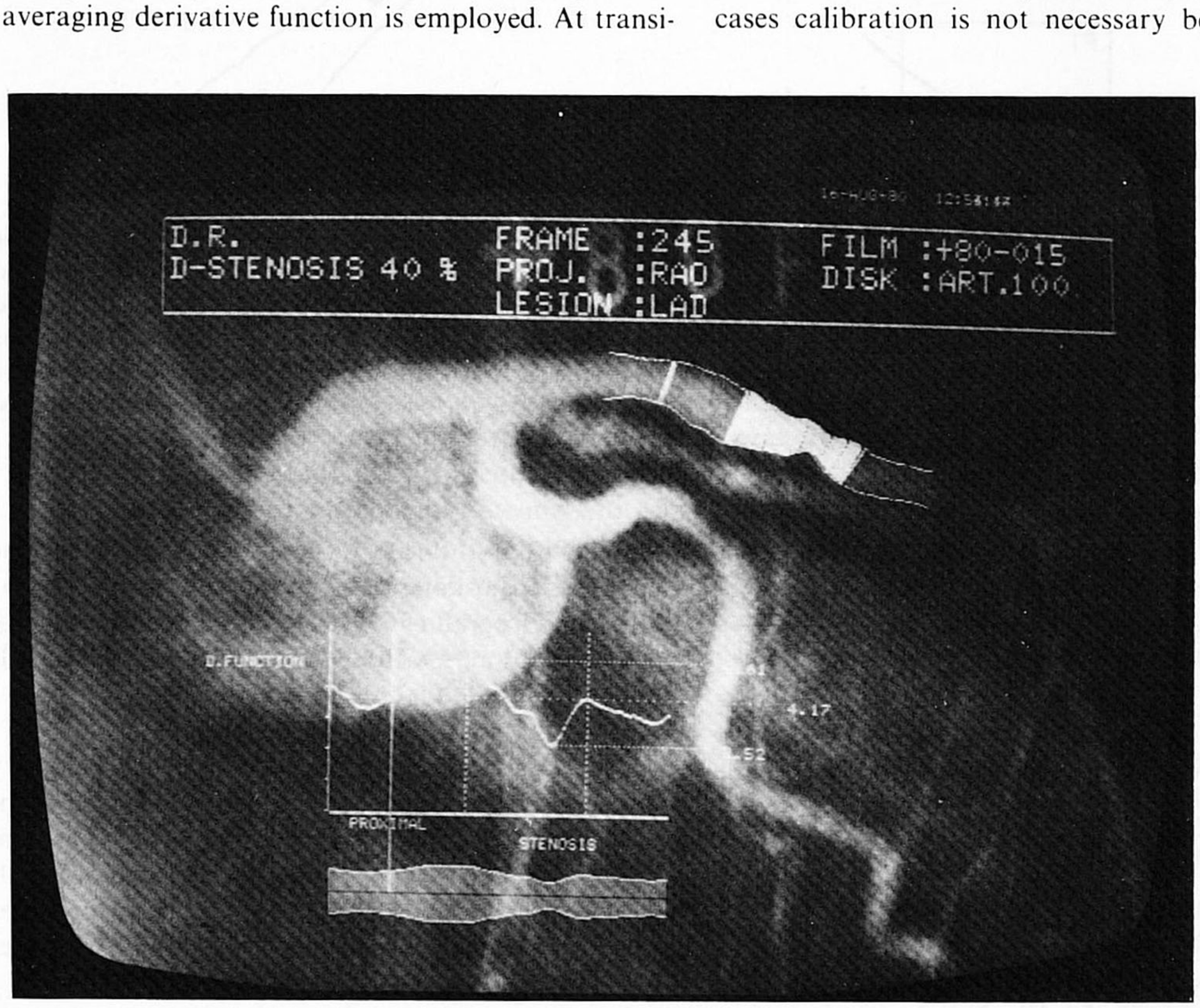


Figure 3 Computer output of the measured lesion in the right anterior oblique orientation. The contours have been detected; from these data the diameter function is determined.

changes in diameter values, with respect to the control situation, are computed as a function of the intervention.

For the second part of the study, 73 patients were selected from 1460 consecutive admissions for various symptoms of coronary artery disease, to the coronary care unit over a 12 month period. All 73 entered with severe precordial pain at rest, which persisted at bedrest. The pain was typical for angina pectoris. In each of the 73 patients, transient ST-T changes but no Q wave formation were documented during angina at rest while under direct observation. All patients were semi-isolated in private rooms, which were directly accessible to the nursing staff. Hemodynamic monitoring was initiated immediately by means of a Swan-Ganz thermodilution catheter. The catheter was advanced from the subclavian vein or the right jugular vein into the pulmonary artery. An arterial line was inserted in the left radial artery under local anesthesia. All were continuously signals monitored and recorded while systemic blood pressure and cardiac output were determined at regular intervals. During and following each attack of pain, a 12-lead ECG was recorded. Upon admission and 6 h after each attack of pain, CPK, CPK-MB and α-HBDH cardiac enzymes were measured.

After initial sedation, usually with oral diazepam (5 to 10 mg), isosorbide dinitrate was given sublingually in a dose of 5 mg every 2 h, or if necessary, it was given intravenously. Also, propranolol was administered intravenously at dosages varying from 1 to 10 mg until a heart rate of 60 beats/min was reached. Thereafter, propranolol was given orally at dosages equivalent to a 24 h dosage of between 400 and 800 mg. When propranolol was contraindicated, as in the presence of lung disease, a cardioselective β-blocker was chosen, usually metoprolol. Since the time to achieve a heart rate of 60 beats/min varied, the recurrence of pain within the first hours after β-blockade was begun was not considered a failure to respond. However, when after 8 h of such therapy with a slow heart rate having been achieved, pain and or ST-T changes were still present, β-blocker therapy was considered a failure.

Of the 73 patients studied, 59 were male and 14 female. Their ages ranged from 29 to 77 years, with a mean of 58.

Results

Data collected from the patients studied during cardiac catheterization are shown in Tables 2 to 4 and Figs 4 to 8.

The changes in left ventricular peak systolic and end-diastolic pressure during the two control cine-angiograms. C_1 and C_2, and during the two post-nifedipine cine-angiograms, N_1 and N_2, are given in Fig. 4 and Table 2. Peak systolic pressure remained constant during both control angiograms, but immediately after the intracoronary injection of nifedipine there was a decrease of 14 mm Hg in peak systolic pressure ($P < 0{\cdot}05$). This acute change was transient and followed by return to control values, within 5 min—so that by the time of the fourth coronary angiogram, the LV pressure had returned to its control value of 135 mm Hg. End-diastolic pressure showed a significant increase ($P < 0{\cdot}01$) from 19 to 25 mm Hg 30 s after the intracoronary injection. During the fourth cinefilm, the end-diastolic pressure was still slightly, but not significantly, elevated.

After the intracoronary injection of nifedipine peak

Table 2 Pressure derived variables and coronary sinus saturation during the two control (C_1, C_2) and the two post-nifedipine cine-angiograms (N_1, N_2). (Mean ± s.e.m)

	Peak LVSP (mm Hg)	LVEDP (mm Hg)	V_{max} (s^{-1})	Peak dP/dt (mm Hg s^{-1})	Peak VCE (s^{-1})	CS_{O_2} sat
C_1	135 ± 11·5	18 ± 2·6	47·8 ± 2·3	1722 ± 191	35·5 ± 3·8	36 ± 3·0
C_2	137 ± 11·6	19 ± 2·6	45 ± 2·10	1607 ± 120	32 ± 2·5	36 ± 3·2
N_1	123 ± 8·4	25 ± 3·1	36·7 ± 2·8	1333 ± 139	24·3 ± 2·4	63 ± 4·7
N_2	135 ± 11	22 ± 2·6	47·5 ± 1·9	1629 ± 139	31·3 ± 2·6	35·3 ± 1·1
C_1 *v.* N_1	$P < 0{\cdot}05$	$P < 0{\cdot}002$	$P < 0{\cdot}005$	$P < 0{\cdot}02$	$P < 0{\cdot}02$	$P < 0{\cdot}01$
C_1 *v.* N_2	NS	NS	NS	NS	NS	NS
C_2 *v.* N_1	$P < 0{\cdot}005$	$P < 0{\cdot}001$	$P < 0{\cdot}002$	$P < 0{\cdot}05$	$P < 0{\cdot}01$	$P < 0{\cdot}005$
C_2 *v.* N_2	NS	NS	NS	NS	NS	NS
N_1 *v.* N_2	$P < 0{\cdot}03$	NS	$P < 0{\cdot}002$	$P < 0{\cdot}02$	$P < 0{\cdot}01$	$P < 0{\cdot}005$

Abbreviations: Peak LVSP = peak left ventricle systolic pressure; LVEDP = left ventricle end-diastolic pressure; V_{max} = maximal velocity of contractile element; peak dP/dt = first derivative LV pressure; peak VCE = peak velocity of contractile element; CS_{O_2} sat = coronary sinus oxygen saturation; $P = P$ value Student's t-test (paired); NS = not significant.

Table 3 Mean diameter values, expressed in pixels (picture element), during the two control (C_1, C_2) and the two post-nifedipine (N_1, N_2) cine-angiograms

	Mean diameter of normal segments (n = 11)	Mean diameter of poststenotic segments (n = 21)
	mean ± s.e.m.	mean ± s.e.m.
C_1	19·86 ± 1·69	17·42 ± 0·76
C_2	20·32 ± 1·89	17·25 ± 0·80
N_1	20·53 ± 1·81	18·34 ± 0·67
N_2	22·07 ± 1·99	19·50 ± 0·76
C_1 *v.* C_2	NS	NS
C_1 *v.* N_2	$P < 0·005$	$P < 5·10^{-6}$
C_2 *v.* N_1	NS	$P < 0·02$
C_2 *v.* N_2	$P < 0·01$	$P < 5·10^{-7}$
N_1 *v.* N_2	$P < 0·0005$	$P < 0·005$

Abbreviations: P = P value, paired t-test of Student; NS = not significant.

Table 4 Luminal diameters of eight stenotic lesions during the control cine-angiogram (C) and after (N) intracoronary administration of nifedipine; luminal diameters are expressed in pixels. Luminal diameter change is defined as: $(N - C)/C \times 100$, and expressed as a percentage

Control (C)	Nifedipine (N)	Luminal diameter change (%)
4·73	6·18	31
9·92	12·59	27
10·93	13·67	25
10·31	12·63	22·5
13·75	16·10	17
13·97	15·29	9·4
8·32	8·68	4·3
9·84	8·90	−9·5

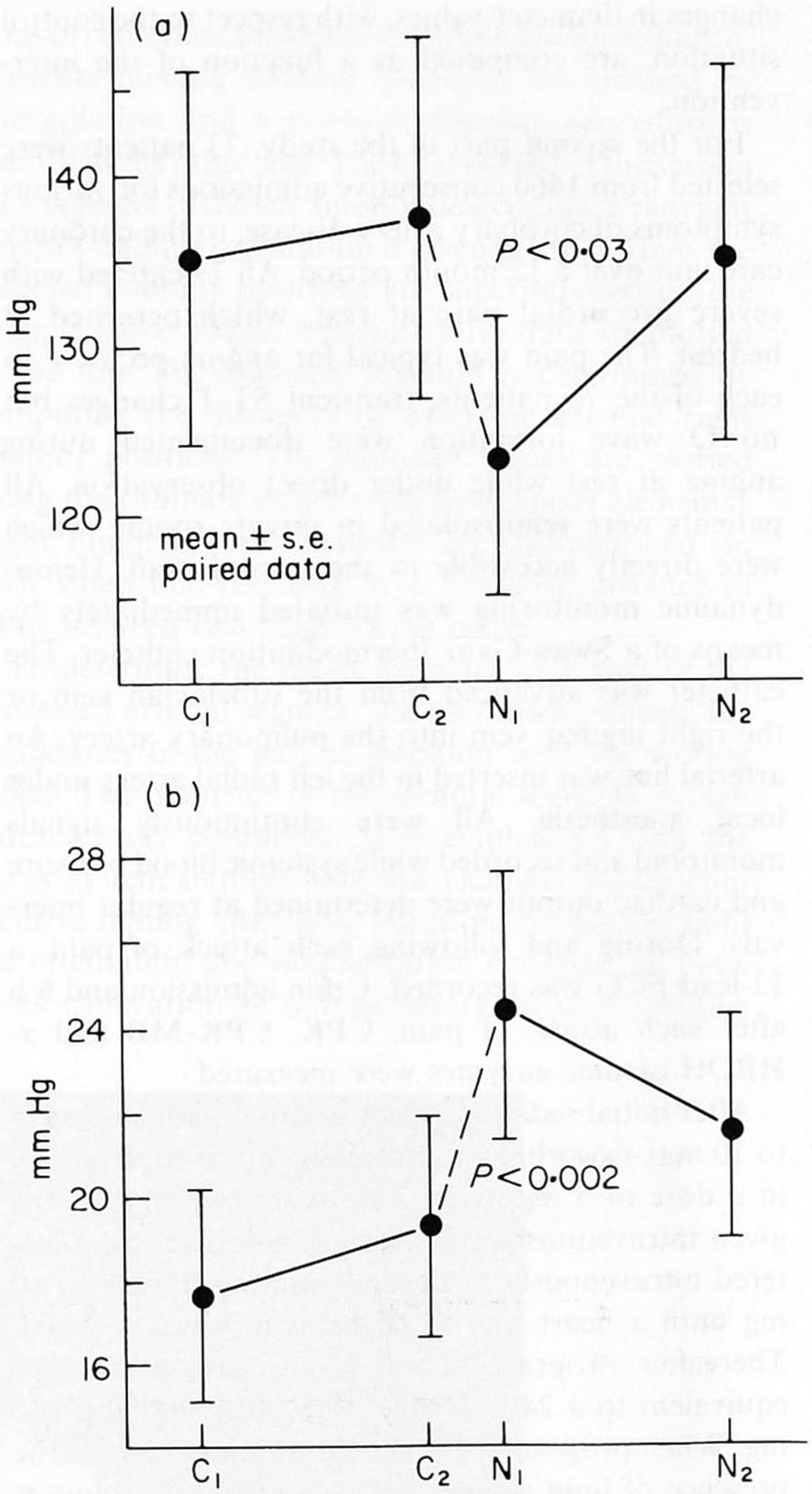


Figure 4 Peak left ventricular pressure (LVP) (a) and end-diastolic pressure (EDP) (b) during the two control (C_1, C_2) and the two post-nifedipine (N_1, N_2) cine-angiograms.

dP/dt and V_{max} decreased simultaneously by 17 and 18%. Both parameters had returned to their control value by the time of the fourth coronary angiogram. It is safe to conclude that nifedipine has a negative inotropic effect when regionally administered. The changes in V_{max} and in the coronary sinus O_2 saturation are shown in Fig. 5. Thirty seconds after the intracoronary administration of nifedipine, there was a marked increase of the coronary sinus O_2 saturation from 36 to 63% occurring simultaneously with the drop in V_{max}. To what extent this increase in coronary sinus O_2 saturation is due to the reduction observed in contractility or to an increase in coronary blood flow was not specifically investigated in this study. However, it must be emphasized that 5 min after the intracoronary injection of nifedipine, there was no detectable effect of nifedipine on the coronary sinus O_2 saturation or on contractility.

The effects of nifedipine on the mean diameter of 11 normal and 21 poststenotic coronary segments are shown in Figs 6 and 9. In both subgroups, there was no significant difference in the mean diameter between the first and the second control cinefilm (Table 3). In other words two consecutive injections of contrast agent do not affect the vasomotility of the coronary system appreciably.

Thirty seconds after the intracoronary injection of nifedipine, there was no vasodilation of the normal

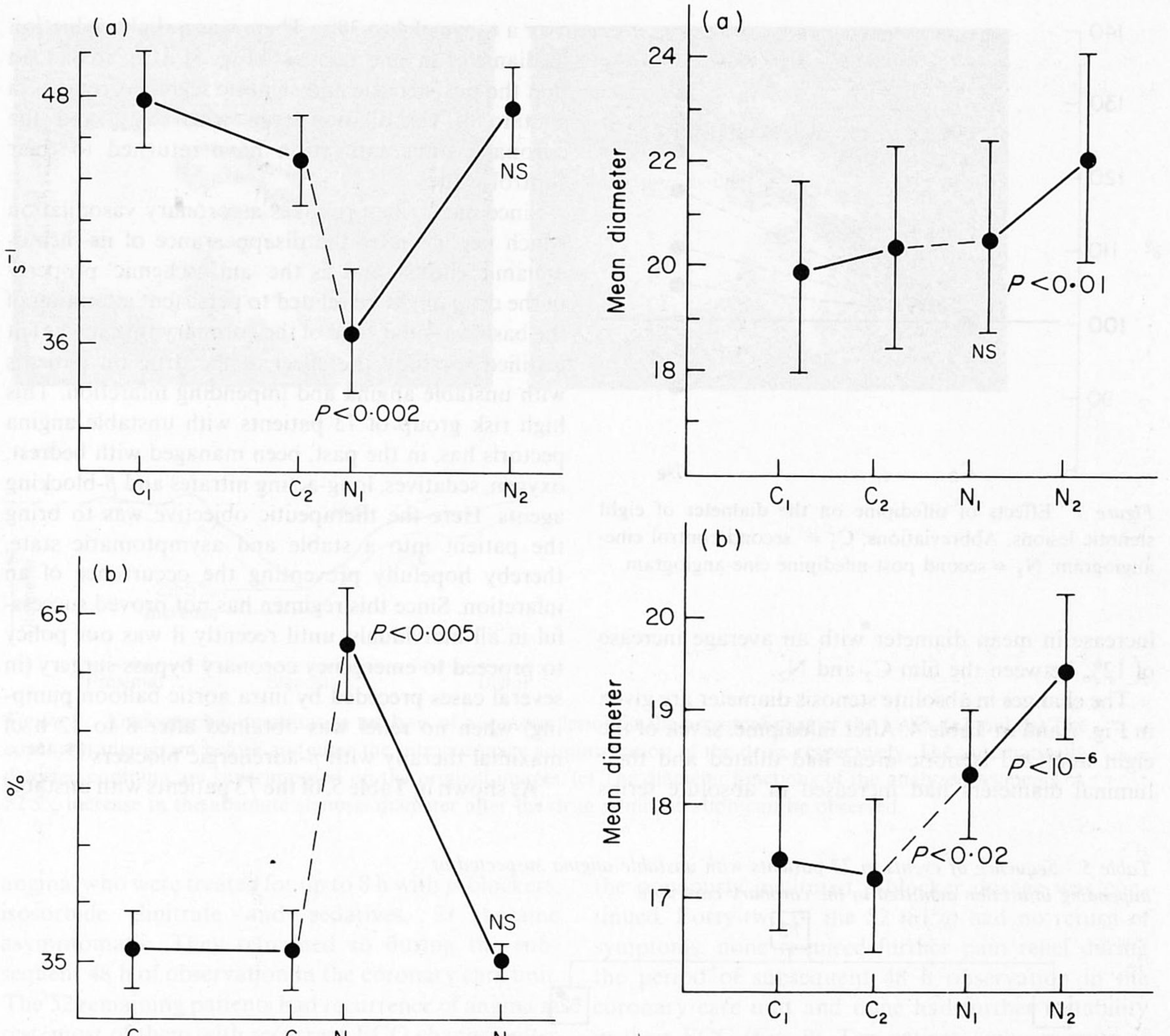


Figure 6 Effects of nifedipine on the mean diameter of (a) 11 normal and (b) 21 poststenotic coronary segments during the two control (C_1, C_2) and the two post-nifedipine (N_1, N_2) cine-angiograms.

coronary segments. However, on the last film, 5 min later, a significant increase of 11% ($P < 0{\cdot}01$) in the mean diameter was observed.

As for the poststenotic segments, at 30 s after the nifedipine administration there was already a significant increase of the luminal diameter. This vasodilation persisted and even increased later on (Table 3, Fig. 6). Without exception, all segments showed an

Figure 5 (left) Changes in V_{max} (a), coronary sinus saturation (b) and mean diameter of the poststenotic segment (c) during the two control (C_1, C_2) and the two post-nifedipine (N_1, N_2) cine-angiograms.

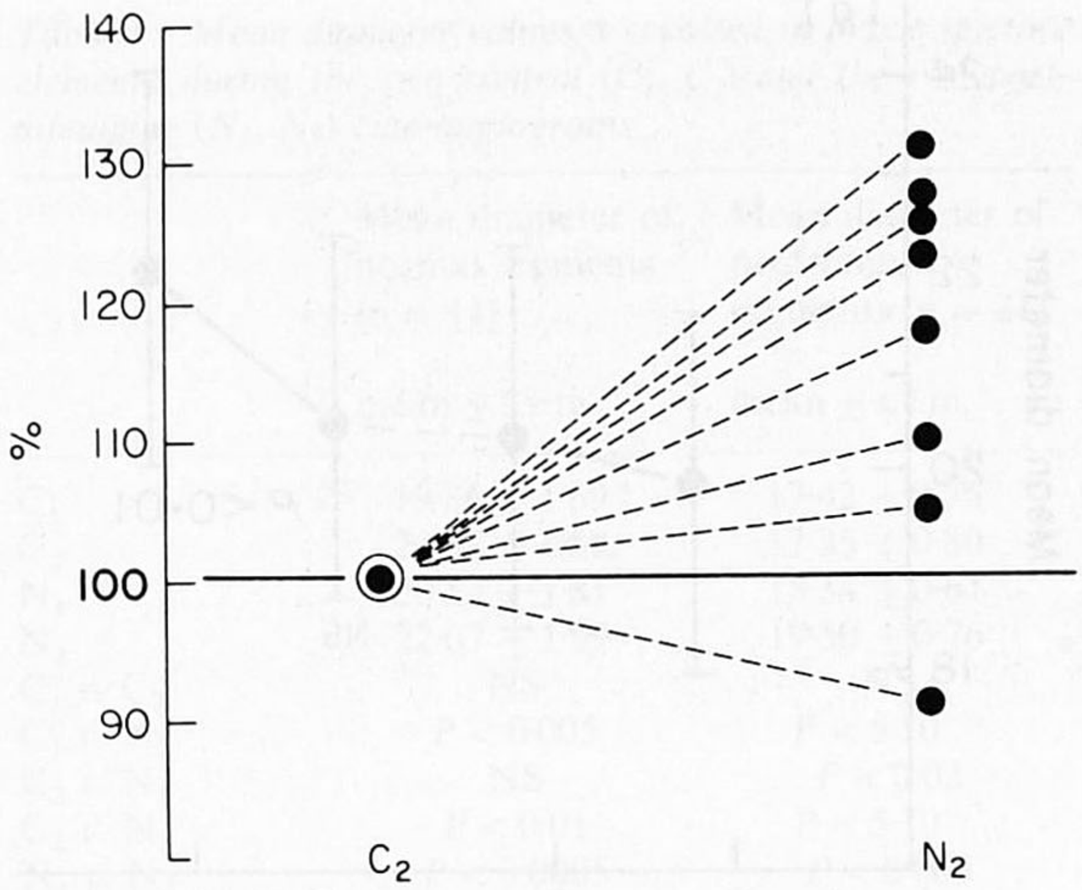


Figure 7 Effects of nifedipine on the diameter of eight stenotic lesions. Abbreviations: C_2 = second control cine-angiogram; N_2 = second post-nifedipine cine-angiogram.

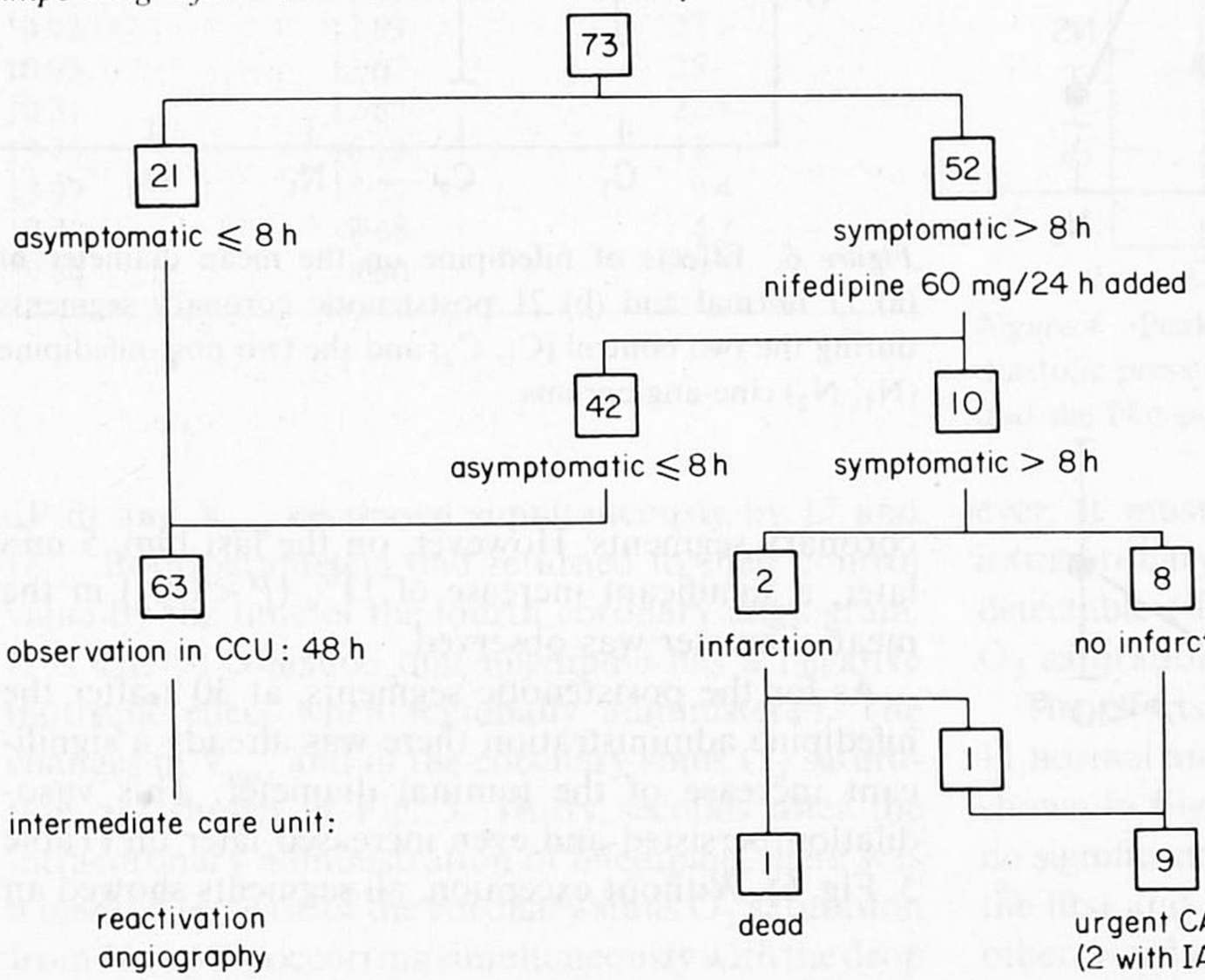
increase in mean diameter with an average increase of 12% between the film C_2 and N_2.

The changes in absolute stenosis diameter are given in Fig. 7 and in Table 4. After nifedipine, seven of the eight analyzed stenotic areas had dilated and their luminal diameters had increased in absolute terms over a range of 4 to 30%. There was a slight reduction in diameter in one segment (Fig. 5). It is concluded that the poststenotic and stenotic segments remain in a state of vasodilation even when V_{max} and the coronary sinus saturation have returned to their control values.

Since nifedipine provokes a coronary vasodilation which persists after the disappearance of its 'hemodynamic effects', and as the 'anti-ischemic' property of the drug might be related to persistent alteration of the basal vascular tone of the coronary tree, it was felt justified to study the effect of the drug on patients with unstable angina and impending infarction. This high risk group of 73 patients with unstable angina pectoris has, in the past, been managed with bedrest, oxygen, sedatives, long-acting nitrates and β-blocking agents. Here the therapeutic objective was to bring the patient into a stable and asymptomatic state, thereby hopefully preventing the occurrence of an infarction. Since this regimen has not proved successful in all individuals, until recently it was our policy to proceed to emergency coronary bypass surgery (in several cases preceded by intra aortic balloon pumping) when no relief was obtained after 8 to 12 h of maximal therapy with β-adrenergic blockers[24, 25].

As shown in Table 5, of the 73 patients with unstable

Table 5 Sequence of events in 73 patients with unstable angina suspected of impending infarction admitted to the coronary care unit



CABG = coronary artery bypass grafting; IABP = intra aortic balloon pumping.

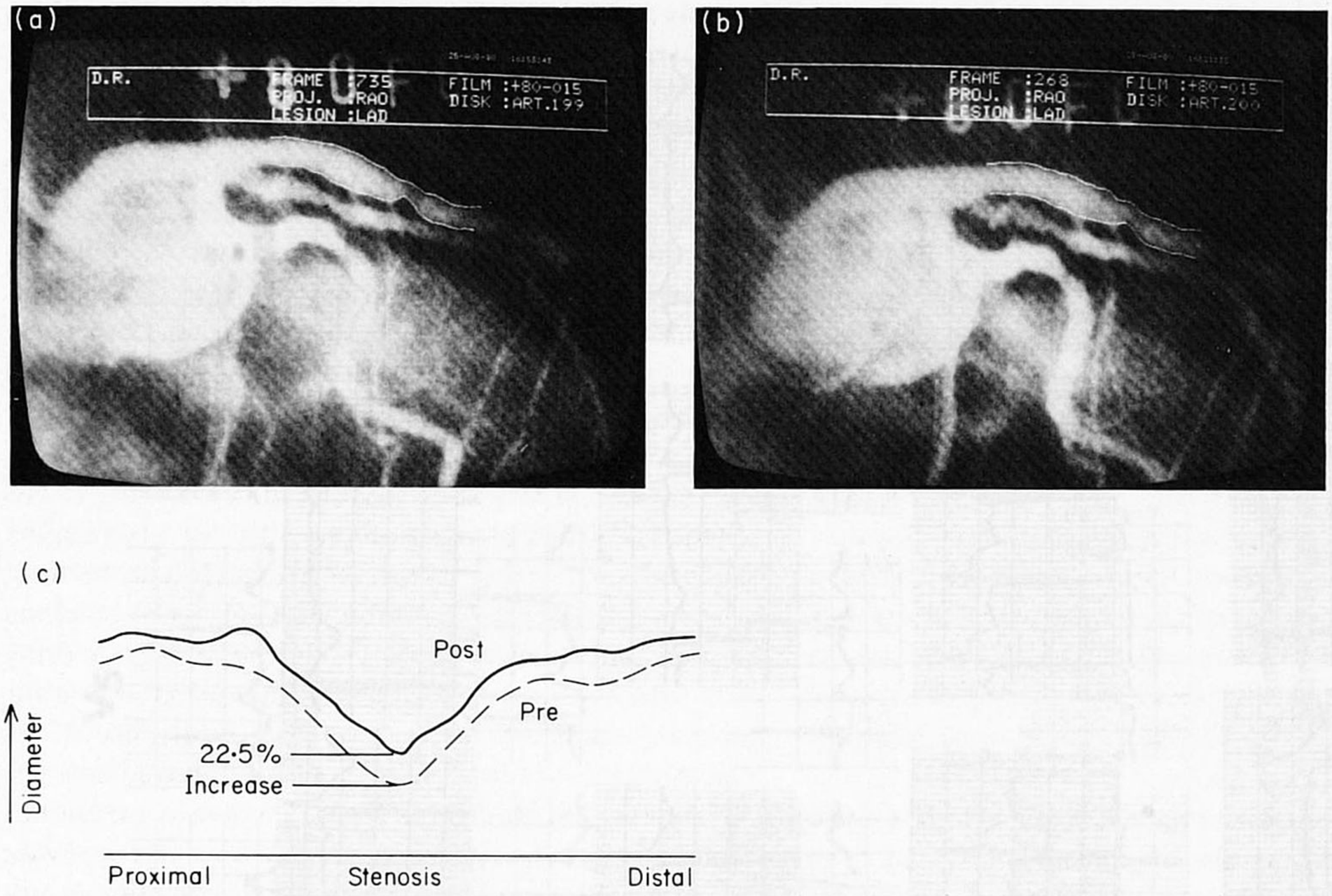


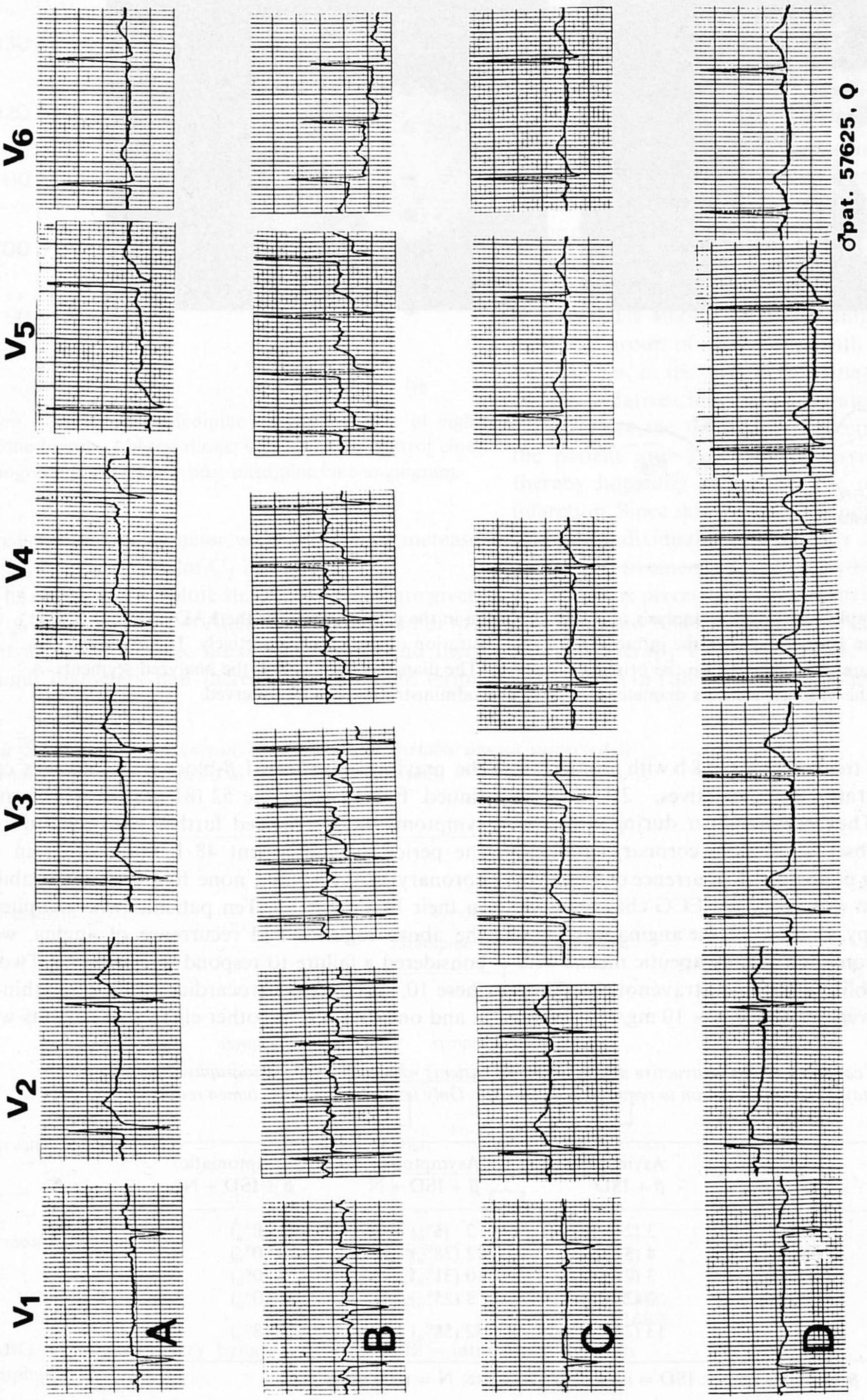
Figure 8 Angiographic quantitative analysis of a stenotic lesion in the proximal part of the LAD. (a) and (b) The coronary angiogram before and after the intracoronary administration of the drug, respectively. The automatically detected contours are superimposed on the original images. (c) The diameter functions of the analyzed segments. A 22·5% increase in the absolute stenosis diameter after the drug administration can be observed.

angina, who were treated for up to 8 h with β-blockers, isosorbide dinitrate and sedatives, 21 became asymptomatic. They remained so during the subsequent 48 h of observation in the coronary care unit. The 52 remaining patients had recurrence of angina at rest, most of them with recurrent ECG changes, after 8 h of such therapy. In these 52, the angina was again controlled with conventional therapeutic means with nitroglycerin sublingually or intravenously. They were then also given nifedipine, 6 × 10 mg/24 h, while the previously instituted β-blocker dosage was continued. Forty-two of the 52 (81%) had no return of symptoms, none required further pain relief during the period of subsequent 48 h observation in the coronary care unit and none had further instability in their ECG (Fig. 9). Ten patients, who in spite of the above regimen had recurrence of angina, were considered a failure to respond to nifedipine. Two of these 10, sustained a myocardial infarction within 24 h and one died. Of the other eight, two patients with

Table 6 Extent of coronary artery obstructive disease in 55/73 patients who underwent angiography during the initial hospital stay, related to reaction to required drug therapy. Only lesions with ≧70% lumen reduction are tabulated

	Total group	Asymptomatic β + ISD	Asymptomatic β + ISD + N	Symptomatic β + ISD + N
LMCA	7 (13%)	3 (23%)	2 (6%)	2 (20%)
3 vessel disease	22 (40%)	4 (31%)	12 (38%)	6 (60%)
2 vessel disease	14 (25%)	3 (23%)	10 (31%)	1 (10%)
1 vessel disease	12 (22%)	3 (23%)	8 (25%)	1 (10%)
	55	13 (24%)	32 (58%)	10 (18%)

Abbreviations: β = β-blocking agents: ISD = isosorbide dinitrate; N = nifedipine.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A
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(a)

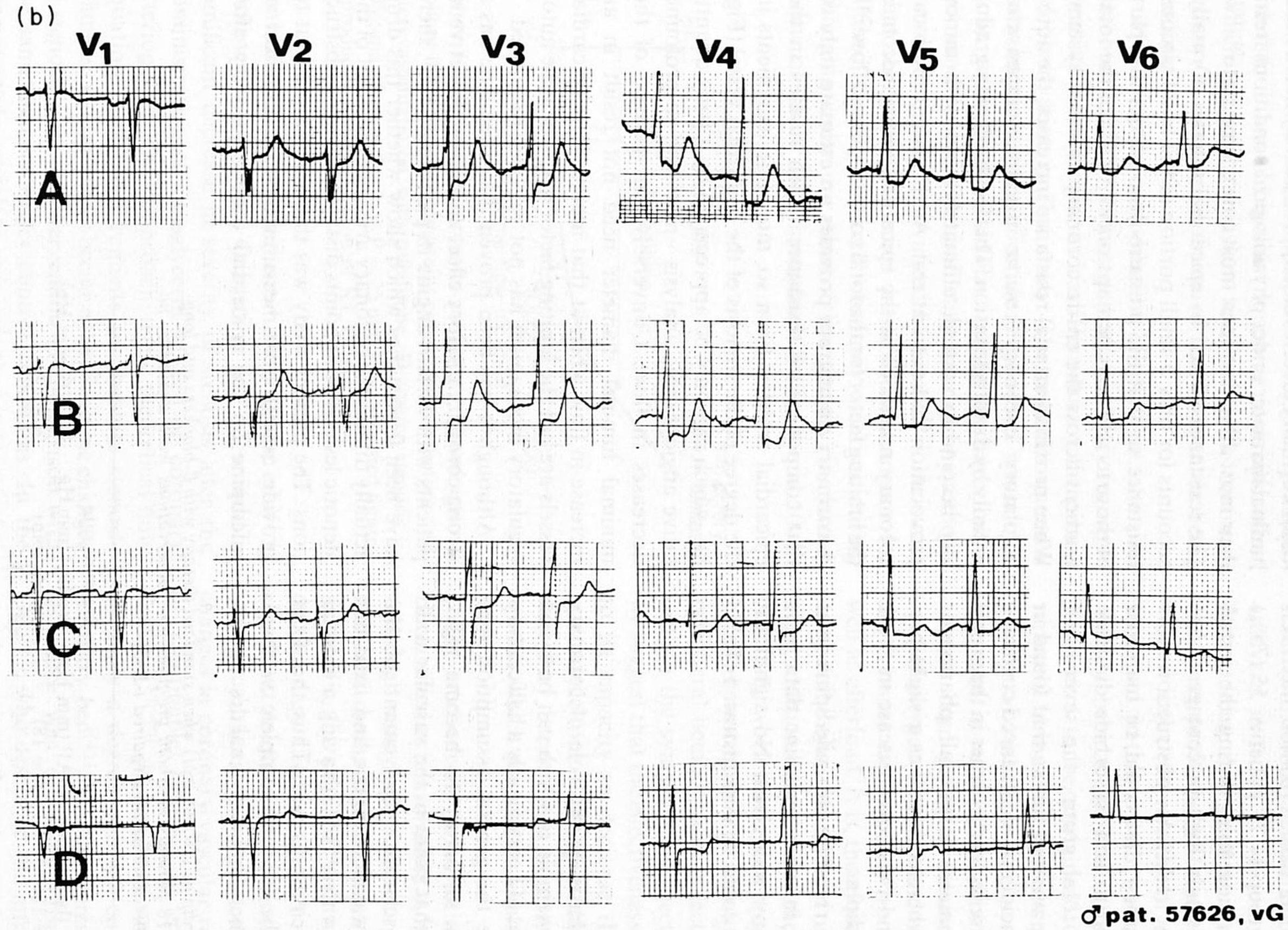

Figure 9 Patient Q, a 56-year-old male with unstable angina was treated with 40 mg propranolol q.l.d., isosorbide dinitrate (5 mg q.2 h) and sedatives. Electrocardiogram (A) was obtained when therapy seemingly had been effective. Forty-five minutes later precordial pain returned, the electrocardiogram (B) shows tachycardia and ST segment depression. Nifedipine (10 mg q.4 h) was given sublingually with disappearance of symptoms and return of the electrocardiogram to baseline value (C). It remained unchanged during the next 24 h (D) and the patient was transferred to the ward. There was no return of symptoms. (b) Patient vG, a 62-year-old male, was transferred from another hospital with metoprolol (50 mg b.i.d.), isosorbide dinitrate (5 mg q.2 h) and sedatives. Despite this medication for 24 h at the other hospital pain had intermittently returned. Upon admission, ECG (A) was recorded and propranolol (40 mg) was immediately given. Twenty-five minutes later ECG (B) was obtained, which shows further ST segment depression, while pain continued unabated. Nifedipine was given (10 mg q.4 h) and the pain subsided. The ECG was repeated 6 h later (C) and 24 h later (D). A general improvement can be noted, the patient remained pain free and was transferred to the ward.

persistent pain, received intra aortic balloon pumping with immediate relief of their symptoms. Nine patients underwent coronary bypass grafting and all are alive as are all patients who were placed on nifedipine.

In Table 6 the extent of coronary artery obstructive disease as seen at cardiac catheterization has been detailed. Of the total group of 73 patients, 55 (75%) underwent coronary angiography during the initial hospital stay. A surprisingly high percentage of left main coronary artery (LMCA) obstruction was demonstrated in the group that could be managed with β-blocking agents (β) and isosorbide dinitrate (ISD) alone. For the total group, the severity of coronary artery disease was not unlike that found in stable angina but the incidence of advanced coronary artery obstructive disease is clearly higher in the group that remained symptomatic despite all pharmacological interventions, whereas there was a slight predominance of single and two vessel disease in those that responded to nifedipine.

The hemodynamic response to nifedipine was studied in 18 patients in whom baseline data were available before therapy was given. No significant hemodynamic changes could be demonstrated (Table 7).

Discussion

Despite earlier emphasis on the role of coronary artery spasm, a good example of which can be found in the pathologic studies of Leary, nearly a half century ago[26], it has become the general assumption that atherosclerosis causes an artery to become rigid, preventing motion at that point in the vascular wall. However, the atherosclerotic involvement of the arterial wall is not always concentric and fixed but may be frequently eccentric[26, 27], leaving a normal wall over part of its circumference. Thus the 'fixed stenosis' concept may be due for a complete overhaul. As proposed by Prinzmetal in his original description, it seems now eminently reasonable to assume that the clinical manifestations of variant angina might be due to normal or excessive arterial coronary vasomotion superimposed on an organically narrowed vessel[1]. Several reports in the recent literature suggest that major coronary arteries can approximately halve their luminal diameter under physiological conditions from their most dilated to their most constricted state[4–10] The resistance offered by epicardial arteries normally accounts for only a small portion of the basal viscous resistance so that the pressure drop across this part of the arterial bed is perhaps only 1 or 2% of the total gradient across the entire coronary vascular system. When proximal arterial resistance increases, the autoregulatory coronary reserve usually compensates initially by distal relaxation. This feedback may gradually become exhausted, ultimately even with minor provocation and even at rest. At this point the local coronary resistance in the epicardial artery becomes the limiting factor for the total coronary blood flow[28]. A coronary angiogram provides an estimate only of that component of resistance which resides in the epicardial arteries. Even so, moderate increments in the degree of the stenosis of the epicardial vessel (Fig. 8)—which can only be appreciated by a truly quantitative angiographic analysis—may lead to profound decreases in flow. Conversely, an increase of the minimal luminal diameter need not result in an increase in flow when at that moment the epicardial vessels are not the limiting factor and when the autoregulatory mechanism has not yet been exhausted.

Although it has been proven that nifedipine has a strong coronary dilatory effect and is very effective in patients with variant angina in particular[11–13], there have been few studies which show whether this drug actually dilates the coronary artery at the point of the stenotic lesions or at points distal to the fixed obstructions. The present study was therefore carried out to provide quantitative measurements of the effect of nifedipine on the epicardial coronary artery after

Table 7 Addition of nifedipine (10 mg oral) when standard therapy with β-blockers and long-acting nitrates failed in 18 patients in whom pre-nifedipine observations were available; no significant change could be demonstrated (paired t-test)

	HR (beat/min.) (n = 18)	$\bar{m}$AP (mm Hg) (n = 18)	Pressure rate product (mm Hg × beat/min) (n = 18)	PCWP (mm Hg) (n = 18)
Pre-nifedipine	65 ± 9	97 ± 17	6445 ± 1562	7 ± 3
1 h post-nifedipine	70 ± 9	95 ± 13	6854 ± 1372	8 ± 3
4 h post-nifedipine	70 ± 16	90 ± 11	6396 ± 1439	7 ± 3

Abbreviations: HR = heart rate in beats/min (mean ± s.d.); $\bar{m}$AP = mean arterial pressure (mean ± s.d.); PCWP = pulmonary capillary wedge pressure (mean ± s.d.).

direct intracoronary administration. This route of administration was employed in order to dissociate its coronary vasodilatory effect from its direct myocardial action and its peripheral afterload reduction effect[20, 29–31]. The data from hemodynamic studies indicate that when nifedipine is regionally administered, it has a transient negative inotropic effect, which induces a transient increase of the coronary sinus O_2 saturation because less oxygen is being utilized.

However, the vasodilation of all three, the prestenotic, stenotic and poststenotic, coronary segments persists much longer, at least than during the period of observation in this study. The essential question now becomes: what effect do large vessel vasomotor tone and distal arteriolar resistance have on a proximal lesion? The conflicting data and hypotheses have been recently reviewed by Gould[32]. He states that there exist different possible mechanisms for altered severity of 'fixed' coronary stenoses during changing vasomotor states of the coronary circulation, some of which are schematized in Figs 8 and 10. In

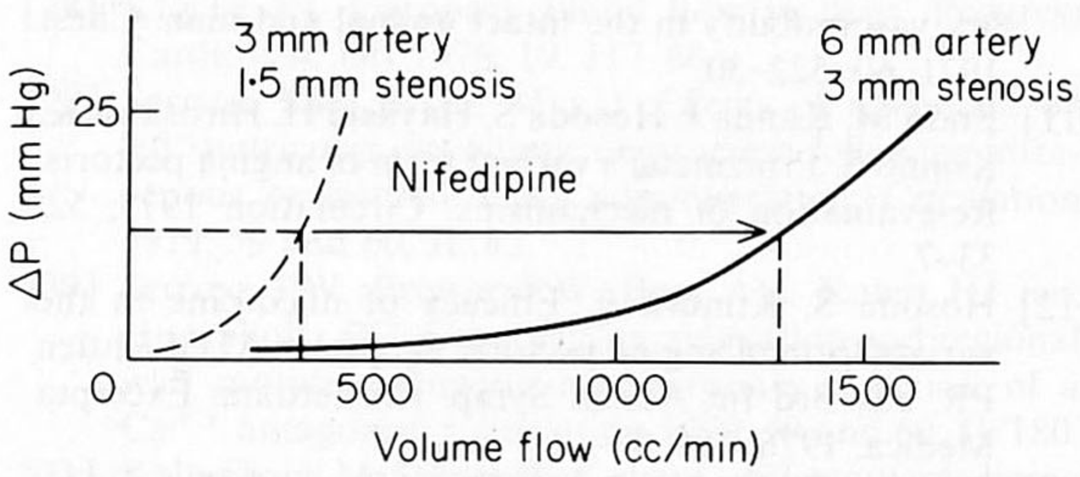

Figure 10 Relation of pressure gradient ($\triangle$P) and arterial volume flow for physiologically equal stenoses before and after vasodilatation with nifedipine. Diameter stenosis = 50%; maxiflow = 4 × ↑; $\triangle$P = 25 mm Hg. (Modified figure, reproduced with permission of KL Gould.)

contrast to these experimental data, Brown *et al.*[7], Doerner *et al.*[33] and Oravetz *et al.*[5] described a significant decrease in severity of stenosis after the administration of nitroglycerin as seen on coronary arteriograms. Their approach, using theoretical flow equations and measurements of absolute stenosis diameter, is appropriate because they examine changes in stenosis after an intervention in comparison with the same stenosis under control conditions. In the current study, absolute stenosis diameter was also obtained in order to compare the geometric severity of the same area in the same artery before and after the administration of nifedipine. The theoretical relationship between the pressure gradient and arterial volume flow for physiologically equally severe stenoses in a vasoconstricted and a vasodilated artery is shown in Fig. 10. The physiologic severity in this example is defined as the capacity to increase flow four times over resting value with a maximal pressure gradient of 25 mm Hg. Thus, stenoses of equal physiological severity in arteries of different sizes appear unequal if analyzed in terms of volume flow equations. These data indicate that small decreases in vasomotor tone may have profound hydraulic effects.

How is the effectiveness of nifedipine in the second group of patients with unstable angina who had already been 8 h on treatment with nitrates and β-blockers to be explained? Given orally or intravenously in man, nifedipine significantly reduces the peripheral resistance and systemic pressure[34, 35]. However, in our patients, β-blockers and nitrates had already been given to maximally reduce the myocardial oxygen demand and its major determinant, the pressure rate product by reducing heart rate as well as afterload. It is, therefore, not too surprising to see that the administration of nifedipine did not result, in an additional decrease of the pressure rate product (Table 7), when these were measured 1 and 4 h later. In other words, in the patients studied, the known peripheral hemodynamic effects of nifedipine do not explain the symptomatic effects of the drug. Rather we suggest that the effectiveness of nifedipine is related to its capacity to decrease the calcium-dependent contractile tone of the epicardial coronary arteries so that they became less sensitive to vasoconstricting stimuli which may have resulted from the ischemic state[15–17].

The mechanisms for adjusting arteriolar tone may be classified as neurohumoral, metabolic or myogenic. Although most basic scientists have regarded neurohumoral mechanism as much less important than metabolic, the potential role of this type of control on coronary vascular smooth muscle has undergone significant re-examination during the last decade[36]. Several authors have demonstrated spontaneous changes in coronary vascular resistance independent of identifiable changes in myocardial metabolic demand[37–40]. It has been suggested that there is normally a degree of basal constrictor tone in the coronary bed[41]. The myogenic control of coronary resistance was originally proposed by Bayliss in 1902[42], who described the intrinsic ability of blood vessels to respond to changes in transmural pressure. This mechanism is not generally considered to have a dominant role, but it must be pointed out that it has been difficult up to now to formulate studies capable of defining the importance of this mechanism in atherosclerotic blood vessels[43]. Berne and co-

workers have tested different vaso-active agents such as adenosine, nitroglycerin and calcium antagonists for their ability to affect the induced action potential of isolated large ($\geqq$1·0 mm) and small ($\leqq$500 μm) coronary arteries[44]. Adenosine blocked the calcium-dependent action potential in small coronary arteries, but had no effect on the action potential in large arteries. In contrast, nitroglycerin blocked the action potential in large coronary arteries, but not in small ones. Calcium antagonists blocked the action potential irrespective of the size of the vessel. Nifedipine is able to block completely the autoregulation of the renal vascular bed whereas glyceryl trinitrate fails to impair this autoregulation[45]. Since autoregulation of blood flow is defined as the intrinsic regulatory mechanism of a vascular bed to maintain its blood flow at a constant rate regardless of changes in perfusion pressure, these experimental data emphasize the advantages of nifedipine over nitrates in affecting the coronary vascular system. In keeping with these observations is the persistent relief of pain in patients with unstable angina pectoris reported in this study who were still symptomatic while on β-blocker therapy. This is probably due to a specific action of nifedipine on the arteriolar tone of the major epicardial and the smaller coronary arteries which persisted over a 48 h period and stabilized what had been a very brittle condition. The fact that in 42 of the 52 such relief, although admittedly induced by yet another dose of nitroglycerin, persisted for the entire period of observation is a strong argument in favor of this mechanism. The hypothesis has also been put forward that the subset of patients with inappropriate vasoconstriction and suspected coronary artery spasm may worsen with β-adrenergic blockade[46]. In fact, Yasue has specifically argued against β-blockers in this group of patients because of the β_1-blocking, and thus potentially vasoconstrictive action. Since in this series of patients, unresponsive to β-blockade, the response to nifedipine was so consistent (and just as effective as had been pain relief from IABP[25]), there is little doubt that nifedipine in this group of patients, was the sole agent which kept the balance in their favor. Does nifedipine in these patients actually relieve excessive vasoconstriction? Only further studies, with direct measurement of coronary blood flow and measurement of coronary anatomy during the attack will answer this question with definity.

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