Postgraduate Medical Journal, 1983, **59** (Suppl. 2), 40–58

SESSION II

Calcium antagonists in the treatment of ischaemic heart disease—II

Chairman: PROFESSOR A. H. HENDERSON

Nifedipine for angina and acute myocardial ischaemia

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Summary

This paper reviews the mechanisms believed to be responsible for myocardial ischaemia and the mode of action of calcium antagonist drugs. The clinical management of patients with myocardial ischaemia is discussed in the context of current knowledge about patho-physiology and drug action.

Introduction

Since their introduction in the early 1970's in Japan and Europe, "calcium antagonists" have elicited great interest in the cardiological community. This is not only due to the fact that they are an entirely new, although heterogeneous, group of compounds with a novel therapeutic principle, the manipulation of calcium ion transport into and inside the cell, but also because they have proved to have great clinical efficacy in hitherto difficult to treat syndromes. Now that these compounds have been introduced in all parts of the world it appears timely to review their profile in order to delineate their position in the therapeutic arsenal available to the practising physician. Only the three main agents, nifedipine, verapamil and diltiazem will be discussed, although several related or derived compounds are currently under development.

While it is certain that calcium transport blockers will provide the practitioner with still more flexibility in the means already at his disposal to manage patients with various forms of angina pectoris and cardiac ischaemia, it means he will need to become familiar with yet another group of compounds and to understand their particular mode of action. It is appropriate therefore to review briefly the mode of action of these new drugs as well as experimental evidence of their efficacy first, to discuss the current understanding of the pathophysiologic derangements which lead to angina pectoris and finally to detail their optimal usage in and outside the clinic with some personal recommendations.

Mechanism of action

All three drugs have in common the ability to block the entry of calcium ions through the pores in the cell membrane into the intracellular space. Normally this flux of calcium ions sets into motion a series of steps which end with the contraction of the muscle fibres. Calcium also plays a key role in the regulation of the extent and rate of relaxation. These "manipulations" of the calcium transmitter constitute therefore the key principle of this new therapy. It provides for a nearly physiological means of regulating and controlling the function of various cells in the body. For example, inhibition of the excitation-contraction coupling in the *smooth muscle cells* in the wall of various arterial systems decreases their contractile tone which in turn results in vasodilatation. In the coronary arterial system this increases coronary blood flow, in the brain it may relieve migraine and in Raynaud's disease, the painful extremities. Furthermore, in the peripheral arterial system, the decrease in resistance can lead to a marked reduction in arterial pressure, particularly when hypertension was previously present and therefore to a reduction in the work of the heart. On the other hand, in the *cardiac muscle cell* itself, the

0032–5473/83/0702–0040 $02.00

inhibition of intracellular calcium activity diminishes the contractile and mechanical activity and thus, by a second mechanism, reduces myocardial oxygen demand. Particularly when angina has led to regional ischaemia, as insufficient oxygen is offered to the myocardium, these drugs have been shown to provide protection for the mitochondrial activity. Under ischaemic conditions the intracellular storage spaces for high energy phosphates are threatened by lack of oxygen. All three drugs have been shown to preserve the high-energy phosphate compounds inside the cell and thus to reduce cellular breakdown in ischaemia, as will be detailed below.

When these actions are taken together—the increased supply of oxygen through the coronary vascular system, the reduction in cardiac workload and the local "protective" effects—they all appear to be highly desirable interventions when the myocardium is threatened by ischaemia such as may occur intermittently during any form of angina. Finally it has also been shown that inhibition of calcium transport across the cell membrane of cardiac (pacemaker) cells can reduce or avoid altogether the cardiac arrhythmias which frequently occur during ischaemic episodes. For supraventricular arrhythmias verapamil has been shown to be particularly effective, but nifedipine is also active against ventricular arrhythmias. These actions can complement the other drugs commonly employed in angina pectoris, such as nitrates and beta-blockers. Since nitrates act mainly on the venous system, by pooling blood in this reservoir, they work in angina pectoris mainly by reducing the return of blood to the heart which in turn diminishes the stress in the ventricular wall. Since the heart now has to provide less work, it uses less oxygen. On the other hand, beta-blockers primarily affect the receptor sites for adrenergic impulses transmitted by catecholamines. This is manifested in particular by a slowing in pacemaker activity, which leads to bradycardia, a desired effect since it reduces myocardial oxygen consumption by that route. Beta-blockers also have an action on the cell metabolism itself, particularly when the cells have become ischaemic. The exact nature of their "protective" action is not clear at this time but it is additive to and probably different from that of the calcium transport blockers, as will be shown later.

Combination therapy of nitrates, beta-blockers and calcium-antagonists has therefore been recommended by several authors. This seems particularly advantageous when the dosages of the individual drugs in combination therapy are lower than with mono-therapy since side effects can be reduced. For example, in a patient with angina pectoris who has hypertension and tachycardia, the combination of a beta-blocker with nifedipine may be particularly advisable since the two main determinants of myocardial oxygen consumption, heart rate and afterload, can be reduced at the same time. Furthermore the reflex induced tachycardia after nifedipine will be blocked by the beta-blocker. A schematic view of their overall interaction is provided in Fig. 1. Now let us return to reality and look at the evidence.

Experimental evidence

Our reperfusion studies in the pig show that when coronary blood flow is reduced to 20–30% of control, mechanical action of the underperfused region of the heart ceases. Yet, if that area is reperfused soon enough, it will contract again normally. When reperfusion with blood is begun after 30 minutes of coronary artery occlusion, the contraction of the myocardial wall returns to only half the preocclusion level. However, when a nifedipine infusion (1 μg/kg/min, i.v.) is started just before reperfusion, myocardial thickening returns to 75% of the preocclusion level (Fig. 2). This protective effect, presumably against reperfusion damage as detailed by Zimmerman *et al.* (1967) and Hearse, Humphrey and Bullock (1978), can also be shown in the same animal preparation after complete occlusion of the coronary artery near its origin. Most animals die of ventricular fibrillation within the first minutes after such ligation. In stark contrast, most animals in whom high doses of nifedipine or a combination of nifedipine and propanolol were administered in the coronary artery just before ligation, survived 3 consecutive 10 minute periods of complete occlusion. Furthermore they did not show serious arrhythmias during reperfusion (Verdouw, Cate and Hugenholtz, 1983) (Fig. 3). In other words, nifedipine given immediately before reperfusion, or better still before ischaemia is induced, preserves the heart's contractile properties much better than reoxygenation by itself can achieve (Verdouw *et al.*, 1981). Nifedipine increases capillary blood flow in non-ischaemic tissue of animals in which one of the coronary arteries has been partially occluded for 30 minutes. This is probably because overall resistance in the coronary vascular circuit is reduced further. However, even in the centre of the ischaemic area, where little flow remains, perfusion increases, even favouring the endocardium (Verdouw *et al.*, 1981) (Fig. 4). This augmentation of capillary flow may well be an important factor in the suppression of reperfusion ventricular arrhythmias. In fact, in our patients submitted for percutaneous transluminal coronary angioplasty or streptokinase fibrinolysis, nifedipine is now given as a routine prophylaxis. In over 200 patients so treated, ventricular fibrillation occurred only twice. Many authors have observed that sudden reperfusion of ischaemic myocardial tissue may cause an extension of myocar-

AIM OF THE THERAPY: TO ACHIEVE OXYGEN DEMAND-SUPPLY BALANCE IN THE MYOCARDIUM

DETERMINANTS OF MYOCARDIAL OXYGEN CONSUMPTION

	HEART RATE	PRELOAD	AFTERLOAD	CONTRACTILITY	CORONARY VASCULAR TONE	CORONARY VASCULAR FLOW
NITRATES	↑	↓	↓	–	↕	↑↑
β-BLOCKING AGENTS	↓	↕	↑	↓	↑	–
CALCIUM-ANTAGONISTS	↑↑	–	↓	↓	↓	↑
INTRA AORTIC BALLOONPUMP Enhancement of coronary perfusion pressure	–	↕	↓	–	–	↑

FIG. 1. Schematic display of the principal effects of the nitrates, beta-blocking agents, calcium antagonists and the intra-aortic balloon pump. Note that when there is increased vasomotor tone, calcium antagonists would seem to provide the best approach.
↑ increase ↓ decrease ↕ variable increase/decrease

dial damage, while Hearse *et al.* (1978) as well as others found that such reperfusion damage in fact may be caused by sudden oxygen-induced transmembrane calcium fluxes. Parratt and Coker (1983) have also shown that under these circumstances reperfusion arrhythmias can be completely suppressed by nifedipine as well as by some of its derivatives.

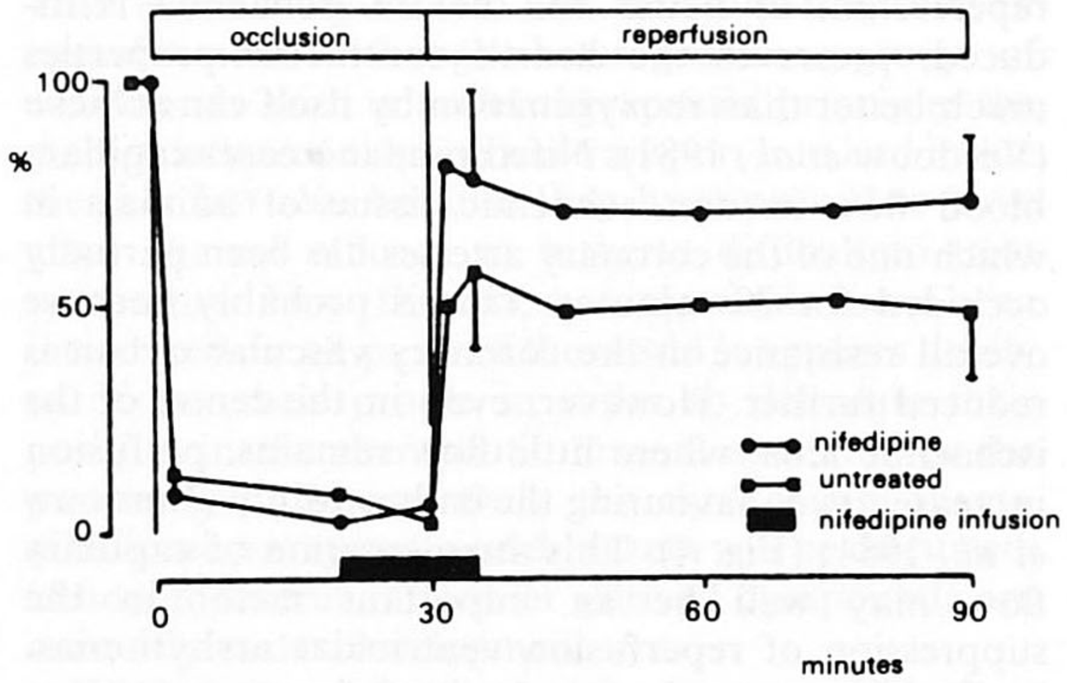

FIG. 2. Experiment reprinted with permission from Verdouw *et al.* (1981). Along the vertical axis is given the extent of wall thickening during systole in %. From a control value of 100%, a 30 minute reduction of coronary blood flow to 20–30% of baseline reduces wall thickening to virtually 0%. In this average of 8 animals studies, reperfusion after 30 minutes of occlusion, allowed a return to 75% of control provided nifedipine was given 10 minutes before removal of the ligature.

Though it is clear that reperfusion with oxygen-rich blood may have a detrimental effect on the left ventricle, whether it is reperfused after a bout of vasoconstriction such as after dissolving a platelet aggregate, or after coronary artery bypass grafting upon coming off the pump, our data provide direct evidence that during the acute ischaemic conditions, the addition of nifedipine preserves local mechanical function and increases capillary blood flow, even within the core of the ischaemic area. Let us now see how these observations in the intact animal can be explained by measurements in the isolated heart, in which high energy phosphate metabolism can be better studied in detail.

It has been shown by a number of authors that various calcium antagonists can reduce high energy phosphate breakdown during hypoxia. Although slow channel blockers vary in their mode of action on the cardiac cells as shown by Opie (1980), Henry (1980), Fleckenstein and Fleckenstein-Gruen (1980), nifedipine certainly acts by arresting mechanical activity thus limiting phosphate utilization. However, there are only limited data supporting this view mainly those published by Nayler, Ferrar and Williams (1980) and Higgins, Allsop and Bailey (1980) although Ichihara, Ichihara and Abikol (1979) could not substantiate these.

We decided therefore to study the effect of nifedipine on the myocardial release of the AMP

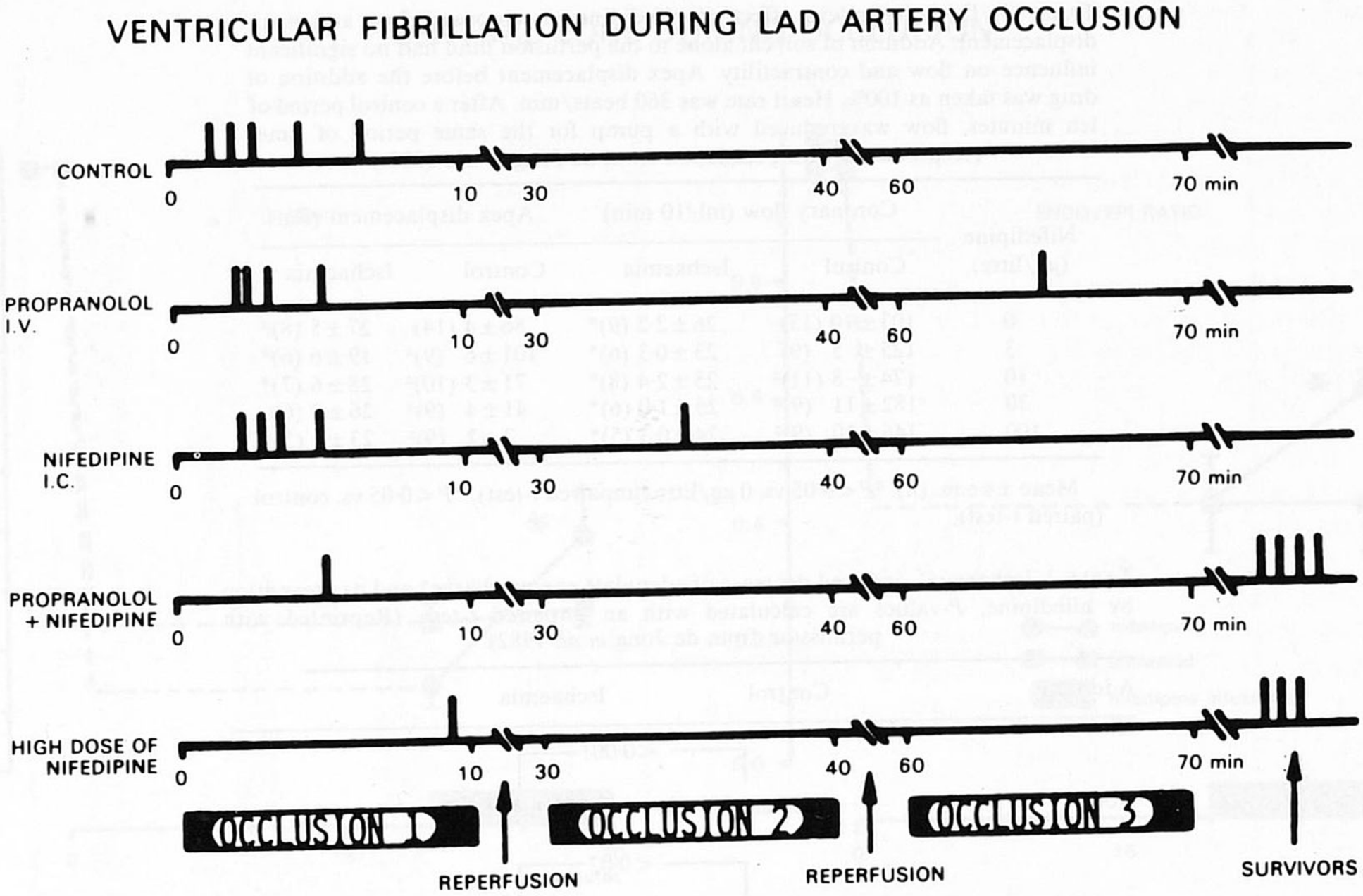

FIG. 3. In this experiment, with 3 periods of complete ligation of the coronary artery (LAD) for 10 minutes each, all control animals died of ventricular fibrillation as did those treated with propanolol or nifedipine (0·05 μg/kg/min). On the other hand, those given intracoronary (IC) nifedipine with propanolol or nifedipine at 2μg/kg plus infusion of 0·05 μg/kg/min just before the induction of ischaemia, suffered no untoward effects, and survived the length of the experiment with nearly complete recovery of normal wall motion.

catabolites adenosine, inosine and hypoxanthine during ischaemia. For that purpose we made isolated rat hearts ischaemic. We showed that breakdown of adenine nucleotides was indeed prevented by nifedipine (de Jong *et al.*, 1982). This evidence is based on measurements of purine nucleosides and oxypurines (Fig. 5), of coronary flow and apex displacement (Table 1) as well as of the adenylate energy charge (Table 2). Nifedipine at 10 μg/litre concentration increased the control flow from 40 to 100 ml/min per gram dry weight (g dwt) ($P<0·001$). When the perfusion pressure was lowered from 72 to 17 mmHg, coronary flow in the untreated hearts decreased by 60% ($P<0·001$). During ischaemia, flow in the presence and absence of nifedipine was comparable, about 15 ml/min per g dwt, while during reperfusion, flow increased again to control levels. In a second series of experiments (Table 1) ischaemia was induced with a pump; it diminished coronary flow in untreated hearts by 75% ($P<0·001$). Nifedipine at a concentration of 10 μg/litre decreased apex displacement by 35% ($P<0·01$) at 100 μg/litre, diminished contractility during the pre-ischaemic perfusion to 10% of the control values observed with its solvent ($P<0·001$). Since during ischaemia, apex displacement was already reduced to about 25% of preperfusion values ($P<0·001$), both in treated and untreated hearts, the heart could deliver a threefold *in*crease ($P<0·02$) in apex displacement when the high dose of nifedipine (100 μg/litre) had been previously present in the perfusate (Table 1). Purine release during the control period was 10±5 nmol/min per g dwt. At the end of the ischaemic period purine release was 46±17 nmol/min per g dry weight ($P<0·05$ vs. control), while nifedipine in as low a dose as 10 μg/litre reduced this release by 75% ($P<0·05$) (Fig. 5).

These relatively mild ischaemic conditions resulted in a lactate release which was 2·6 times higher than the control value ($P<0·02$). This too was completely abolished by 10 μg/litre nifedipine ($P<0·05$). During reperfusion, purine and lactate production after an initial sharp rise decreased again, but the hearts released more of these compounds in the untreated group than in the treated group.

When ischaemia was made more severe by reducing flow to a larger extent and by increasing heart rate, the highest dose of nifedipine, 100 μg/litre, prevented adenosine release during 10 min of ischaemia by more than 90% ($P<0·02$, Fig. 6). This dose also decreased the release of inosine, hypoxanthine and xanthine during ischaemia by 85% ($P<0·002$),

TABLE 1. Dose-dependent effect of nifedipine on coronary flow and apex displacement. Addition of solvent alone to the perfusion fluid had no significant influence on flow and contractility. Apex displacement before the addition of drug was taken as 100%. Heart rate was 360 beats/min. After a control period of ten minutes, flow was reduced with a pump for the same period of time. (Reproduced with permission from de Jong *et al.*, 1982.)

Nifedipine (μg/litre)	Coronary flow (ml/10 min)		Apex displacement (%)	
	Control	Ischaemia	Control	Ischaemia
0	103 ± 10 (15)	26 ± 2·2 (9)*	86 ± 4 (14)	27 ± 5 (8)*
3	125 ± 5 (9)	23 ± 0·3 (6)*	101 ± 6 (9)$^{\Delta}$	19 ± 6 (6)*
10	174 ± 8 (11)$^{\Delta}$	25 ± 2·4 (8)*	71 ± 3 (10)$^{\Delta}$	28 ± 6 (7)*
30	182 ± 11 (9)$^{\Delta}$	25 ± 1·0 (6)*	41 ± 4 (9)$^{\Delta}$	26 ± 9 (6)
100	146 ± 10 (9)$^{\Delta}$	24 ± 0·3 (5)*	7 ± 2 (9)$^{\Delta}$	23 ± 6 (5)*

Mean ± s.e.m. (n), $^{\Delta}P<0·05$ vs. 0 μg/litre (unpaired t-test), $^{*}P<0·05$ vs. control (paired t-test).

TABLE 2. Ischaemia—induced decrease of adenylate energy charge* and its prevention by nifedipine. *P*-values are calculated with an unpaired t-test. (Reprinted with permission from de Jong *et al.* 1982)

Addition	Control	Ischaemia	
		<0·001	
None	0·890 ± 0·007 (5)	0·793 ± 0·012 (7)	
		<0·02	
Vehicle	0·896 ± 0·004 (4)	0·761 ± 0·029 (4)	<0·02
			<0·05
Nifedipine (100 μg/litre)	0·897 ± 0·007 (4)	0·864 ± 0·024 (4)	

Mean ± s.e.m (n); *(ATP + 0·5 ADP)/(ATP + ADP + AMP).

75% ($P<0·05$), and 64% ($P<0·05$). In these experiments the solvent itself also had an effect on purine production during the control period as the release of adenosine rose from levels <1 nmol/10 min to 7–11 nmol/10 min. Differences in lactate release during the control period were only observed with 3 μg/litre nifedipine: this induced a 42% decrease ($P<0·05$). The nifedipine dose had to be increased to 100μg/litre to prevent ischaemic lactate release ($P<0·001$).

We were unable to measure a significant decrease in myocardial ATP content when flow was restricted to as little as 2·5 ml/min with a heart rate of 360 beats/min. However, adenylate energy charge decreased by about 15% due to ischaemia ($P<0·02$, Table 2). This decrease was prevented by 100 μg/litre nifedipine ($P<0·05$ vs. solvent). Although we found that the release of lactate, a marker of myocardial ischaemia (de Jong, 1979) was reduced by nifedipine, Ichihara *et al.* (1979) were unable to detect an effect of nifedipine on myocardial lactate release during ischaemia in the dog. Perhaps species differences exist to explain this.

These protective effects found in our experiments are not primarily due to the negative inotropic action of nifedipine, because we found that the drug did not affect contractility further when as a result of ischaemia mechanical action had been reduced. Similarly, Perez, Sobel and Henry (1980) found at these doses no nifedipine or diltiazem-induced depression of the mechanical activity of ischaemic canine heart but, instead, as in our experiments, observed a significant enhancement of its performance. In fact, with the highest dose of nifedipine we found an actual increase in apex displacement (Table 1), concomitant with the decrease in purine release.

Atkinson (1977) has reviewed the activities of important regulatory enzymes *in vitro* as a function of energy charge. With an increase in energy charge from 0 to 1, the regulatory enzymes in ATP-using sequences increase in activity and those which regenerate ATP decrease in activity. Nifedipine appears capable of increasing the energy charge to the levels necessary for the proper functioning of the heart (Table 2), even when under ischaemic conditions less oxygen is available. Perhaps its beneficial

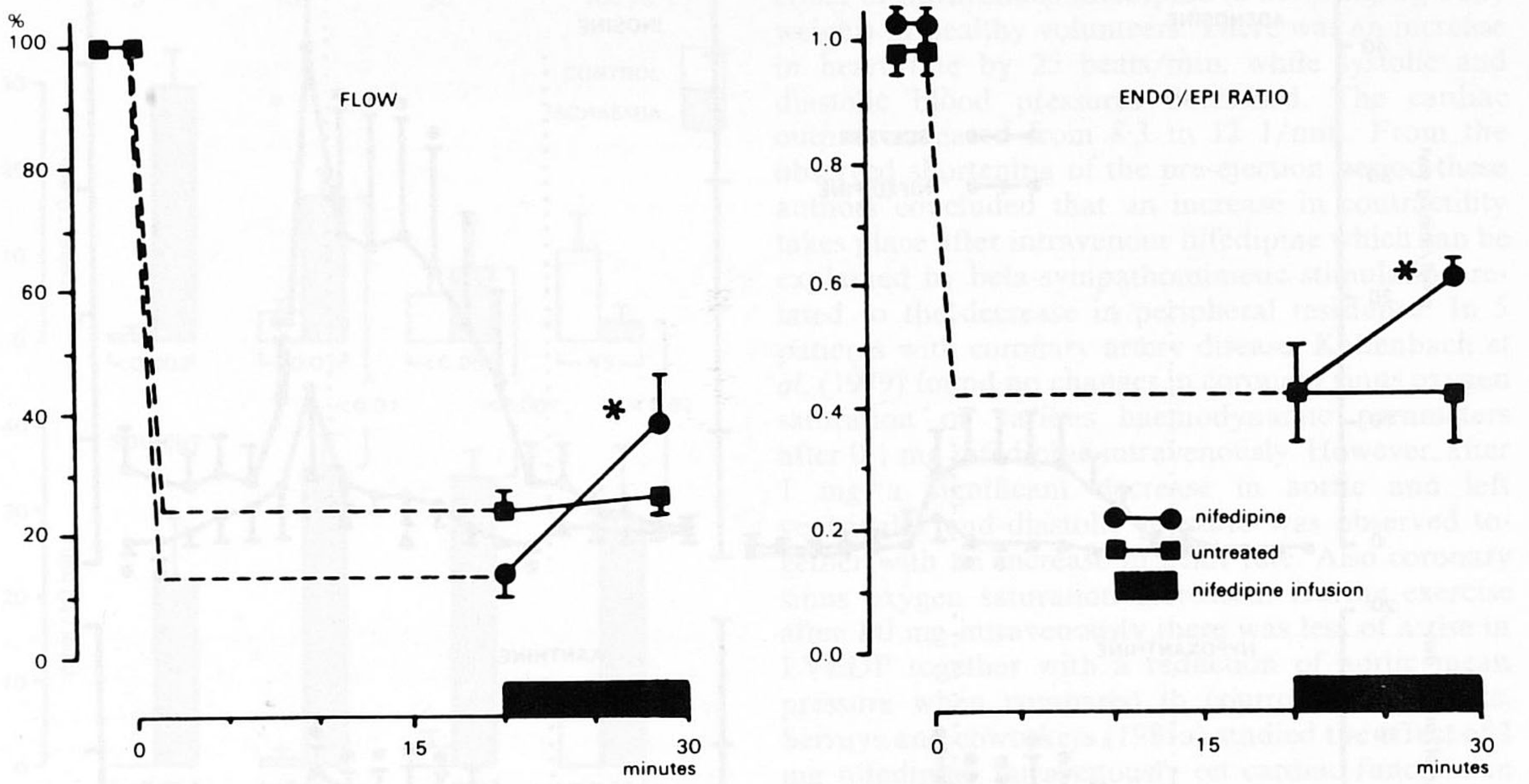

FIG. 4. Experiment reprinted with permission from Verdouw *et al.* (1981). These data were obtained with radio-active labelled micro-spheres injected at three successive moments. They show that capillary flow improves from 16 to 35% of control in the central core of experimentally induced infarction during nifedipine infusion. In addition, the increase in capillary flow appeared to favour the endocardial segments (endo) more than the epicardial segments (epi) (*$P<0{\cdot}05$).

intracellular action is related to this regulatory function.

It is of interest that rat heart produces relatively large amounts of xanthine during ischaemia (de Jong *et al.*, 1983). Xanthine oxidase, which converts hypoxanthine to xanthine (and xanthine to urate) is reported to be absent or to be present in low amounts (Maguire *et al.*, 1972). Because the extent to which xanthine oxidase in heart and blood vessels is present has been implicated as a causative factor in atherosclerosis (Carr *et al.*, 1975), further studies are clearly needed in this area. Could nifedipine be a primary anti-atherosclerotic agent by this mechanism as suggested by the data of Fleckenstein and Henry, described elsewhere in this supplement (Fleckenstein and Henry, 1983)?

Nayler, Ferrar and Williams (1980) were among the first to show that hearts from rabbits treated with nifedipine, verapamil or propranolol were protected against the ischaemia-induced decline in the ATP-generating and O_2-utilizing capacity of the mitochondria. According to Nayler and Poole-Wilson (1981) at that time, no simple explanation for the protection afforded by calcium antagonists to hypoxic and ischaemic heart muscle could be given. However, from our experiments we conclude that nifedipine prevents myocardial adenine nucleotide breakdown in ischaemic rat heart, and presumably in the ischaemic intact pig heart, by an energy regulatory action on and above its negative inotropic action. The precise mechanism remains to be solved but little doubt can remain of its beneficial action and further investigation in the human heart appears in order.

Observations in patients. Effects on haemodynamics

To demonstrate the direct effect of nifedipine on the human heart, the intracoronary route of administration was used by Kaltenbach, Schulz and Kober (1979). While 0·1 mg intravenously administered nifedipine had no effects on systemic haemodynamics or coronary sinus oxygen saturation, intracoronary injection (i.c.) of the same dose caused a significant increase of coronary sinus oxygen saturation, which terminated 5 min after infusion. During exercise 15 min after 0·1 mg nifedipine i.c., an anti-ischaemic effect, documented by a reduction in exercise-induced increase in left ventricular-end-diastolic pressure (LVEDP) and exercise-induced ST-T segment depression was apparent. The authors stated that this effect could not be entirely explained

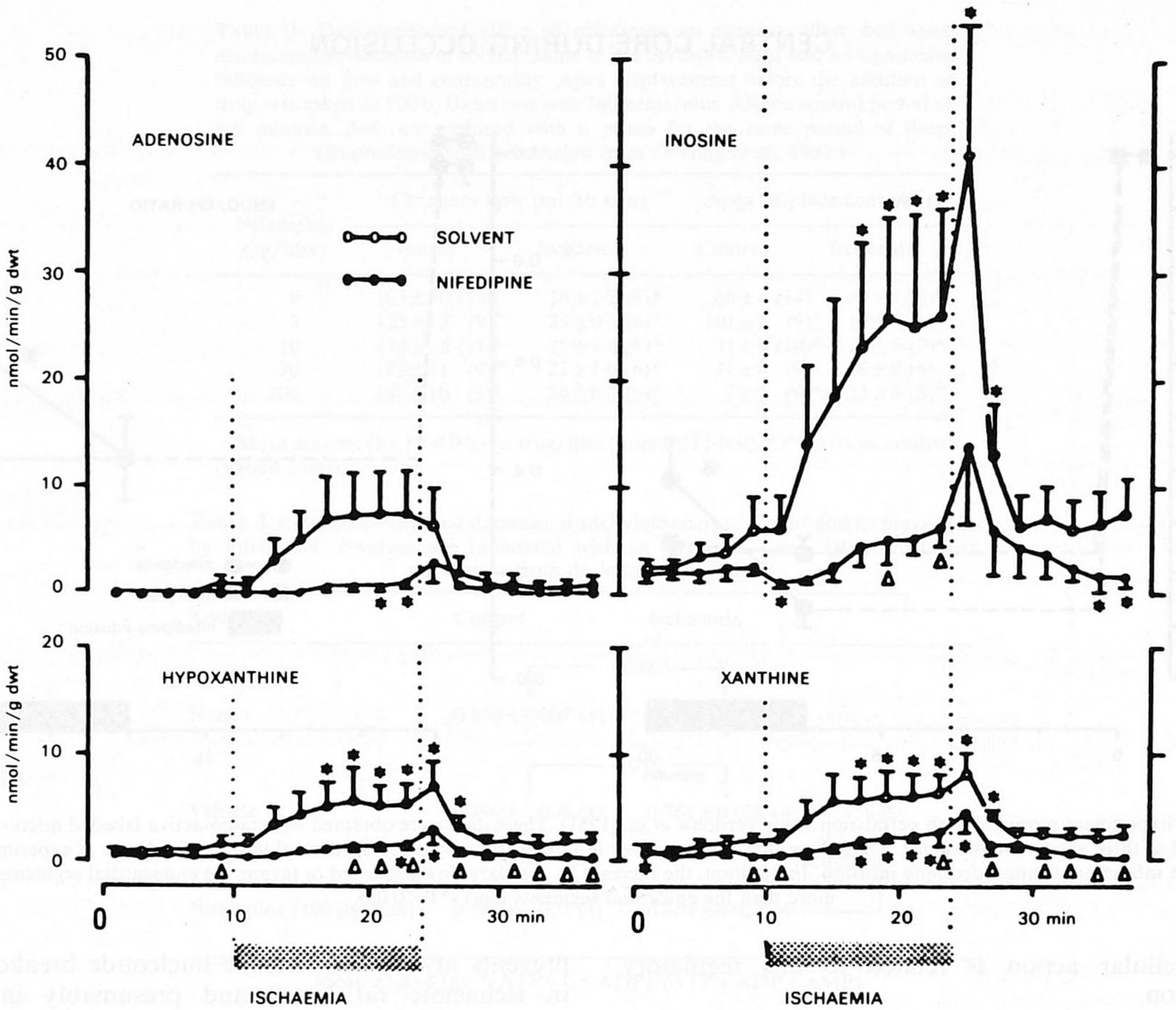

FIG. 5. Nifedipine (10 μg/litre) reduced the myocardial release of purine nucleosides (upper panel) and oxypurines (lower panel). Heart rate was 300 beats/min and flow reduction 60% Means ± s.e.m. (n = 5) indicates significance at the 5% level vs solvent (unpaired t-test), * denotes significance at the 5% level vs control (paired t-test with values at t = 9 min.). Note how nifedipine virtually blocks all release of adenosine. Experiment reprinted with permission from De Jong *et al.* (1982).

by the effects on the coronary arteriolar reserve because it persisted after coronary flow had returned to normal. A central effect of the drug on cardiac metabolism and/or contractility was considered as an alternative explanation.

The effects of intracoronary nifedipine on left ventricular contractility were further studied by Serruys and coworkers (1981a). Epicardial wall motion was shown to be decreased and delayed by measuring the distances between metal markers which had been sutured on the epicardium during prior surgery in regions directly supplied by bypasses. Simultaneously measured pressure-derived variables demonstrated a direct negative inotropic effect after an intra-bypass injection of 0·1 mg nifedipine with a decrease in left ventricular systolic pressure, a decrease of Vmax and max. dP/dt and an increase in left ventricular end-diastolic pressure (Fig. 7). No changes in wall motion were seen in the independently perfused areas. Asynchrony was induced by nifedipine and considered responsible for the slowed isovolumic contraction. Relaxation of the ventricle as a whole was also impaired as evidenced by a prolonged time constant of relaxation and a diminished peak negative dP/dt. All these changes in left ventricular wall motion lasted less than 5 minutes. The same transient negative inotropic effect was demonstrated by these authors (Serruys *et al.*, 1981b) in another group of patients after injection of 0·2 mg nifedipine in the left main coronary artery. Here frame to frame analysis of the regional wall motion from left ventricular angiograms again showed that intracoronary nifedipine delays, prolongs and depresses the anterior wall motion.

An impaired left ventricular relaxation pattern after intracoronary injection of 0·1 mg nifedipine was also demonstrated by Rousseau *et al.* (1980) both in patients and normal subjects. In addition, several

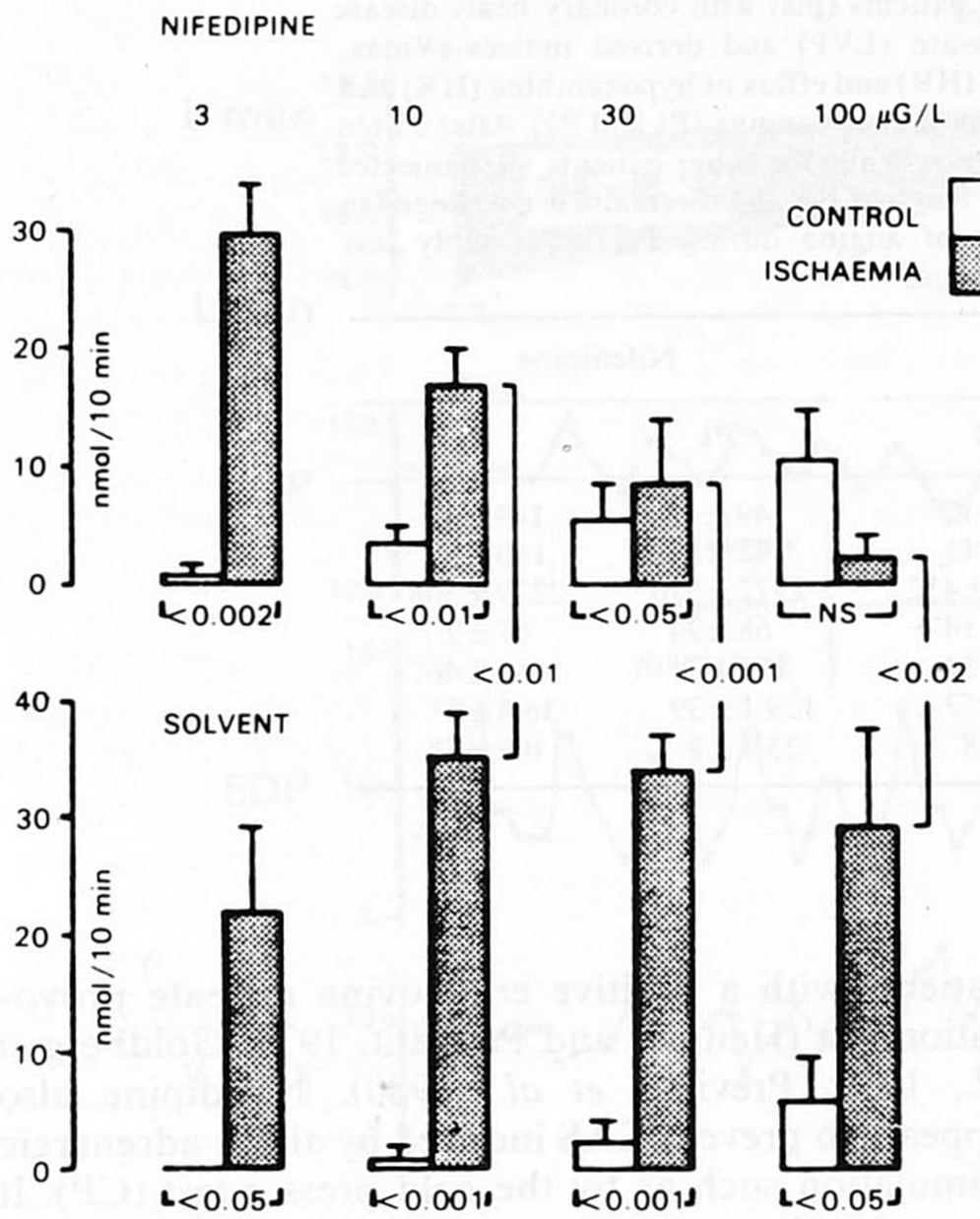

FIG. 6. Nifedipine reduced adenosine release from the ischaemic heart dose dependently. Means ± s.e.m. values vs control with nifedipine at various doses (upper panel, paired t-test) and vs solvent (lower panel, unpaired t-test). Experiment reprinted with permission from de Jong *et al.* (1982).

authors have shown a powerful spasmolytic and vasodilating effect after i.c. nifedipine (Bertrand, Lablanche and Tilmant, 1980, 1981; Hugenholtz *et al.*, 1981; Serruys *et al.*, 1982). This effect is seen in normal, stenotic and post-stenotic segments of the injected coronary artery (Serruys *et al.*, 1982). Shortly after intracoronary injection, coronary blood flow increases and myocardial oxygen consumption decreases. This effect again is of short duration and lasts about 5 minutes. However, the increase in vascular diameter persists after the myocardial oxygen uptake (MVO_2) and coronary sinus blood flow have returned to normal (Fig. 7). The duration of the effect of intracoronary nifedipine on cardiac metabolism was also studied by Serruys *et al.* (1982) during atrial pacing with heart rates up to 150 beats/min. Pacing-induced angina pectoris threshold was not affected 25 min. after 0·1 mg intracoronary nifedipine, but at that time the efflux of hypoxanthine and lactate became significantly reduced, although a lesser degree of efflux of these catabolites was also seen after injection of the solvent which acted as a placebo (Table 3). This indicates an O_2 sparing effect and also that the cause of induced anginal pain is not only the release of high energy phosphate catabolites. This action may reflect increased efficiency of oxygen utilization.

Lydtin *et al.* (1975) studied the haemodynamic effect of intravenous nifedipine (0·0075 mg/kg body weight) in healthy volunteers. There was an increase in heart rate by 25 beats/min, while systolic and diastolic blood pressures decreased. The cardiac output increased from 8·3 to 12 1/min. From the observed shortening of the pre-ejection period these authors concluded that an increase in contractility takes place after intravenous nifedipine which can be explained by beta-sympathomimetic stimulation related to the decrease in peripheral resistance. In 5 patients with coronary artery disease, Kaltenbach *et al.* (1979) found no changes in coronary sinus oxygen saturation or various haemodynamic parameters after 0·1 mg nifedipine intravenously. However, after 1 mg a significant decrease in aortic and left ventricular end-diastolic pressure was observed together with an increase in heart rate. Also coronary sinus oxygen saturation increased. During exercise after 1·0 mg intravenously there was less of a rise in LVEDP together with a reduction of aortic mean pressure when compared to control exercise data. Serruys and coworkers (1981a) studied the effect of 1 mg nifedipine intravenously on cardiac function in 11 patients with coronary artery disease. Peak left ventricular pressure was lowered from 152 to 128 mmHg. The basal heart rate rose from 71 to 87 beats/min. During atrial pacing, there was a reduction in peak left ventricular pressure at all pacing rates after nifedipine. Regional shortening fraction, measured from pairs of radiopaque markers implanted during surgery, was increased over the entire pacing range and at the highest paced rate, and increased maximal velocity (V_{max}) of the contractile elements was present. There was therefore no evidence of negative inotropic effects, but rather an increase in regional function.

The differences between the intrinsic negative inotropic effect of nifedipine shown after direct intracoronary injection of the drug in humans, and its absence after intravenous administration of nifedipine, can be explained by the reflex sympathetic drive due to baroreceptor stimulation after the reduction in peripheral vascular resistance. Joshi *et al.* (1981) at a constant atrial paced rate, administered 10 mg of nifedipine sublingually to 10 coronary artery disease patients already pretreated with atenolol (400 mg/day). They observed a significant decrease of peak dP/dt and peak dP/dt/P which suggested the negative inotropic effect of the drug was more evident after beta-blockade. In their experiments, cardiac output, however, remained unchanged. Koch (1980) gave 10 mg nifedipine sublingually to patients with coronary artery disease pretreated with metoprolol. An increase of adrena-

TABLE 3. Effect of pacing on hypoxanthine and lactate release. The direct effect of nifedipine on cardiac cellular metabolism was studied in 20 patients (pts) with coronary heart disease during induced ischaemia. Left ventricular pressure (LVP) and derived indices (Vmax, Pk + dP/dt), coronary blood flow (CBF), heart rate (HR) and efflux of hypoxanthine (HX) and lactate (LC) were measured during sequential pacing-induced angina (P1 and P2). After P1 ten patients received 0·1 mg nifedipine in both coronaries, while the other patients were injected with the solvent. P2 was carried out 25 min later. Anginal threshold remained *unchanged* in both groups during P2. Despite the recurrence of angina during P2, appreciably less hypoxanthine and lactate were released in both groups.

	Placebo		Nifedipine	
Parameters studied	P1	P2	P1	P2
HR (beats/min)	144 ± 15	144 ± 17	149 ± 15	149 ± 16
LVP (mmHg)	137 ± 14	137 ± 11	142 ± 17	140 ± 17
Pk + dP/dt (mmHg/s)	2472 ± 516	2438 ± ± 432	2372 ± 570	2279 ± 508
Vmax (s^{-1})	70 ± 14	70 ± 14	68 ± 24	67 ± 2
CBF (ml/min)	189 ± 46	186 ± 54	198 ± 71	161 ± 46°
HX (nmol/min)	74·3 ± 33	26·0 ± 17	159·1 ± 39	36·8 ± 7*
LC (μmol/min)	23·4 ± 8	13·8 ± 8°	23·4 ± 8	0·9 ± 7*

(Mean ± s.d., *$P<0·01$ vs P1; °$P<0·05$ vs. P1).

line and noradrenaline plasma levels was observed after nifedipine. Stroke volume increased and the left ventricular filling pressure, which had increased after metoprolol alone, was reduced. These studies indicate that the stimulation of the sympathetic nervous system after nifedipine administration, can be blocked by beta-receptor antagonists. Although the intrinsic negative inotropic effect of the drug thereby may become more apparent after beta-blockade, the vasodilatory effect of nifedipine appears to predominate.

There is now considerable evidence from the literature (Stone *et al.*, 1980; Servi *et al.*, 1980) which shows that major coronary arteries can approximately double their luminal diameter from their most constricted to their most dilated state. When partial vasoconstriction takes place around an already pre-existing fixed, often eccentric, obstruction, critical reduction in flow may occur much earlier. In fact, when such increased vasomotor tone of the coronary vascular wall is invoked by a variety of stimuli, sudden reduction in flow may lead to irreversible ischaemia. This must be the current understanding of the mechanisms lying behind unstable angina and, often the next step, impending infarction (Figs. 8, 9).

Clinical experience has convinced all but perpetual sceptics of the spasm-relieving properties of nifedipine. Treating 127 patients with symptoms of myocardial ischaemia associated with electrocardiographic or angiographic evidence of coronary artery spasm (CAS), Antman *et al.* (1980) demonstrated complete control of anginal attacks in 63% of all patients and marked relief in 89%. They considered the drug highly effective for CAS. Similar positive results were obtained by other authors in CAS patients with a positive ergonovine maleate provocation test (Heupler and Proudfit, 1979; Goldberg *et al.*, 1979; Previtali *et al.*, 1980). Nifedipine also appears to prevent CAS induced by alpha-adrenergic stimulation such as by the cold pressor test (CP). It decreases the coronary vascular resistance enhanced by the CP-test in CAD patients with coronary artery disease (Goldberg *et al.*, 1979; Servi *et al.*, 1980). Coronary resistance usually increased during hand-grip isometric exercise also decreases after nifedipine (Servi *et al.*, 1980). With the xenon-133 clearance technique at rest, Engel *et al.* (1980) and Heeger, Katia and Aldor (1975) observed an increase in coronary blood flow after nifedipine. According to Lichtlen's group (Engel *et al.*, 1980), this increase is present in normal as well as in post-stenotic areas of coronary arteries. This increase in regional myocardial blood flow in post-stenotic areas was confirmed by Malacoff *et al.* (1982) although they observed a decrease in flow in regions with normal coronary arteries. During angina pectoris induced by atrial pacing, Engel *et al.* (1980) also observed a tendency towards an increase in blood flow in post-stenotic and a decrease in normal areas after nifedipine. Thus blood (re)distribution during atrial pacing appeared to become more homogeneous. As the xenon washout technique cannot differentiate between flow of subendocardial, medial or subepicardial layers and only measures transmural flow, there remains the possibility that flow after nifedipine is only increased in the non-ischaemic subepicardium, but the animal data from our laboratory shown earlier would argue against this.

The effects of nifedipine on coronary sinus blood flow have been investigated by other authors. Kohler (1975) observed in six patients with mitral stenosis, a

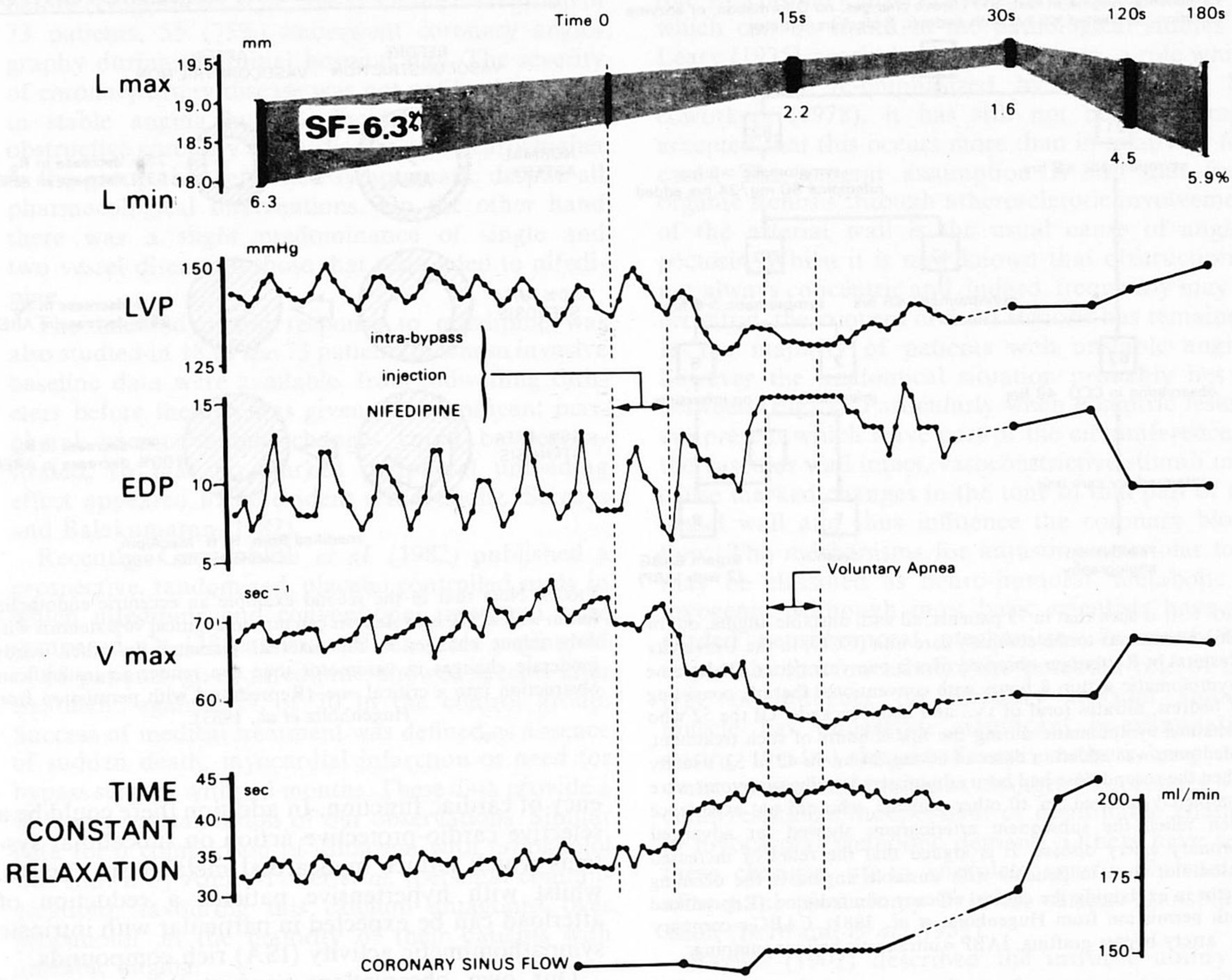

FIG. 7. Continuous plot of marker distance (L_{max}, L_{min}) with shortening fraction, left ventricular systolic and enddiastolic pressures (LVP and EDP), V_{max} and the relaxation time constant of the region perfused by an injection of nifedipine into a patent bypass graft. In this patient, coronary sinus flow was measured continuously. Shortly after intra-bypass injection of nifedipine, the shortening fraction (SF) decreased from 6·3 to 2·2% accompanied by a rapid rise in EDP and decreases in V_{max} and LVP. Simultaneously, coronary sinus flow increased from 150 to more than 200 ml/min. Note that the SF returns to control levels, followed by return of LVP and EDP to base-line, while coronary blood flow remains high.

rise in coronary sinus blood flow (CSBF) by 40% after fifteen minutes while a maximal increase of 70% was present after one half hour. Merillon *et al.* (1978) observed an increase in CSBF and a decrease in coronary vascular resistance (CVR) in 20 patients with coronary artery disease. Almost identical changes in CSBF (+16%) and CVR (−18%) were seen by Simonsen and Nitter-Hauge (1978) fifteen minutes after administration of nifedipine. Neither Merillon *et al.* (1978), Simonsen and Nitter-Hauge (1978) nor Schaefer *et al.* (1975) could, however, demonstrate a significant increase in flow during atrial pacing induced tachycardia. The last named authors suggested that coronary artery disease in their patients was too severe and that the vessels were already maximally dilated, preventing an additional effect of nifedipine. Such an explanation would also fit some of our clinical observations in unstable angina pectoris described in the next section. Experimental data from our laboratory confirm that low doses of intracoronary nifedipine while having no effect on myocardial global and regional function, will significantly lower the oxygen consumption of the myocardium (Verdouw *et al.*, 1982). It has lead to the hypothesis of a metabolic effect of the drug. Could nifedipine reduce the oxygen wasting

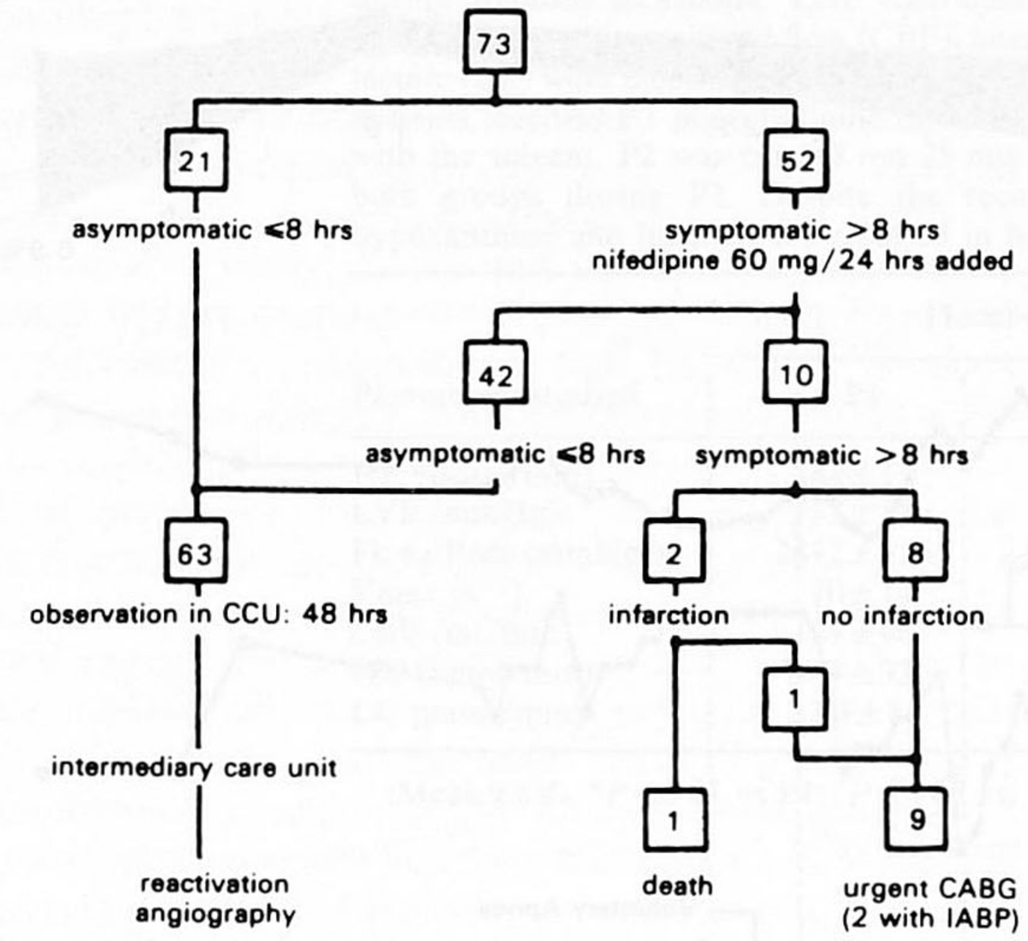

FIG. 8. It is seen that in 73 patients, all with unstable angina, out of 1263 admissions to the coronary care unit (CCU) in the University Hospital in Rotterdam observed over a one-year period, 21 became asymptomatic within 8 hours with conventional therapy consisting of bedrest, nitrates (oral or i.v.) and beta-blockade. Of the 52 who remained symptomatic during the first 8 hours of such treatment, nifedipine was added in doses of 60 mg/24 hr. In 42 of 52, usually when the second dose had been administered orally, symptoms were completely relieved. In 10 other patients, who did not experience such relief, the subsequent arteriograms showed far advanced coronary artery disease. It is argued that the relief of increased vasomotor tone in patients with unstable angina is the deciding factor in explaining the clinical efficacy of nifedipine. (Reproduced with permission from Hugenholtz *et al.*, 1981). CABG = coronary artery bypass grafting, IABP = intraaortic balloonpumping.

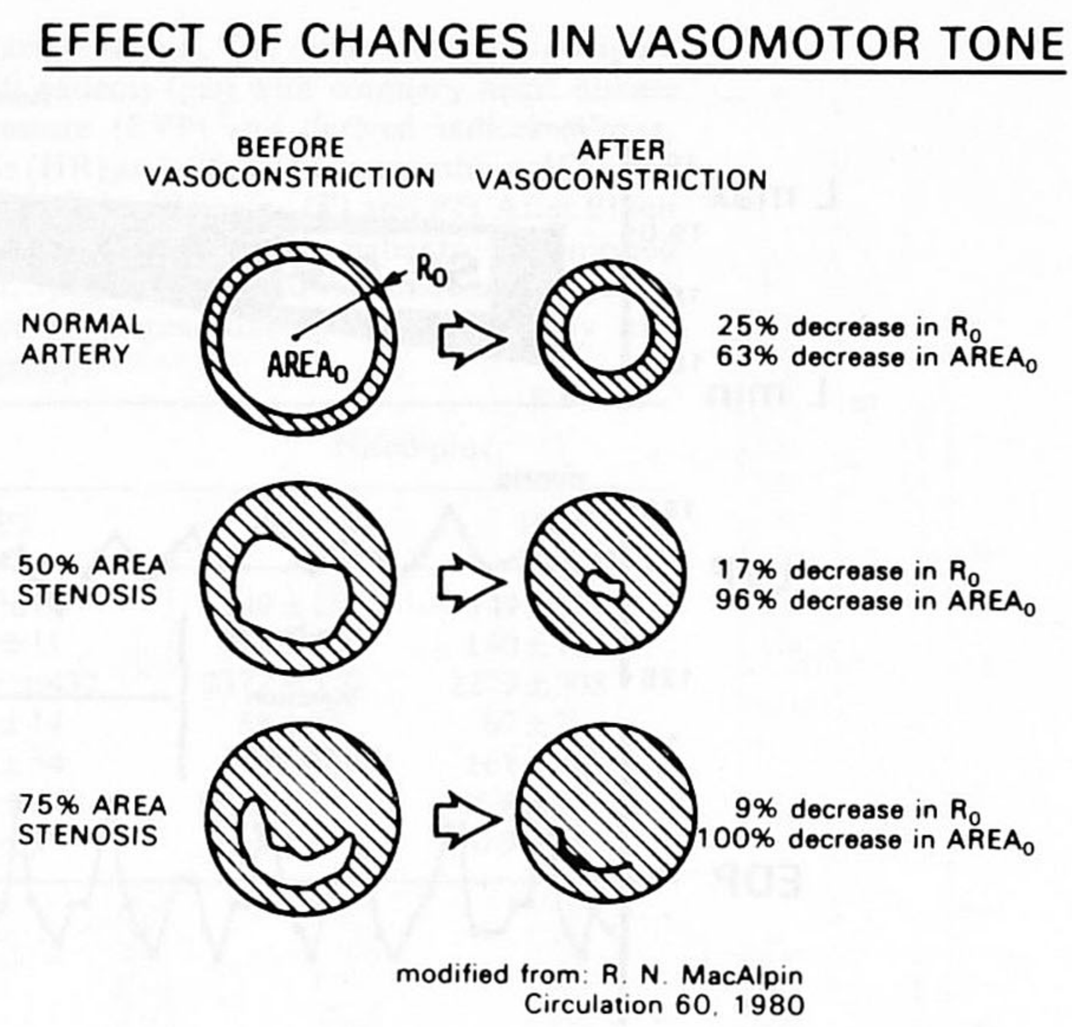

FIG. 9. Note that in the second example an eccentric endothelial lesion with a 50% area stenosis can turn to a critical 96% stenosis with only minor changes in the external diameter. In other words, moderate changes in vasomotor tone can render an insignificant obstruction into a critical one. (Reproduced with permission from Hugenholtz *et al.*, 1983).

effect of free fatty acids by blocking intramyocardial lipolysis without affecting the overall dynamic state?

Angina and ischaemia

At first sight, the differing (Serruys, Vanhalewei and Hugenholtz, in press), and perhaps complementary, actions of calcium-antagonists and betablockers would make it seem advisable to combine both in the clinical treatment of unstable angina and other acute ischaemic states of the myocardium. This part of the presentation deals with the evidence that is in favour of such concerted action while in addition available reports on unwanted effects with this combination of drugs will be reviewed.

The possible clinical beneficial actions of beta-blockers in coronary artery disease can be summarized as follows: they may reduce or improve the ischaemic state by a reduction of cardiac work, mainly through bradycardia and by suppression of ventricular arrhythmias which improves the efficiency of cardiac function. In addition there could be a selective cardio-protective action on subcellular systems which reduce myocardial metabolism further, whilst with hypertensive patients a reduction of afterload can be expected in particular with intrinsic sympathomimetic activity (ISA) rich compounds.

Our own observations support this concept of concerted action. During a one year period, out of 1263 admissions to our coronary care unit, 73 patients were identified with unstable angina (Hugenholtz *et al.*, 1981) (Fig. 8). Each of these individuals had persistent pain during bedrest, coincident with intermittent changes in the electrocardiogram with elevation or depression of the ST-segment and changes in the T-waves without any evidence of myocardial necrosis such as the development of Q-waves or an elevation of the various cardiac enzymes. Of these 73, 21 became asymptomatic within 8 hours on beta-blockers with nitrates alone. In the 52 remaining patients, nifedipine in a dose of 60 mg, in divided doses of 10 mg, was added to the treatment. Forty-two out of the 52 then became asymptomatic, usually after the second dose. Ten patients remained symptomatic, 9 of whom required urgent bypass grafting. Two patients with persistent pain received intra-aortic balloon pumping with immediate relief of their symptoms.

The extent of coronary artery obstructive disease as seen at cardiac catheterization has been detailed

before (Hugenholtz *et al.*, 1981). Of the total group of 73 patients, 55 (75%) underwent coronary angiography during the initial hospital stay. The severity of coronary artery disease was not unlike that found in stable angina but the incidence of advanced obstructive coronary artery disease was clearly higher in the group that remained symptomatic despite all pharmacological interventions. On the other hand there was a slight predominance of single and two vessel disease in those that responded to nifedipine.

The haemodynamic response to nifedipine was also studied in 18 of the 73 patients in whom invasive baseline data were available, from indwelling catheters before therapy was given. No significant peripheral haemodynamic changes could be demonstrated, so that no marked peripheral unloading effect appeared to be evident (Hugenholtz, Serruys and Balakumaran, 1982).

Recently, Gerstenblith *et al.* (1982) published a prospective, randomized, placebo controlled study in which nifedipine and conventional treatment were compared. Of 138 patients with unstable angina, 38 of 68 patients, given nifedipine, showed success after treatment against 27 of 70 in the control group. Success of medical treatment was defined as absence of sudden death, myocardial infarction or need for bypass surgery within 4 months. These data provide a welcome substantiation of our observations. Similar data for a comparison of diltiazem with propanolol was shown by Andre-Fouet *et al.* (personal communication), favouring this calcium antagonist over propanolol, in the majority of their patients with unstable angina.

It is also evident from other published reports that the interactions between beta-blockade on the one hand and calcium inhibition on the other hand can be highly supportive of each other when the cardiac cell is threatened by ischaemia. In stable exertional angina pectoris, Broustet and coworkers (1980) have shown that when nifedipine is used in conjunction with atenolol, the suppression of symptoms induced during exercise testing may be maximal. Schmutzler (1981) has shown similar data for the combination of metoprolol and nifedipine. These observations are, however, in stable angina pectoris and there the explanation for the increased efficacy of the combination is readily at hand: reduction in heart-rate together with decreased afterload seem to be the main factors responsible for increased exercise tolerance, decreased incidence of angina pectoris attacks and diminished nitroglycerin usage.

In unstable angina pectoris, however, there is relatively little information in the literature regarding mechanisms of action. This is readily explicable because of the uncertainties surrounding the causes of unstable angina pectoris. Despite emphasis on the role of coronary artery spasm, a good example of which can be found in the pathological studies of Leary (1935) nearly half a century ago, a role which was recently re-emphasized by Maseri and his coworkers (1978), it has still not been generally accepted that this occurs more than in relatively few cases. The general assumption is still that fixed organic stenosis through atherosclerotic involvement of the arterial wall is the usual cause of angina pectoris. Whilst it is now known that obstruction is not always concentric and, indeed, frequently may be eccentric, the concept of fixed stenosis has remained. In the majority of patients with unstable angina however the anatomical situation probably lies in between (Fig. 9). Particularly when eccentric lesions are present which leave part of the circumference of the vascular wall intact, vasoconstrictive stimuli may cause marked changes in the tone of that part of the vessel wall and thus influence the coronary blood flow. The mechanisms for adjusting arteriolar tone may be classified as neuro-humoral, metabolic or myogenic. Although most basic scientists have regarded neurohumoral mechanisms as much less important than metabolic, the potential role of this type of influence on coronary vascular smooth muscle has undergone significant re-examination during the last decade. Several authors have now demonstrated spontaneous changes in coronary vascular resistance independent of identifiable changes in myocardial metabolic demand. Others have seen these changes, up to complete spastic obstruction after total plexectomy or even cardiac transplantation (Bertrand *et al.*, 1981).

Bayliss (1902) 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. Berne and coworkers (1980) have tested different vasoactive agents such as adenosine, nitroglycerin and calcium antagonists for their ability to affect the induced action potential of isolated large and small coronary arteries. 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. Indeed nifedipine is capable of blocking completely the autoregulation of the renal vascular bed, whereas glyceryl trinitrate fails to affect this regional autoregulation. 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 the changes in perfusion pressure, these experimental data emphasize the advantages of nifedipine over nitrates in affecting the coronary vascular system. In the syndrome of unstable angina with the combination of an eccentric fixed endothelial lesion and a (hyper)sensitive, but otherwise healthy vascular wall opposite, the influence of nifedipine is such that it promptly relaxes the excessive vascular tone. In keeping with this concept are the observations of the rapid and persistent relief of pain in the majority of patients with unstable angina pectoris reported in this study (Hugenholtz *et al.,* 1981), and the striking results in Prinzmetal's angina (Antman *et al.,* 1980). The specific action of nifedipine on the arteriolar tone of the major epicardial and the smaller coronary arteries over the 48 hour observation period, stabilized what had been a very brittle condition. The fact that in 42 of the 52 such relief persisted for the entire period of observation is a further strong argument in favour of this mechanism.

The hypothesis has also been put forward that there is a subset of patients with inappropriate vasoconstriction or suspected coronary artery spasm, who may worsen with beta-adrenergic blockade. In fact, Yasue *et al.* (1976) have specifically argued against beta-blockers in these individuals, as they showed that beta-blockade may induce vasoconstriction. Since in our series of patients who had remained unresponsive during 8 hours of beta-blockade, the response to nifedipine was so consistent (and just as effective as had been pain relief by intra-aortic balloon pumping in our previous experience (Michels *et al.,* 1980) with the same kind of patients, there is little doubt that nifedipine in these unstable angina patients was the sole agent which tipped and kept the balance in their favour. Recently Braunwald (1980) has reviewed current clinical evidence and stated that there now might very well be a preference for the use of calcium antagonists over beta-blocker in patients suspected of having abnormally increased coronary vasomotor tone.

Such an opinion is supported by several reports in the literature (Hugenholtz, Serruys and Simons, in press; Fleckenstein *et al.,* 1979; Robertson *et al.,* 1982; Yasue *et al.,* 1979; Robertson *et al.,* 1979) which indicate that angina pectoris occurring in Prinzmetal's syndrome may be worsened by treatment with beta-blockers, and in particular with propranolol. The first observation by Yasue and co-workers appeared in 1976, after having postulated earlier that in the Prinzmetal's syndrome beta-blockade could potentially lead to further vasoconstriction and thus worsen symptoms. In a recent report (Yasue *et al.,* 1979) they observed 4 patients in whom periodic attacks during rest were relieved by nitroglycerin but made more severe by propranolol. In fact the combination of propranolol and isoproterenol infusion induced "Prinzmetal" attacks very similar to spontaneous attacks, while infusion of isoproterenol alone did not do so. Coronary arteriography at the time showed severe spasm of the coronary arteries. These observations are similar to those described by Fleckenstein *et al.* (1979) on an isolated vascular system. In these experiments, Fleckenstein proved conclusively that the addition of beta-blockade caused severe vasoconstriction of the coronary arteriolar wall, which could be relieved however by calcium antagonists.

Yasue *et al.* (1979) in their later study analyzed the circadian variation of exercise capacity in patients with Prinzmetal's syndrome. They found that propranolol was ineffective in suppressing the attacks and actually aggravated them in 8 out of 13 patients so studied. ST-segment elevation with attacks following exercise were repeatedly induced in all patients in the early morning, but only in 2 out of 13 in the afternoon. Since it is now known that the calcium-ion level varies in the human reaching its maximum early in the morning it can readily be understood why in their studies diltiazem suppressed the morning attacks completely in 11 out of 13 patients and partially in the remaining 2, whereas beta-blockers failed to do so. They also observed a circadian variation in the tone of the large coronary arteries. Robertson *et al.* (1982) observed 1045 spontaneous episodes of ST-segment elevation over a total of 72 days of continuous monitoring. Controlled trials with propranolol showed no beneficial effect but a significant increase in the length of episodes of ST-segment elevation in one patient with increased ventricular irritability. Fuller *et al.* (1980) recently studied with thallium-201 scintigraphy the responses to nitrates, beta-adrenergic blockade, calcium flux blockade and prostaglandin inhibition. The pain episodes could be prevented by oral nitrates but not totally eliminated by the other drugs. In addition beta-adrenergic blockade appeared to be detrimental. A 69-year-old man treated by Carile and Civerra (1980) with pindolol, had his attacks of angina worsen with further ECG signs of anterior ischaemia. Replacement by nifedipine led to total relief. This was also the conclusion of Marx (1980) in his overview of the subject. He concluded: "in spasm-induced angina, propranolol may exacerbate symptoms while calcium antagonists of various kinds would appear to be the drug of choice". This concept of dynamic coronary obstruction in the presence of "normal" or diseased coronary arteries implies a direct role for coronary vasodilators in patients with any form of angina pectoris, even when frank coronary spasm is absent. Also implicit in the hypothesis is the concept that dynamic and fixed components to obstruction (Fig. 10) may contribute variably to the degree of obstruction in different

patients, and it should not be surprising that in patients with largely fixed obstructions benefit will mainly come from attempts to lower MVO_2 with nitrate and beta-blocking agents. In extreme cases only the balloon catheter dilation of the coronary artery or bypass surgery can provide adequate relief.

Side effects and dosages

Clinical experience with pharmacological agents in general has taught us, however, that no drug is "perfect" or without unwanted actions. While major side effects have rarely been reported thus far with nifedipine (Anastassiades, 1980; Motte *et al.*, 1980; Brooks *et al.*, 1980; Opie and White, 1980; Robson and Vishwanath, 1982), this and other agents in the group of calcium antagonists such as verapamil may result in severe hypotension. In the latter, presumably this is due to its strong influence on A-V conduction, and in the former because of its primary negative inotropic action on cardiac contractile behaviour. One can readily visualize situations, for example in acute myocardial infarction with an attendant hypotensive state, in which the negative inotropic characteristics of these drugs override their other actions. Details of these untoward side effects can be found in the quoted references. By and large, they are few however, and readily reversible upon interrupting the drug and also predictable as they exclusively seem to occur at endstages of cardiac disease. The daily dosage of nifedipine ranges from 30 to 120 mg, with 6×10 mg daily the average. The drug is usually given orally but an intravenous solution is available. As the drug is rapidly and fully absorbed, oral dosing is usually sufficient. Verapamil is given in the same manner in dosages between 240 and 360 mg per day, while diltiazem is effective at dosages between 180 and 360 mg. As the biological half life ranges between 3 and 7 hours, divided doses 4–6 times a day usually suffice. Unavoidable side effects relate to their mode of action: headache, flushing and gastrointestinal symptoms are dose related, usually are minor and are rarely a contraindication. Particular caution should be given to the use of verapamil in hypotensive states or in situations where the negative inotropic action is unwanted i.e. in congestive heart failure and when beta-blockade is also given. With nifedipine hypotensive episodes have also been described but they are rare, given the hundreds of patient years of treatment.

Practical and personal recommendations

The first decision the physician therefore has to make is to which of the 3 conditions, stable angina pectoris, unstable angina pectoris or Prinzmetal's syndrome exists. Efforts at diagnosis should first of all exhaust a detailed history, which if inconclusive should in ambulatory males lead to an exercise test. Various aspects of the haemodynamic and electrocardiographic response to exercise should be evaluated. Only if a suspicion of angina pectoris persists in the face of a negative exercise electrocardiogram should a thallium-201 exercise test be carried out. If positive and with stable angina, we would recommend a therapeutic trial either with nitroglycerin, nifedipine or beta-blockade. The choice of the initial agent depends on the frequency and variety of the attacks, the preliminary diagnosis of the cause of angina pectoris and ancillary signs and symptoms. For example in a hypertensive patient with tachycardia, we would prefer to begin with a combination of beta-blockade and nifedipine rather than with nitroglycerin tablets. Contrariwise in an elderly patient with infrequent attacks, nitroglycerin tablets sublingually might be sufficient. At any rate, an individual assessment of that patient's cause for angina pectoris and his response to that therapy should be the basis for initial management. If a response is not adequate, rather than persist we would change the drug, since it could well be that the pathophysiology is different then suspected. Consider the schemes illustrated in Figs. 10 and 11.

When unstable angina including the Prinzmetal type is suspected, it is our current view that nifedipine (or diltiazem) should be given at the outset with the usual supportive therapy. Certainly when ischaemic conditions are repeatedly evident, this would be the first line of attack. When not so sure the initial pharmacological therapy should be with nitroglycerin tablets and isosorbide dinitrate, adequate beta-blockade with an effective agent such as propranolol, acebutalol or metoprolol, with which we have most experience, in combination with nifedipine. Only when this is not successful (obviously assuming appropriate doses), coronary artery bypass grafting must be considered. In a small subset of patients percutaneous transluminal coronary artery dilatation can be considered. For the long term out of hospital phase, particular emphasis should be given to the combination therapy: our current experience indicates that a combination of relatively small doses of nifedipine (20 to 30 mg per day) with an effective beta-blocker leads to marked symptom relief in most of the patients and a considerable reduction in the incidental use of nitroglycerin sublingually. This would seem the more advisable as many patients with angina pectoris have coexistent hypertension. The ultimate decision of the relative roles of beta-blockade and calcium antagonists will have to await the results of further large randomized, double blind and placebo controlled studies, one of which is currently in progress in The Netherlands (Interuniv-

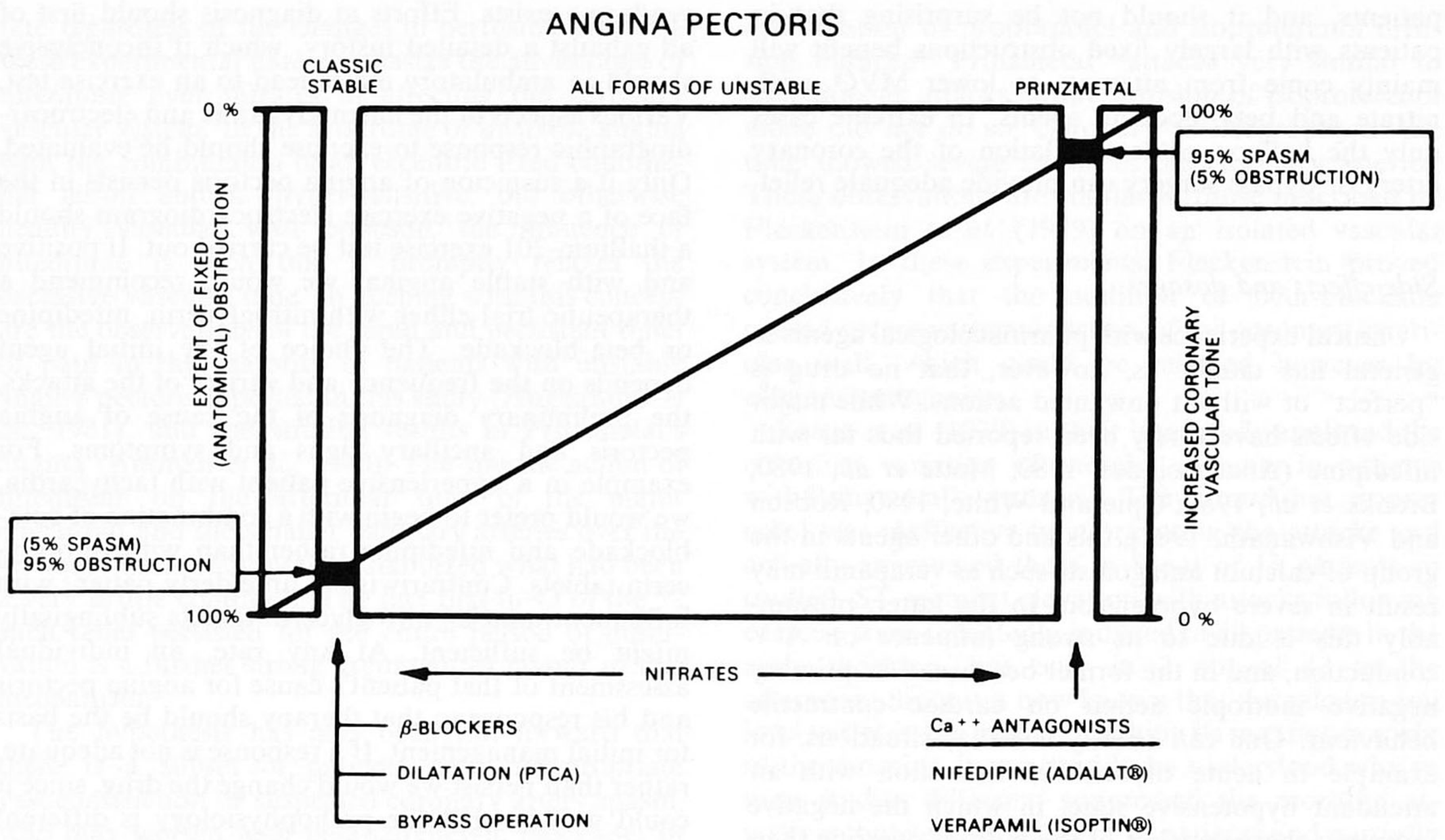

FIG. 10. The therapeutic approach to the various forms of angina pectoris depends on the clinician's awareness of the underlying pathophysiology. If "fixed" stenosis is suspected, the first choice of therapy will be quite different from when spasm is the most likely cause of symptoms. Most cases will lie in between and therefore require, as always in clinical circumstances, individual assessment of the situation in order to achieve optimal choice of therapy. PTCA = percutaneous transluminal coronary angioplasty.

ersity Cardiological Institute),* while other trials are certain to come in various acute ischaemic conditions such as those during open-heart surgery (Clark *et al.*, 1979).

Conclusions

Three main causes have been implicated in the development of angina pectoris.

The first is fixed stenosis, a permanent narrowing of the coronary arteries, with pain occurring only on exertion. This condition is called chronic stable angina, which is usually predictable and reverses when exertion is stopped.

The second cause, which has been the focus of much recent interest, is spasm in which dynamic changes in vessel diameter cause transient arterial obstruction. Here the manifestations may be non-exertional pain or even silent ischaemic episodes evidenced by ST-T-segment changes and arrhythmias. In its extreme form, the manifestations correspond to Prinzmetal's (variant) angina, which can occur even when there is no fixed coronary artery obstruction.

*(Study design available on request).

Thirdly, excessive platelet aggregation can lead to partial, and occasionally total, coronary vessel blockage and myocardial infarction, often coincident with excessive thromboxane A_2 release and spasm. All of these causes may interact to produce unstable angina—the main focus of this chapter.

In the particular case of patients with unstable angina, two outcomes can result from myocardial ischaemia. The ischaemia either resolves spontaneously, ending the attack, or a multiplier mechanism comes into play, widening the gap between demand and supply, exacerbating the ischaemia, and increasing myocardial oxygen requirements. If oxygen reserves are available, the ischaemic episode may end; if there are no oxygen reserves, ischaemia increases and may ultimately cause arrhythmias, mechanical dysfunction and myocardial infarction.

The concept that a transient dynamic obstruction caused by changes in coronary artery tone may lead to ischaemia is therefore an important consideration not only in Prinzmetal's angina, for which it was originally postulated, but also for unstable angina, —and probably even for many cases of chronic stable angina.

In unstable angina pectoris a specific management is proposed: bedrest and aggressive medical therapy

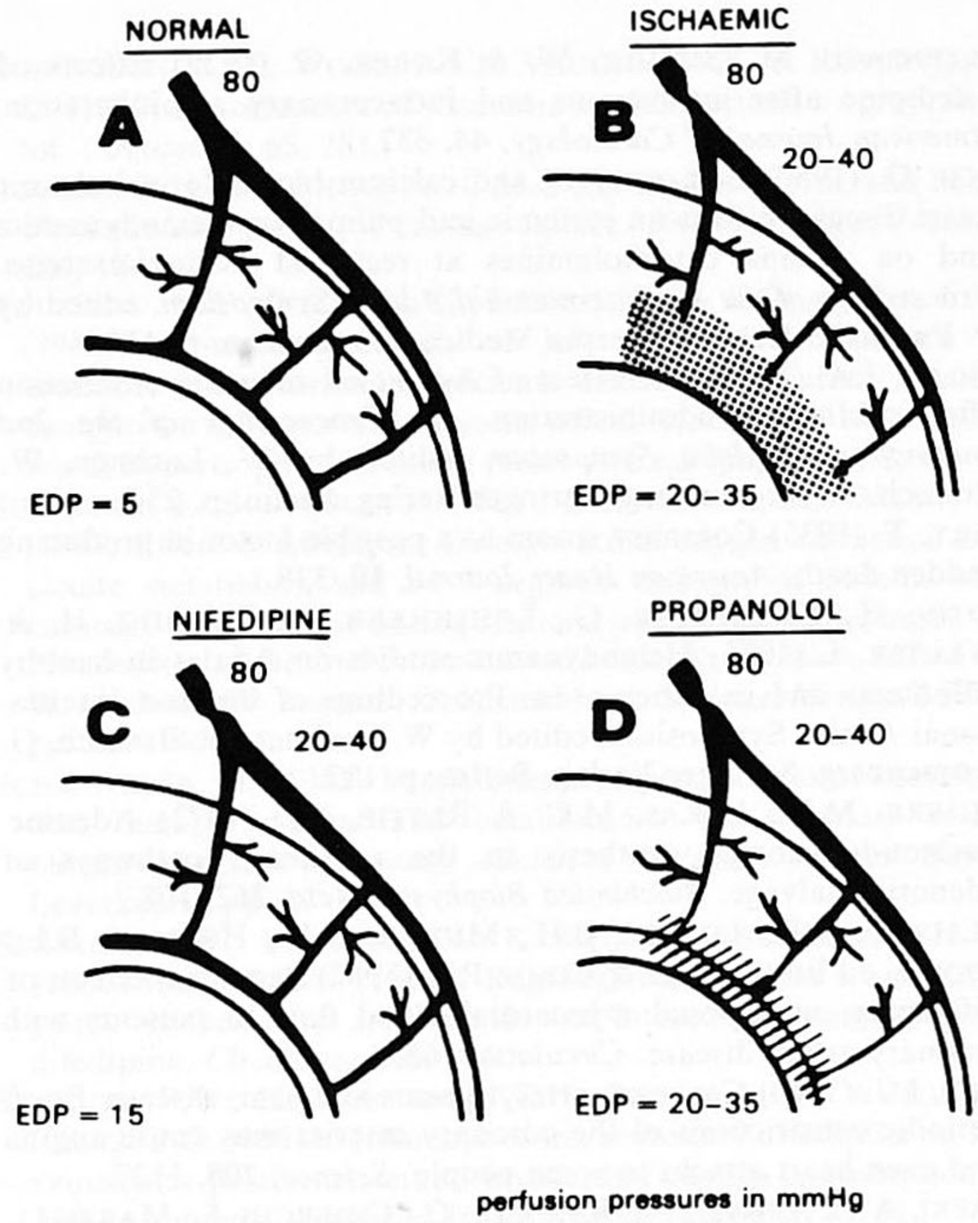

FIG. 11. Schematic drawing of haemodynamic conditions in the normal coronary vascular tree (A). During ischaemia (B) perfusion pressure distal to the obstruction drops to 20 mmHg. When intraventricular diastolic pressure rises it can readily be understood why the subendocardial layers are not perfused adequately. During nifedipine treatment (C) coronary vascular tone is relaxed and perfusion via the penetrating arteries and the capillary bed is enhanced. As afterload is reduced end diastolic pressures will be lowered which results in still better perfusion of the subendocardial layers. When propranolol is given (D) there is no direct effect on coronary vascular tree and diastolic pressures remain high, so that there is no major reduction in subendocardial ischaemia.
EDP = end diastolic pressure.

(including sedatives, nifedipine, propranolol or metoprolol and long-acting nitrates) must constitute the initial approach, when pain and transient ECG changes at rest indicate the threat to an infarction. When symptoms persist despite this approach, intravenous nitroglycerin or isosorbide dinitrate may offer benefit in the short term, while nifedipine must early be brought to maximal dosages, especially when variant forms of angina with spasm are suspected. The intra-aortic balloon pump should be instituted only when symptoms worsen despite optimal pharmacological therapy. Candidates for early revascularization are those not responding to 48 hours of maximal medical therapy. Early catheterization, preferably during the initial hospitalization, is recommended for all patients and often leads to elective revascularization. Revascularization is obligatory in patients with significant left main coronary artery obstructions and patients with proximal narrowing of the left anterior descending coronary artery, who have not yet sustained a massive anterior myocardial infarction. The extent of coronary artery disease determines the later recurrence of symptoms and the subsequent need for surgery in patients who initially could be managed by medical means alone. Aggressive medical therapy may save these patients, and despite the hazards of emergency procedures and the burden to clinical and nursing staff, they have reduced mortality to a few percent.

In patients without extensive coronary artery disease of left main stem, or proximal left anterior descending coronary artery, who remain symptomatic after discharge, elective surgery does not seem to have an advantage over medical therapy. Surgical risk may exceed that of medical management alone. If these patients remain asymptomatic during careful follow-up and do not reveal a seriously diminished physical capacity with early pain and ischaemic electrocardiographic changes or decrease in arterial pressure during exercise testing, bypass grafting does not appear mandatory.

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Discussion

DR. J. RAJ (*North Birmingham*): There have been in the past theoretical reasons not to use a combination of a beta blocker and a calcium channel antagonist.

PROFESSOR HUGENHOLTZ: About 1977, we began to feel our way around the role of nifedipine and verapamil, and we found that their effect combined with a beta blocker in the unstable angina group was seemingly beneficial. We are doing a randomised trial and hope to establish which of the compounds or combination is most beneficial. In stable angina there is a lot of data in the literature suggesting combination in lower dosage can achieve a greater effect.