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The Haemodynamic Effects of Nifedipine, Verapamil and Diltiazem in Patients with Coronary Artery Disease
A Review

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Summary

Of the 3 most widely used calcium antagonists – nifedipine, verapamil and diltiazem – nifedipine is the most potent arterial vasodilator. Increases in cardiac output and coronary blood flow following nifedipine administration result in part from the afterload reduction. Reflex adrenergic stimulation produces an increase in heart rate and masks a direct inhibitory effect on myocardial contractility. The negative inotropic action of nifedipine is observed during intracoronary administration or may be made apparent by concurrent β-blocker therapy.

While verapamil is also a potent vasodilator, negative inotropic and dromotropic properties are more apparent in therapeutically used dosages. Reflex sympathetic activation is also triggered by verapamil, with an offsetting of the negative inotropic effects such that little change in cardiac output results. A decrease in myocardial oxygen consumption, with or without a decrease in coronary sinus blood flow, has regularly been observed following verapamil administration. Reduced oxygen demand appears to be a major mechanism of its antianginal effect. The heart rate × systolic pressure product is decreased both by the fall in arterial pressure and, particularly after oral administration, by a decrease in heart rate.

Diltiazem produces similar haemodynamic and electrophysiological effects to those of verapamil but has less potency in inducing arterial dilatation and more of a tendency to slow the heart rate. Diltiazem does not appear to cause significant increases in coronary blood flow or bring about improvement in ejectional and isovolumic indices of myocardial contraction – evidence of its intrinsic negative inotropic effect.

Since their introduction in Japan and Europe in the early 1970s, the calcium antagonists have proved useful in treating various cardiac disorders. They form an incongruous group of compounds sharing a common mechanism of action not utilised by previously available drugs and have been the subjects of much clinical research. The aim of this article is to provide a haemodynamic profile of the three most commonly used agents: nifedipine, verapamil and diltiazem. The overview is subdivided into sections dealing with the haemodynamic effects of the 3 drugs after intracoronary, intravenous and oral or sublingual administration. Attention is given to similarities and differences, some of the contraindications to the use of these drugs, and some of the areas in which our know-

ledge is lacking. The haemodynamic interactions which occur when they are combined with β-adrenoceptor blocking agents are also reviewed.

Where possible, haemodynamic effects in normal individuals are discussed as well as those in patients with atherosclerotic coronary artery disease.

1. Nifedipine

1.1 Clinical Pharmacology

Studies of the pharmacokinetics and plasma concentration-effect relationships of nifedipine have been hampered by early difficulties in the development of sensitive and specific assay techniques. Hamann and McAllister (1983) found a linear relationship between plasma concentrations and haemodynamic effects with intravenous nifedipine administration in dogs. In hypertensive patients, Taburet et al. (1983), using a tablet preparation, found a significant correlation between plasma concentrations of nifedipine and decreases in supine mean arterial pressure over a wide range of drug plasma concentrations from 10 to 250 μg/L. Although Aoki et al. (1982) found a similar correlation, Pederson et al. (1980a), using a capsule preparation, found none. Some of these differences may have occurred because of variations in assay methods or the nifedipine formulation used. The most commonly used formulation in clinical practice is the capsule. Peak plasma drug concentrations occur about 30 minutes after oral administration (McAllister et al. 1985). Wide variability in the calculated bioavailability with this route has been reported (Foster et al. 1983), with 4 of 12 normal study subjects having a pharmacokinetic profile suggesting delayed drug absorption: peak plasma concentrations were found 4 hours after nifedipine administration, reaching only about 25% of the peaks found in the other subjects. Clinical studies have found a highly variable dose-response relationship between patients with regard to subjective and objective improvement in anginal complaints, which suggest that careful individual titration of nifedipine dosage is needed (Deanfield et al. 1983).

The usual oral dose of nifedipine is 10 to 40mg every 6 to 8 hours, although doses up to 160 mg/day have been used safely. Unlike verapamil, and to a lesser extent, diltiazem, nifedipine exerts little or no effect on cardiac conduction and is not useful in the treatment of supraventricular tachyarrhythmias. Adverse effects, including headache, dizziness, flushing, peripheral oedema and paresthesias occur in up to 40% of patients but are sufficiently severe to require its discontinuation in only about 5% (Antman et al. 1980).

1.2 Haemodynamic Effects after Intracoronary Administration

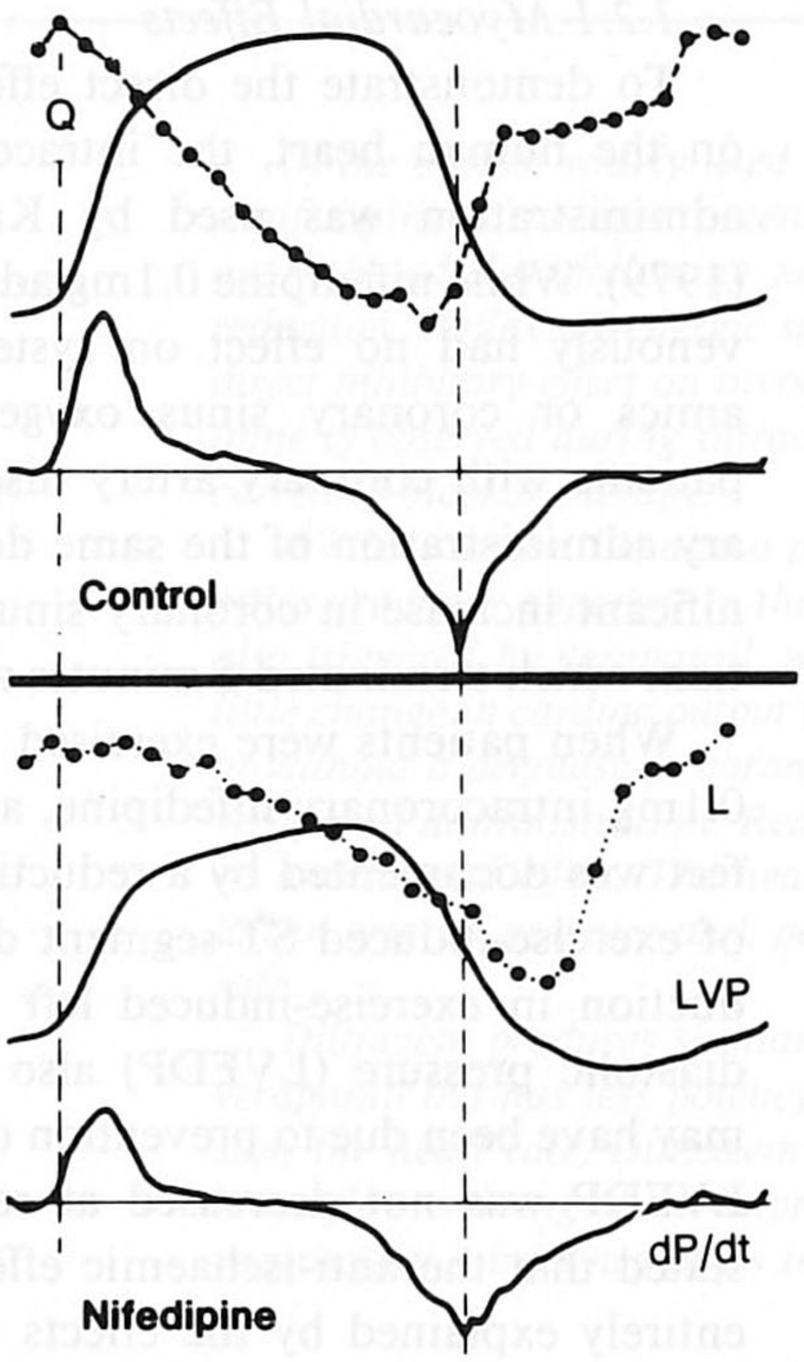
1.2.1 Myocardial Effects

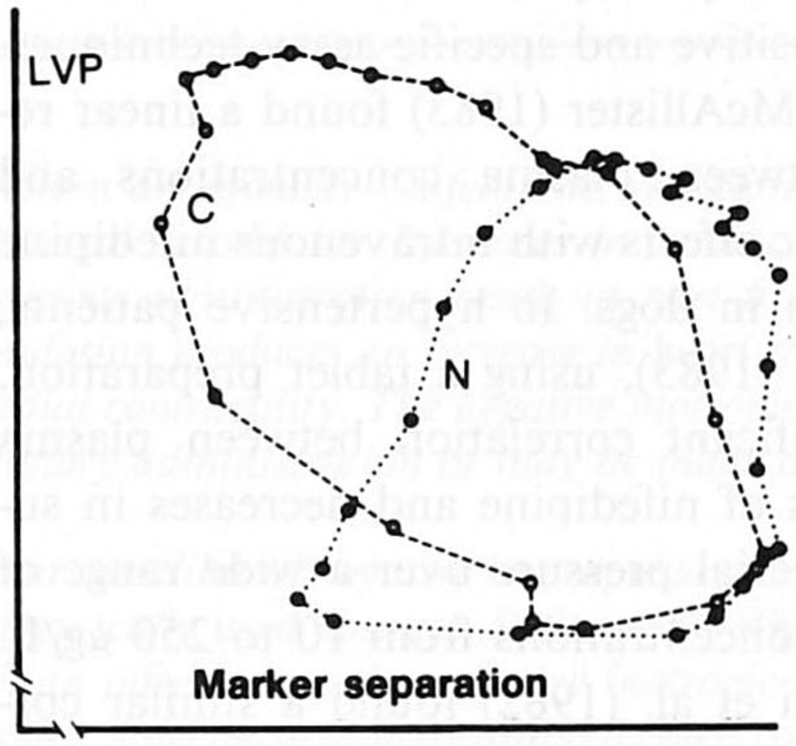
To demonstrate the direct effect of nifedipine on the human heart, the intracoronary route of administration was used by Kaltenbach et al. (1979). While nifedipine 0.1mg administered intravenously had no effect on systemic haemodynamics or coronary sinus oxygen saturation in patients with coronary artery disease, intracoronary administration of the same dose caused a significant increase in coronary sinus oxygen saturation, which terminated 5 minutes after the infusion.

When patients were exercised 15 minutes after 0.1mg intracoronary nifedipine, an antianginal effect was documented by a reduction in the degree of exercise-induced ST-segment depression. A reduction in exercise-induced left ventricular end-diastolic pressure (LVEDP) also occurred which may have been due to prevention of ischaemia, and LVEDP was not decreased at rest. The authors stated that the anti-ischaemic effect could not be entirely explained by the effects on the coronary arteriolar resistance because it persisted after coronary flow had returned to normal. An effect of the drug on cardiac metabolism and/or contractility was considered as an alternative explanation.

Further insight into the action of intracoronary nifedipine was obtained when the drug was administered directly into coronary artery bypass grafts during cardiac catheterisation (Serruys et al. 1981b). By measuring the distances between metal markers which had been sutured onto the epicar-

dium during surgery in regions directly supplied by the grafts, epicardial wall motion was shown to be decreased and delayed following nifedipine (fig. 1). Simultaneously measured pressure-derived variables demonstrated a direct negative inotropic effect after an intra-bypass injection of 0.1mg nifedipine with a decrease in left ventricular pressure, a decrease of the maximum velocity of muscle contraction (V_{max}) and maximum left ventricular instantaneous rate of rise in pressure (dP/dt), and an increase in LVEDP (figs 1 and 2). No changes in wall motion were seen in the areas perfused by vessels which did not receive nifedipine. Asynchrony was induced by nifedipine and was considered responsible for the slowed isovolumic contraction. Relaxation of the whole ventricle was also impaired as evidenced by a prolonged time constant of relaxation and a diminished peak negative dP/dt. All these changes in LV wall motion lasted less than 5 minutes.





	C	N
LVP (mm Hg)	196	161
EDP (mm Hg)	26	33
V_{max} (sec^{-1})	58	41
TCR (sec)	38	59.5
L_{max} (mm)	24.6	24.8
L_{min} (mm)	20.1	21.1
SF (%)	18.7	14.9
SR (sec^{-1})	1.33	0.93

Fig. 1. Regional shortening in relation to left ventricular pressure in the control situation and after intra-bypass injection of 0.2mg nifedipine is shown as simultaneously recorded (left panel) and the pressure-marker separation loop (right panel). It is apparent that the point of minimal marker separation after intracoronary nifedipine occurs clearly (60 msec) after aortic closure (L_{min} occurs at a pressure of 22mm Hg). Thus, while left ventricular pressure is falling, regional contraction continues and regional dys-synergy is observed. *Abbreviations:* EDP = end-diastolic pressure; LVP = peak left ventricular pressure; V_{max} = extrapolated maximum velocity of shortening of the contractile element; TCR = time constant of relaxation; L_{max}: maximum marker separation; L_{min} = minimal marker separation; L = marker separation. Shortening fraction (SF) and shortening rate (SR) are calculated as follows (Ts is the time interval between L_{max} and L_{min}): $SF = [(L_{max} - L_{min}) \times 100]/L_{max}$ and $SR = (L_{max} - L_{min}) / (L_{max} \times Ts)$ [from Serruys et al. 1980b; with permission].

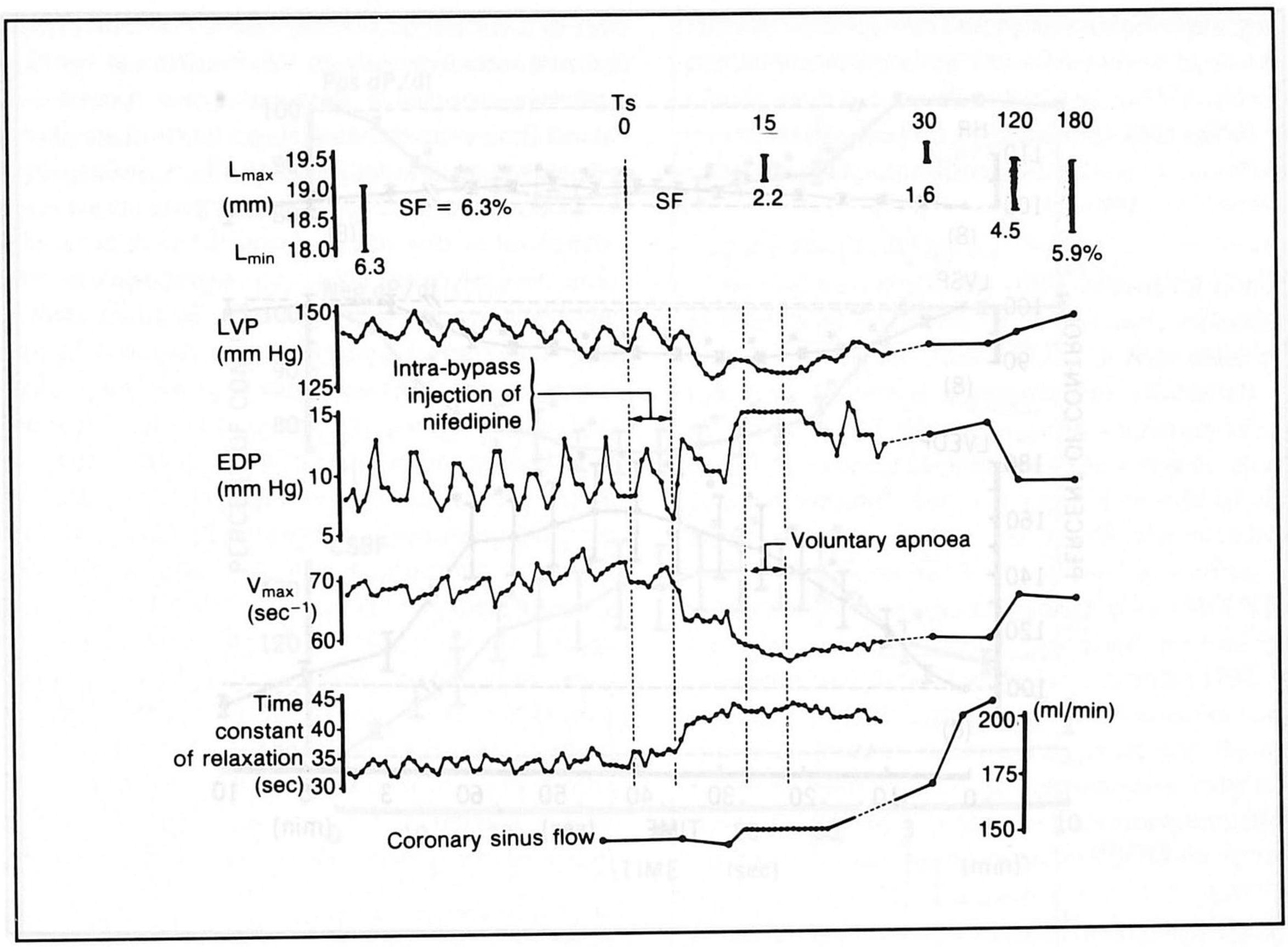


Fig. 2. The beat-to-beat analysis of myocardial function following a single intra-bypass injection of nifedipine. See legend to figure 1 for abbreviations (from Serruys et al. 1980b; with permission).

This transient negative inotropic effect was again demonstrated by the same authors in another group of patients after injection of 0.2mg nifedipine into the left main coronary artery (Serruys et al. 1983a). Frame-by-frame analysis of the regional wall motion from left ventricular angiograms again showed that intracoronary nifedipine delayed, prolonged and depressed anterior wall motion. An impaired left ventricular relaxation pattern after intracoronary injection of 0.1mg nifedipine was also demonstrated by another group of researchers in patients with coronary disease and in normal subjects (Rousseau et al. 1980).

The infusion of 0.1mg nifedipine into saphenous vein bypass grafts supplying the left ventricle wall and septum was also observed to depress both left ventricular systolic and diastolic function (Amende et al. 1983). Coronary sinus blood flow was augmented and remained increased long after the changes in left ventricular contraction and relaxation had subsided. It was concluded that these temporal differences were consistent with animal studies which had shown a differential depressant effect of nifedipine on calcium uptake in smooth muscle and cardiac muscle (figs 3 and 4).

1.2.2 Coronary Vascular Effects

In addition, several authors have shown a powerful spasmolytic and vasodilating effect of intracoronary nifedipine (Bertrand et al. 1980, 1981; Hugenholtz et al. 1981; Serruys et al. 1983b). This effect is seen in normal, stenotic, and post-stenotic

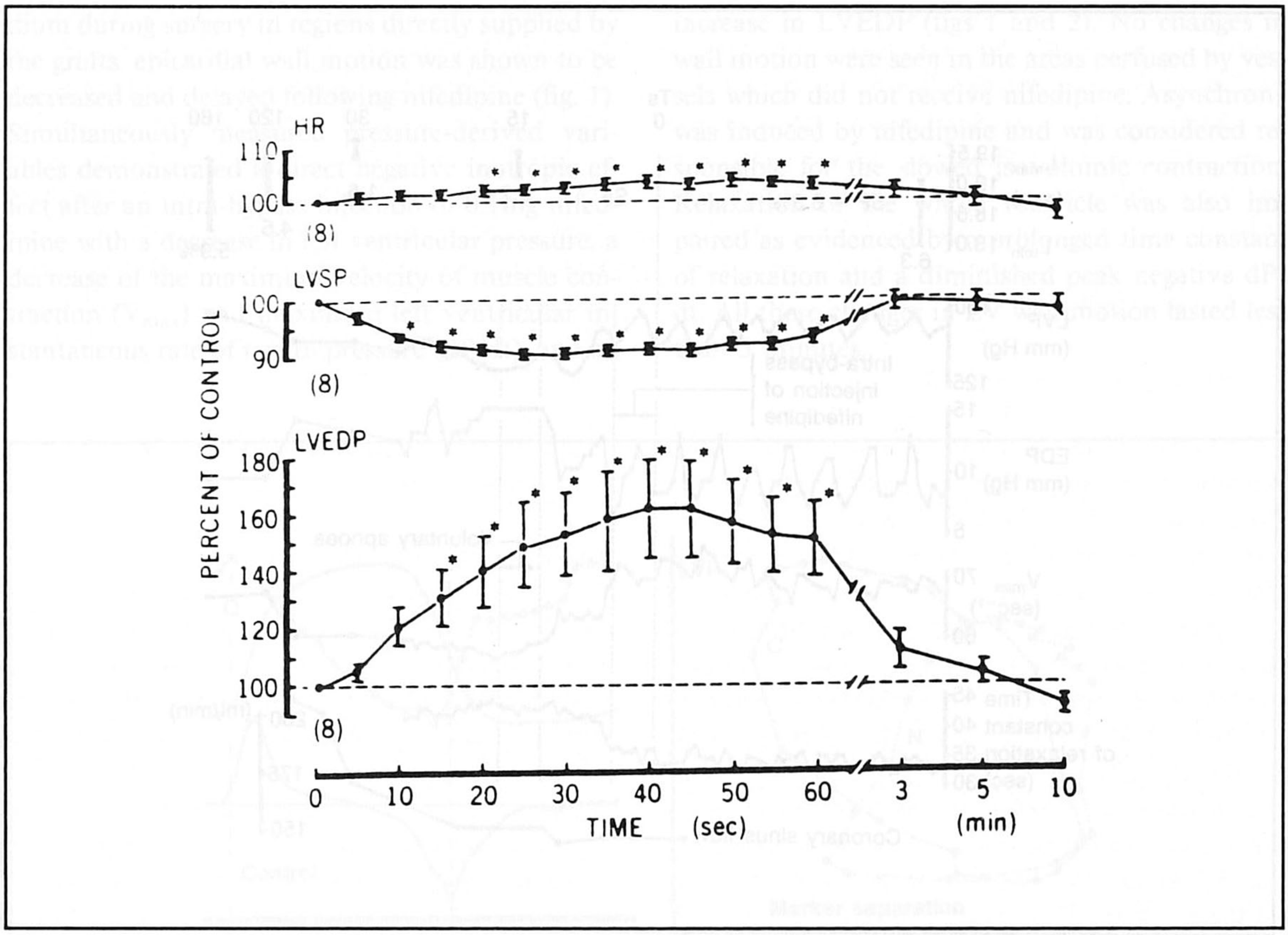


Fig. 3. Effect of intracoronary nifedipine on heart rate (HR), left ventricular systolic pressure (LVSP), and left ventricular end-diastolic pressure (LVEDP). Values represent group means ± 1 standard deviation (from Amende et al. 1983; with permission).

segments of the injected coronary artery, one of the mechanisms by which nifedipine, and indeed other calcium antagonists, may be beneficial in treating angina.

The effects of intracoronary and intravenous nifedipine have been contrasted and compared. Both intracoronary and intravenous nifedipine resulted in a marked increase in coronary blood flow as measured by the coronary sinus thermodilution technique, and had similar potencies in reducing coronary vascular resistance (Schanzenbächer et al. 1983). There were no significant changes in myocardial oxygen consumption after the intravenous infusion of 1mg nifedipine. In contrast, the intracoronary injection of 0.1mg nifedipine resulted in a significant reduction of myocardial oxygen consumption, due to the direct negative inotropic effect of the drug which becomes apparent when peripheral circulatory effects are absent.

The effect of intracoronary nifedipine on myocardial oxygen consumption and coronary blood flow is of a short duration (Schanzenbächer et al. 1983; Serruys et al. 1983a) but the increase in vascular diameter persists after the oxygen consumption and coronary sinus blood flow have returned to normal (fig. 5).

1.2.3 Cardiac Metabolic Effects

The transient regional 'cardioplegic' effect of intracoronary nifedipine – associated with an increase in coronary blood flow, a reduction in myocardial oxygen consumption and vasodilation of the

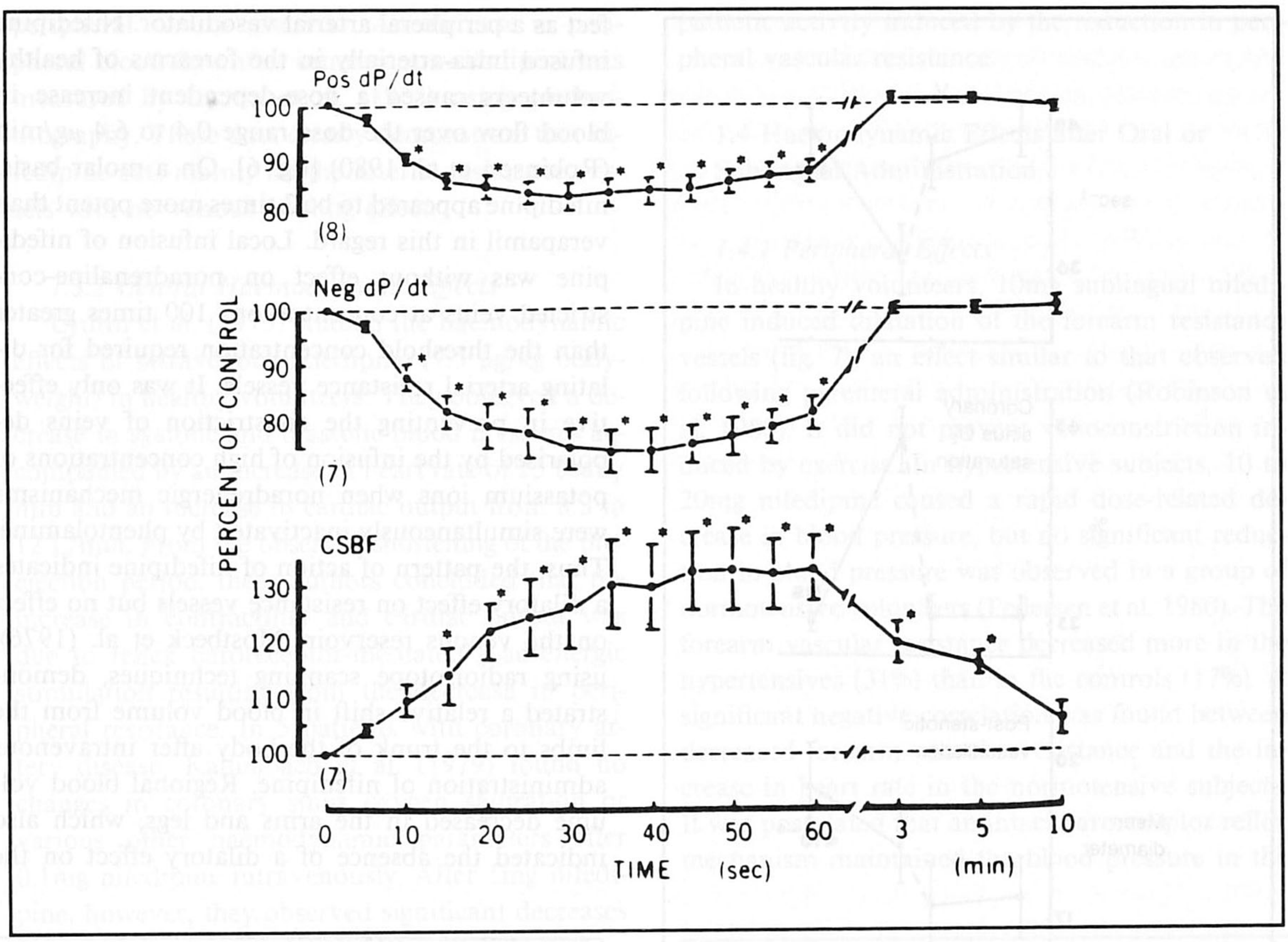


Fig. 4. Effects of intracoronary nifedipine on maximal + dP/dt and − dP/dt and on coronary sinus blood flow (CSBF). Values represent group means ± 1 standard deviation (from Amende et al. 1983; with permission).

epicardial vessels – is likely to be beneficial during temporary coronary occlusion, as occurs during spasm or transluminal angioplasty. Indeed, the release of lactate from the anterior wall, made ischaemic for a short period of time during transluminal angioplasty, has been shown to be reduced by nifedipine when the drug is given selectively into the artery supplying this area, immediately before ischaemia is induced (Serruys et al. 1983b). This protective effect of intracoronary nifedipine is primarily due to selective electromechanical uncoupling. When such uncoupling is not achieved, the lactate production shows clear evidence of myocardial ischaemia. The specific inhibitory action of nifedipine on contractile energy expenditure may thus protect cardiac cells from ischaemic damage during an otherwise beneficial angioplasty procedure.

Nifedipine may also exert an important effect on myocardial metabolism. It was demonstrated in isolated but functioning rat hearts that, although no difference in contractility between nifedipine-treated and untreated ischaemic hearts could be detected, the drug reduced the release of cyclic AMP catabolites in a dose-dependent manner during ischaemia and during reperfusion (De Jong et al. 1982). The duration of the effect of intracoronary nifedipine on cardiac metabolism was also studied by Serruys et al. (1982) who observed that although the pacing-induced angina threshold was not affected 25 minutes after nifedipine 0.1mg, the efflux of catabolites of ATP remained significantly re-

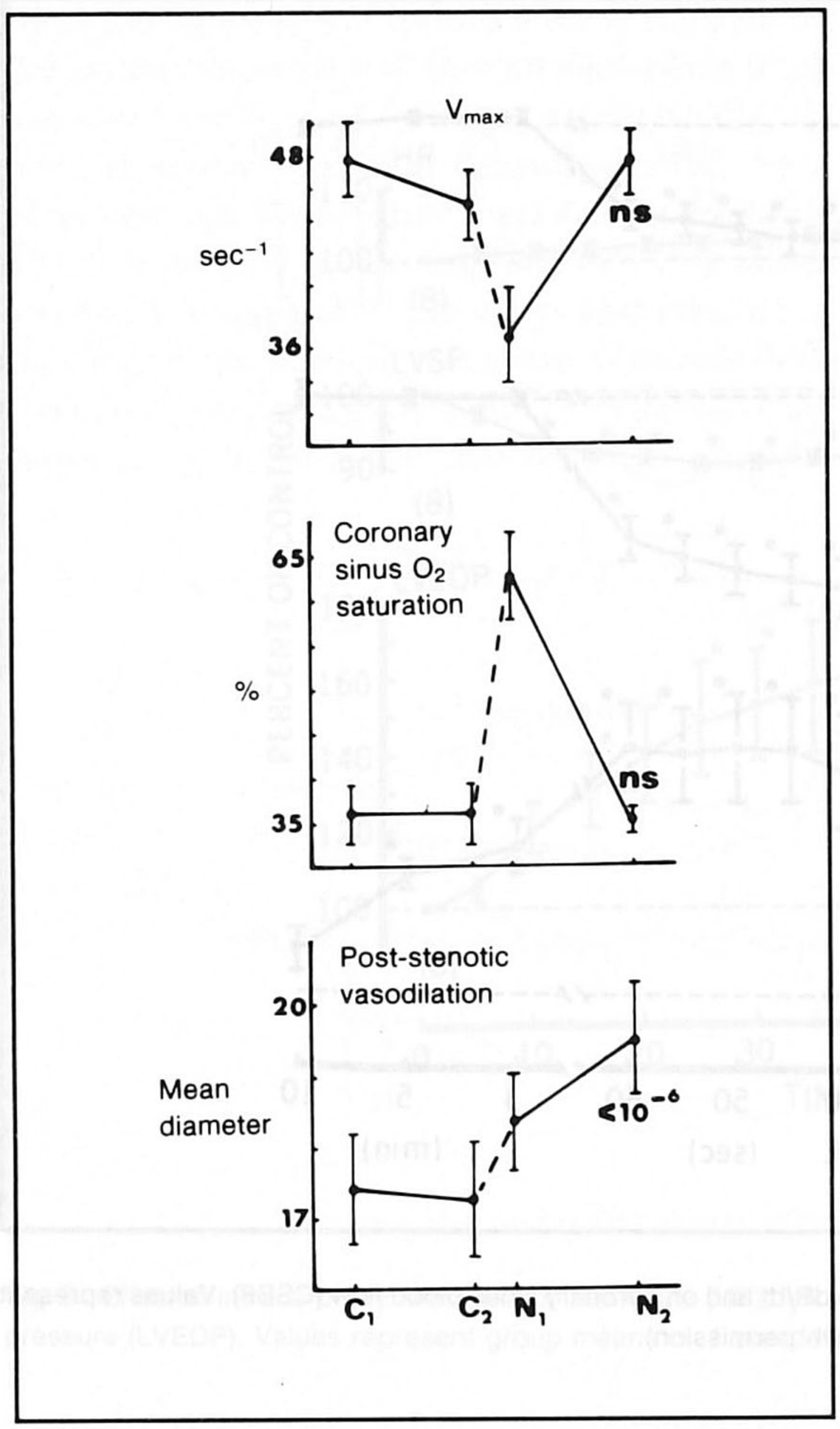


Fig. 5. Changes in V_{max}, coronary sinus O_2 saturation and mean diameters (arbitrary units: pixels) of the post-stenotic segment during 2 control (C_1, C_2) and 2 post-nifedipine (N_1, N_2) cineangiograms: N_1 = 30 seconds after nifedipine injection; N_2 = 5 minutes after nifedipine injection (from Serruys et al. 1981a; with permission).

duced at that time. A prolonged effect of nifedipine on cardiac metabolism is therefore likely. The drug appears to exert a powerful effect on myocardial adenine nucleotide metabolism in man, possibly by increasing the efficiency of oxygen utilisation.

1.3 Haemodynamic Effects after Peripheral Intravascular Administration

1.3.1 Peripheral Effects

Nifedipine causes a significant decrease in systemic vascular resistance through its powerful effect as a peripheral arterial vasodilator. Nifedipine infused intra-arterially in the forearms of healthy volunteers caused a dose-dependent increase in blood flow over the dose range 0.4 to 6.4 μg/min (Robinson et al. 1980) [fig. 6]. On a molar basis, nifedipine appeared to be 3 times more potent than verapamil in this regard. Local infusion of nifedipine was without effect on noradrenaline-constricted veins at concentrations 100 times greater than the threshold concentration required for dilating arterial resistance vessels. It was only effective in preventing the constriction of veins depolarised by the infusion of high concentrations of potassium ions when noradrenergic mechanisms were simultaneously inactivated by phentolamine. Thus, the pattern of action of nifedipine indicates a dilatory effect on resistance vessels but no effect on the venous reservoir. Mostbeck et al. (1976), using radioisotope scanning techniques, demonstrated a relative shift in blood volume from the limbs to the trunk of the body after intravenous administration of nifedipine. Regional blood volume decreased in the arms and legs, which also indicated the absence of a dilatory effect on the

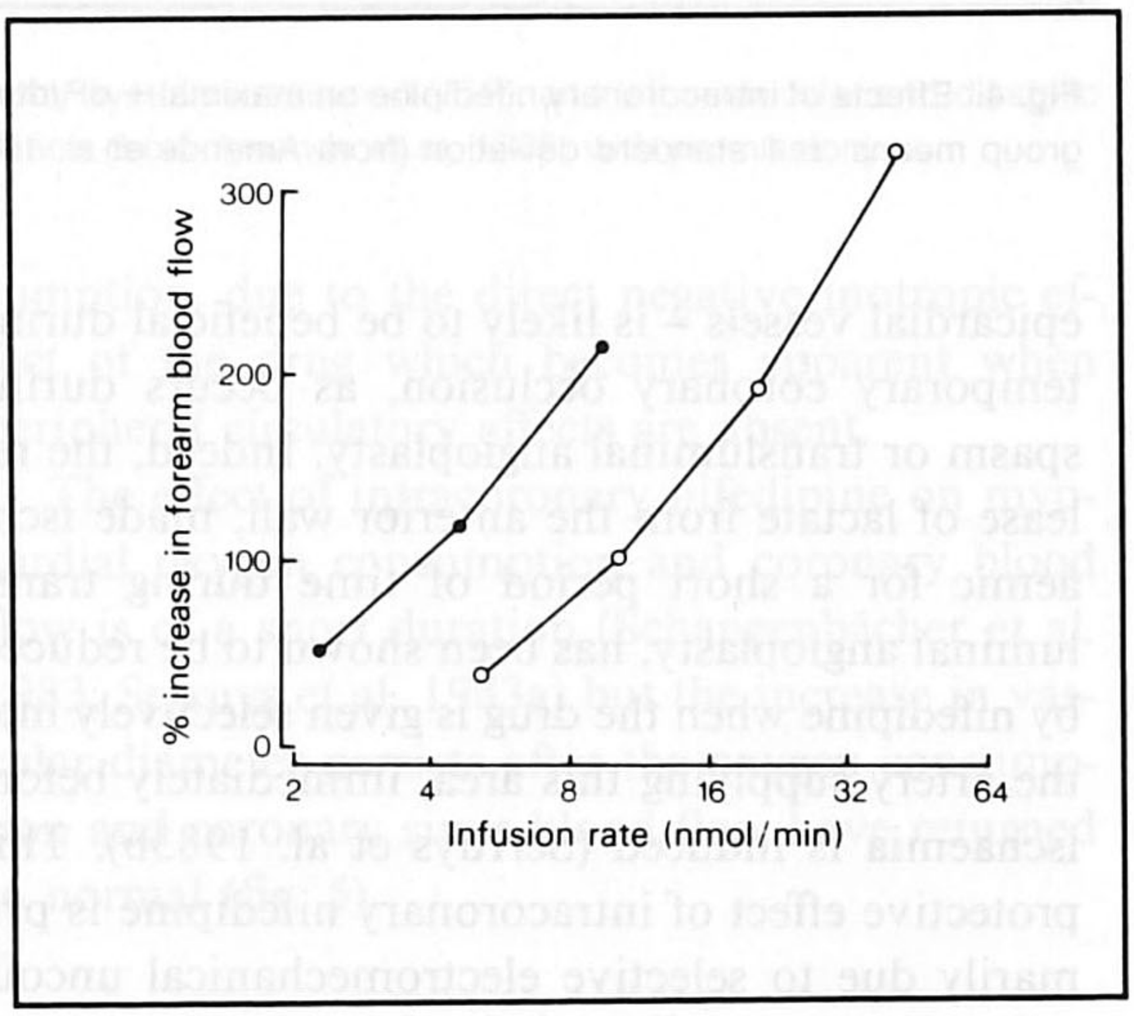


Fig. 6. Comparative effects of local intra-arterial infusion of nifedipine (left) and verapamil (right) on forearm blood flow. Nifedipine is about 3 times more potent than verapamil (●–● = nifedipine; ○–○ = verapamil) [from Robinson et al. 1980, with permission].

peripheral venous reservoir. An increase in peripheral blood flow after intravenous nifedipine was measured by Lydtin et al. (1975) using plethysmography. These data clearly demonstrate that nifedipine acts mainly on the arterial resistance vessels with no venous pooling effect.

1.3.2 Central Haemodynamic Effects

Lydtin et al. (1975) studied the haemodynamic effects of intravenous nifedipine (7.5 μg/kg bodyweight) in healthy volunteers. They observed a decrease in systolic and diastolic blood pressures accompanied by an increase in heart rate of 25 beats/min and an increase in cardiac output from 8.3 to 12 L/min. From the observed shortening of the preejection period, these authors concluded that the increase in contractility and cardiac output was due to reflex baroreceptor-mediated β-adrenergic stimulation resulting from 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 other haemodynamic parameters after 0.1mg nifedipine intravenously. After 1mg nifedipine, however, they observed significant decreases in aortic pressure and LVEDP, and increases in coronary sinus oxygen saturation and heart rate.

1.3.3 Myocardial Effects

Serruys et al. (1981b) studied the effect of 1mg nifedipine intravenously on cardiac function in 11 patients with coronary artery disease. Peak left ventricular pressure was reduced from 152 to 128mm Hg, accompanied by an increase in basal heart rate 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 radio-opaque markers implanted during surgery, was increased over the entire pacing range and, at the highest paced rate, an increase in V_{max} was observed. There was no evidence of the negative inotropic effect seen after the direct intracoronary injection of the drug. Its presence in this setting is masked by the baroreceptor-mediated reflex sympathetic activity induced by the reduction in peripheral vascular resistance.

1.4 Haemodynamic Effects after Oral or Sublingual Administration

1.4.1 Peripheral Effects

In healthy volunteers, 10mg sublingual nifedipine induced dilatation of the forearm resistance vessels (fig. 7), an effect similar to that observed following parenteral administration (Robinson et al. 1980). It did not prevent venoconstriction induced by exercise. In hypertensive subjects, 10 to 20mg nifedipine caused a rapid dose-related decrease in blood pressure, but no significant reduction in blood pressure was observed in a group of normotensive volunteers (Pedersen et al. 1980). The forearm vascular resistance decreased more in the hypertensives (31%) than in the controls (17%). A significant negative correlation was found between decreased forearm vascular resistance and the increase in heart rate in the normotensive subjects. It was postulated that an intact baroreceptor reflex mechanism maintained the blood pressure in the

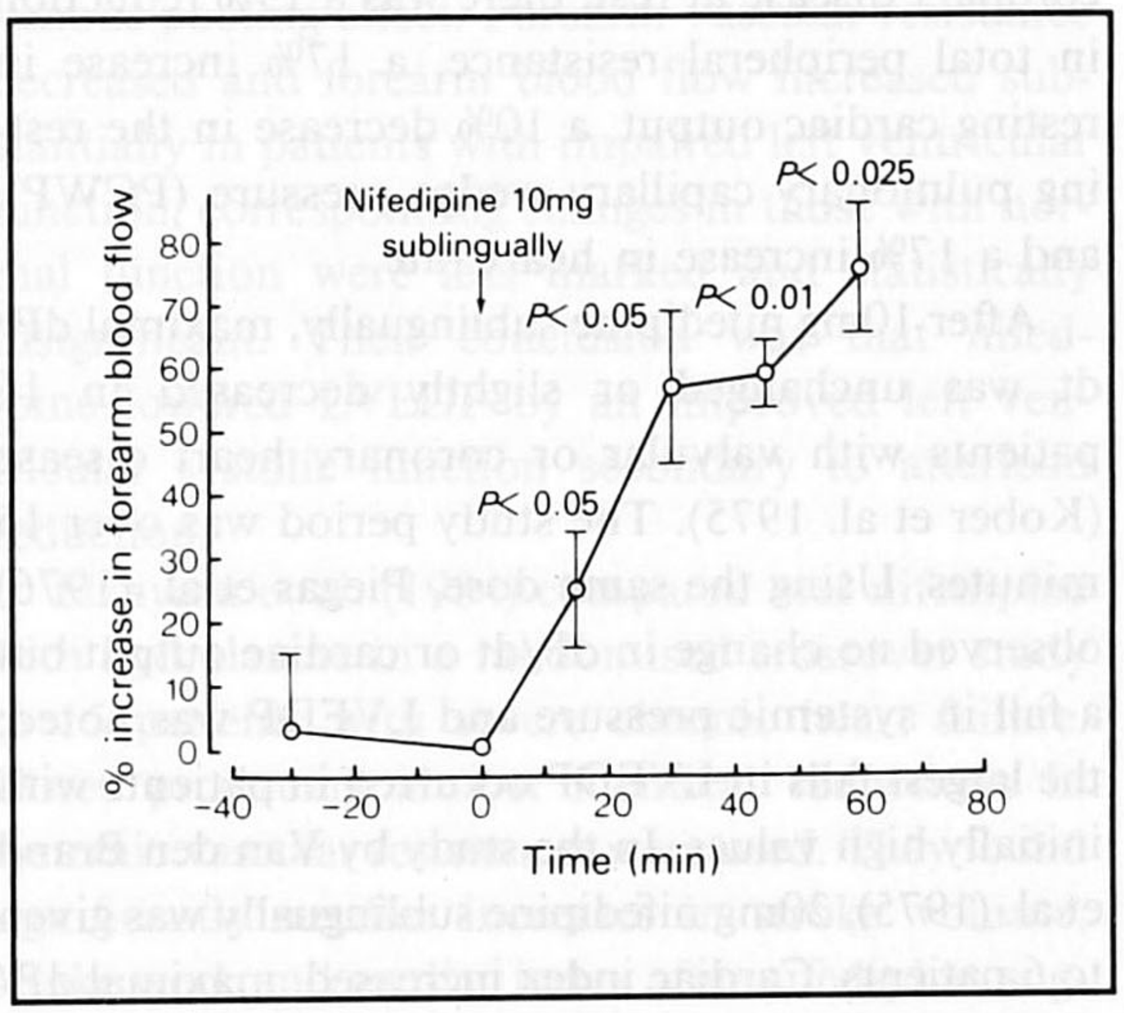


Fig. 7. Effects of sublingual nifedipine (10mg) on forearm blood flow in 5 subjects. The results have been related to the control flow determined immediately before the drug was given and are expressed as the percentage increase (mean ± SEM) [from Robinson et al. 1980; with permission].

normotensives while in the hypertensive patients the reflex mechanism was impaired.

An increase in peripheral blood flow was also demonstrated by Lydtin et al. (1975) and Merillon et al. (1978). The latter authors also found no change in venous tone by plethysmographic studies, as did Kurnik et al. (1984). Mostbeck et al. (1976) observed an increase in radioisotope activity in the liver half an hour after 20mg nifedipine was administered sublingually to 5 patients. This observation suggested an increase in blood volume in the liver, while the observed decrease in activity in the limbs suggested a lowered blood volume and no significant venous pooling effect.

1.4.2 Myocardial Effects

Effects at Rest

Similar to the effects observed following intravenous administration of nifedipine, oral or sublingual administration causes a reduction in ventricular afterload with an increase in cardiac output and heart rate (fig. 8). Lydtin et al. (1980) observed that 15 to 20 minutes after a single oral dose of 20mg nifedipine administered to 26 patients with coronary disease at rest, there was a 19% reduction in total peripheral resistance, a 17% increase in resting cardiac output, a 10% decrease in the resting pulmonary capillary wedge pressure (PCWP), and a 17% increase in heart rate.

After 10mg nifedipine sublingually, maximal dP/dt was unchanged or slightly decreased in 16 patients with valvular or coronary heart disease (Kober et al. 1975). The study period was over 15 minutes. Using the same dose, Piegas et al. (1976) observed no change in dP/dt or cardiac output but a fall in systemic pressure and LVEDP was noted; the largest falls in LVEDP occurred in patients with initially high values. In the study by Van den Brand et al. (1975), 20mg nifedipine sublingually was given to 6 patients. Cardiac index increased, maximal dP/dt was unchanged and there was a rise in V_{max} which achieved statistical significance at 60 minutes. Lichtlen (1975) also found a decrease in LVEDP and an increase in dP/dt after 20mg nifedipine. Increases in contractility parameters are

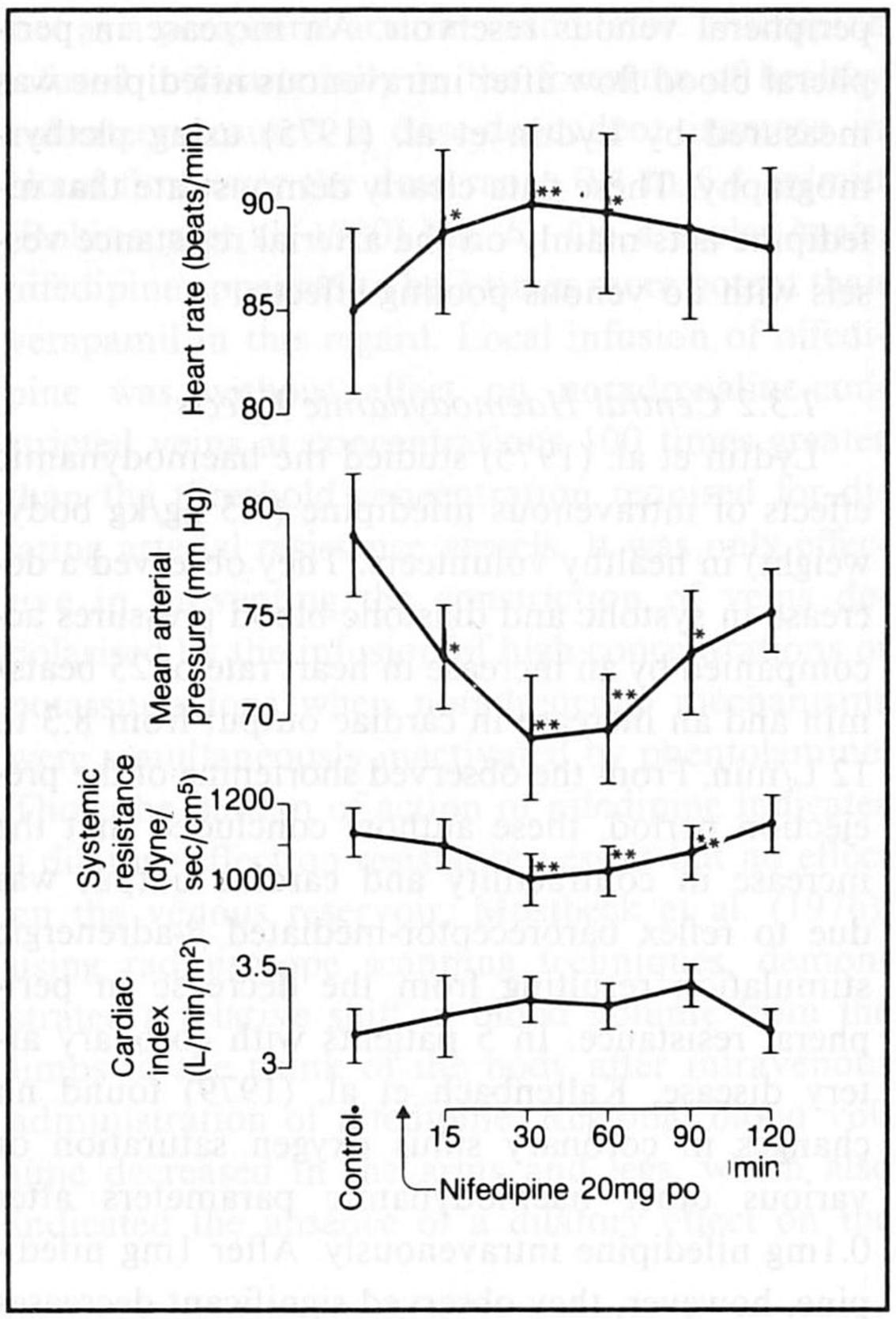


Fig. 8. Mean haemodynamic effects (± SEM) of 20mg nifedipine in 12 patients. Heart rate increases by 6% ($p < 0.01$) while mean arterial blood pressure decreases by 12% ($p < 0.01$). Cardiac index rises by 4% (NS) and systemic vascular resistance decreases by 15% ($p < 0.01$). The p value was calculated by the Student's t-test modified for multiple comparisons: * $p < 0.05$; ** $p < 0.01$ (from Theroux et al. 1980; with permission).

secondary to a combination of reflex β-adrenergic stimulation and afterload reduction, which mask the intrinsic negative inotropic effects of nifedipine. Positive inotropic effects have been more commonly observed after 20mg than after 10mg sublingual doses.

More recently Amende et al. (1980) showed that sublingual nifedipine is accompanied by a fall in left ventricular relaxation rate and a slight increase in diastolic volume and muscle stiffness which they interpreted as an early depressant action of nifedipine on diastolic left ventricular function. To

characterise the acute effects of nifedipine on left ventricular systolic and diastolic function, Ludbrook et al. (1982) studied 32 patients with varying degrees of left ventricular function before and 30 minutes after nifedipine (20mg sublingually). In the group as a whole, nifedipine lowered left ventricular afterload and improved systolic function: ejection fraction increased 14%, cardiac index 16%, mean velocity of circumferential fibre shortening (Vcf) 41%, mean normalised systolic ejection rate 25%, and the end-systolic pressure/volume ratio by 19% ($p < 0.05$ for each when compared with the administration of placebo). Overall, left ventricular diastolic function did not change. Striking differences in the effect of sublingual nifedipine were evident when the patients were stratified according to left ventricular function. Patients were divided into those with well preserved left ventricular function (end-diastolic volume < 90 ml/m^2, end-diastolic pressure < 20mm Hg) and those with some evidence of left ventricular decompensation (end-diastolic volume > 90 ml/m^2, end-diastolic pressure > 20mm Hg). Nifedipine enhanced cardiac performance much more in those patients with impaired left ventricular function than in patients with well preserved function. In the group with poor left ventricular function, nifedipine significantly decreased systolic and end-diastolic pressures, end-diastolic and end-systolic volumes, and systemic and pulmonary vascular resistances. Enhancement of ejection fraction, cardiac index, Vcf, and mean normalised systolic ejection rate was much greater in those patients with impaired left ventricular function than in those with normal baseline function. Relaxation and diastolic stiffness were not significantly changed in either group, although in the patients with impaired function the diastolic pressure-volume curves were consistently shifted downward and leftward following administration of nifedipine.

A single-dose study of 20mg nifedipine sublingually in 10 patients with idiopathic congestive cardiomyopathy and a mean ejection fraction of 27%, found salutary effects both at rest and during exercise (Magorien et al. 1984). Coronary blood flow as assessed using a thermodilution technique was augmented by 32% at rest and cardiac index increased 37% at rest and 28% with exercise after nifedipine. Similarly, improvements in cardiac index, Vcf and reductions in PCWP and left ventricular diastolic diameter measured echocardiographically were found by Guazzi et al. (1984) following 20mg nifedipine orally in 15 patients with hypertension and impaired left ventricular function. These changes were accompanied by a marked sustained fall in systemic vascular resistance. These responses persisted during a 1-month treatment period. Other studies of the beneficial effects of nifedipine in the treatment of congestive heart failure have also been published (Belloci et al. 1982; Cantelli et al. 1983; Klugman et al. 1980; Matsumoto et al. 1980; Polese et al. 1979).

Further insight into the mechanism of the beneficial effects of nifedipine in abnormal left ventricular function was provided by Kurnik et al. (1984). Forearm plethysmography was performed during cardiac catheterisation in 32 patients who were randomly assigned to placebo or 20mg nifedipine sublingually. They found a fall in LVEDP after nifedipine only in patients with impaired left ventricular function and confirmed the absence of a venous pooling effect. Forearm vascular resistance decreased and forearm blood flow increased substantially in patients with impaired left ventricular function; corresponding changes in those with normal function were less marked and statistically insignificant. Their conclusion was that nifedipine lowered LVEDP by an improved left ventricular systolic function secondary to afterload reduction.

Elkayam et al. (1984) compared oral nifedipine with hydralazine in a randomised crossover study in 15 patients with severe chronic heart failure. Doses producing almost identical reductions in systemic vascular resistances were used. They found significantly smaller increases in stroke volume, stroke work and cardiac index after nifedipine, suggesting that a direct myocardial depressant effect of nifedipine is only partially offset by its vasodilatory action. Case reports (Brooks et al. 1980; Gillmer & Kark 1980) suggest that in some patients with severe heart failure the direct depressant ef-

fect of nifedipine may be clinically deleterious and hence caution should be employed in these patients.

In conclusion, therapeutic doses of oral or sublingual nifedipine at rest exert beneficial effects on systolic and diastolic determinants of myocardial oxygen requirements in man. Most authors agree that under resting conditions, the direct negative inotropic effect of nifedipine, which is observed in isolated tissue preparations and after direct intracoronary administrations in humans, is not evident when the drug is administered orally. Systemic and pulmonary haemodynamics, left ventricular systolic performance, cardiac output, and diastolic pressure/volume relationships are favourably influenced, particularly in patients with impaired baseline left ventricular function, after sublingual and oral administration of nifedipine. There is, however, a variation in dose-responses among individuals and this should be taken into consideration in clinical practice.

Effects During Stress

Esper et al. (1976) observed that nifedipine administration shortened the PEP/LVET ratio during isometric handgrip exercise in healthy subjects as well as patients with coronary artery disease, indicating the operation of β-adrenergic reflex stimulation secondary to systemic vasodilatation. Hollman et al. (1975) observed a slight decrease in blood pressure particularly in the presence of raised peripheral resistances. He noted that total cardiac work was unaltered, but observed a shift from pressure to volume work. Oxygen uptake measured during exercise by spiroergometry was not affected by nifedipine, although the oxygen uptake per heart beat was diminished.

Lydtin et al. (1980) found that when patients with coronary disease were given 20mg nifedipine orally and then exercised in the supine position on a bicycle (mean of 80 W/min over 4 minutes), total peripheral resistance decreased by 17%, cardiac output increased by 13%, heart rate increased 10% and PCWP decreased 25%. All of these results were highly significant when compared with control exercise studies in the same patients. The reduction in exercise PCWP appeared to be more pronounced in those patients with higher pretreatment levels of exercise PCWP. The beneficial effect of nifedipine on exercise PCWP persisted after 3 weeks' treatment with 10mg 3 times daily.

During exercise, Kurita et al. (1975) found that nifedipine led to a decrease in LVEDP, accompanied by a reduction in V_{max}, while cardiac index and heart rate were not affected. Lichtlen et al. (1975) also observed that LVEDP decreased during exercise when nifedipine was administered, accompanied by a decrease in left ventricular systolic pressure, but observed that both heart rate and maximal dP/dt significantly increased. On the other hand, Silke et al. (1984) and Nelson et al. (1984b) found no changes in cardiac output or left ventricular filling pressures during upright bicycle exercise after 20mg nifedipine sublingually when compared with a control exercise period, despite falls in systemic arterial pressure. All patients studied had coronary artery disease. The former group of researchers noted an attenuation of the angina induced during the control period while the latter observed no deterioration after nifedipine in a subgroup of patients with severely impaired left ventricular function.

During atrial pacing following the administration of nifedipine, Merillon et al. (1978) found a decrease in blood pressure with an increase in cardiac output. The substantial elevation in PCWP seen during pacing in 3 patients could not be reproduced after nifedipine. Majid and de Jong (1982) studied the acute haemodynamic effects of 20mg nifedipine sublingually in 8 patients during exercise-induced pain and in 6 patients during pacing-induced angina. In both groups, nifedipine significantly shortened the duration of ischaemic pain and reduced ST-segment depression on the ECG. Nifedipine also reversed the exercise-induced or pacing-induced haemodynamic disturbances which were observed prior to the administration of nifedipine, such as increases in the LVEDP, end-diastolic and end-systolic volumes and impaired ejection fraction. Sublingual nifedipine 30mg was given to 11 patients with chronic coronary artery disease by Bagger and Nielsen (1985) and the effects on coronary haemodynamics and cardiac metabolism

were studied during 2 identical periods of atrial pacing. All experienced angina during pacing. Although nifedipine reduced pacing time to angina, this did not reach statistical significance. Nifedipine decreased blood pressure (12%), the rate-pressure product and coronary vascular resistance, while coronary sinus blood flow tended to increase. Myocardial oxygen uptake remained unchanged. The rate-pressure product, which correlates with myocardial oxygen uptake in patients subjected to atrial pacing, is, however, insensitive to changes in contractility. Thus, nifedipine may have failed to reduce overall heart energy expenditure in this study because of increased left ventricular contractility. The authors noted some changes in myocardial metabolism, including augmented free fatty acid extraction and uptake and a less negative lactate extraction in patients showing lactate production during control pacing, which suggested improvement with regard to ischaemia.

Zacca et al. (1982) assessed the effects of nifedipine on left ventricular function and regional myocardial perfusion with exercise radionuclide ventriculography and exercise thallium scintigraphy. All patients had stable angina pectoris and angiographically proven coronary artery disease. Ejection fraction determined in 15 patients improved at rest from 49 to 52% and at peak exercise from 42 to 47%. Administration of nifedipine also resulted in an improved segmental wall motion score. Improved exercise myocardial perfusion occurred in 5 of 11 patients and in 7 of 28 segments with reversible hypoperfusion. Thus, they concluded, nifedipine has beneficial effects on resting and exercise left ventricular function in patients with chronic stable angina pectoris. Peripheral mechanisms as well as improvement in regional myocardial perfusion appear to be involved.

The long term effects of nifedipine on left ventricular function have not been as well documented as short term effects. In a study of 15 patients, 1 to 3 years after coronary bypass surgery during which radio-opaque epicardial markers had been sited, Bos et al. (1985) investigated the short term effects of 2 doses of 10mg given simultaneously orally and sublingually and then the long term effects of nifedipine 40mg daily in 4 divided oral doses for 3 months. Haemodynamic parameters and epicardial marker motion were studied during supine bicycle exercise. The short term changes of decreased blood pressure and increased heart rate at rest were attenuated but still evident after 3 months. The heart rate response during exercise parallelled the response at rest, both during short and long term administration; however, neither systolic nor diastolic blood pressure showed a significant change. Left ventricular dimensions as assessed from marker separation were unchanged at rest but showed significant reductions in systolic and diastolic regional dimensions during exercise after the short term as well as after long term oral administration. The authors discounted afterload reduction as a cause of the smaller left ventricular dimensions, as these latter changes persisted up to 3 months without a comparable reduction in blood pressure. Reflex catecholamine-induced positive inotropic effects were considered possible causes but, interestingly, 6 of the 15 patients were using β-blockers and the results in these patients followed the same trends as other patients. An antiischaemic effect with improved coronary blood distribution and better mechanical emptying of the heart was considered the most likely explanation.

Hanrath et al. (1982) studied 14 patients with left ventricular dysfunction, at rest and during a supine bicycle exercise test before and 60 minutes after taking 30mg nifedipine sublingually. At rest and during exercise, nifedipine produced a significant increase in cardiac index from 2.9 to 3.6 L/min/m^2 and from 4.1 to 4.9 L/min/m^2, respectively. A marked reduction in systemic vascular resistance occurred but pulmonary artery pressure remained unchanged at rest. This dropped significantly during exercise.

Goldhaber et al. (1983) obtained radionuclide angiograms prior to and during the cold pressor test both before and after administration of 10mg nifedipine bucally. In patients with coronary artery disease, nifedipine abolished the decrease in left ventricular ejection fraction observed during the control cold pressor test and concluded that nifed-

ipine may be of value in protecting patients from cold-induced left ventricular dysfunction.

1.4.3 Coronary Haemodynamic Effects

There have been extensive studies investigating the effects of nifedipine on the coronary vasculature in patients with classic exertional angina, using a variety of techniques to measure coronary flow and coronary vascular resistances. Using coronary sinus blood flow measurements, an increase in coronary flow has been demonstrated after nifedipine administration, usually associated with a significant decrease in coronary vascular resistance (Kohler 1975; Merillon et al. 1978; Simonsen & Nitter-Hauge 1978; Stone et al. 1983).

Emanuelsson and Holmberg (1983) performed coronary haemodynamic and myocardial metabolic measurements in 14 patients at rest and during pacing, before and after sublingual administration of 10mg nifedipine. After nifedipine, no change in coronary blood flow occurred, but as a result of the drop in coronary perfusion pressure, there was a significant fall in the calculated coronary vascular resistance both at rest and at the control pacing rate. Increasing the pacing rate to that which induced pain before nifedipine did not induce angina in any patient after nifedipine administration. Lactate production during control turned into extraction after nifedipine and the double-product was reduced. To explain the symptomatic improvements, the authors felt that both direct cardiac effects and the influence of nifedipine on the systemic and coronary circulation should be taken into account. Other studies have confirmed this lack of increase in coronary blood flow during atrial pacing-induced tachycardia after nifedipine. It was suggested by Simonsen and Nitter-Hauge (1978) that local metabolic factors associated with pacing-induced ischaemia produce maximal vasodilatation and therefore prevent an additional vasodilatory effect from nifedipine.

Specchia et al. (1983) suggested that nifedipine might have differing effects in subgroups of patients with coronary artery disease with respect to the coronary circulation. They investigated the mechanism by which nifedipine improves exercise tolerance in 14 patients with stable exertional angina and left anterior descending disease. Great cardiac vein flow and anterior regional coronary resistance were measured during exercise before and after administration of 20mg nifedipine sublingually. Seven patients had no increase in exercise capacity and showed a similar magnitude of ST-segment depression at peak exercise, while 7 other patients had a prolonged exercise duration and less ST-segment depression at peak exercise after nifedipine. In the latter group this effect was achieved despite a significant increase in the double-product. In the same group of patients, nifedipine significantly increased great cardiac vein flow at rest and at peak exercise (by 53 and 67%, respectively). Furthermore, the regional resistance at rest and during exercise was decreased. The coronary haemodynamic changes, present in patients with increased exercise capacity, were not seen in the patients who did not have an increase in exercise capacity. The data show that nifedipine may increase great cardiac vein flow and decrease regional coronary resistance at rest and during exercise in patients with left anterior descending artery disease. This increase in myocardial oxygen supply is a likely mechanism by which nifedipine may improve exercise capacity in patients with stable exercise angina.

Using the xenon-133 clearance technique in patients at rest, Engel et al. (1980) and Heeger et al. (1975) observed an increase in coronary blood flow after the administration of nifedipine. According to Engel and co-workers this increase occurs in normal as well as in the post-stenotic areas of coronary arteries. This increase in regional myocardial blood flow in post-stenotic areas at rest was confirmed by Malacoff et al. (1982), although they observed a decrease in flow in regions perfused by 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 areas and a decrease in normal areas. This redistribution during atrial pacing appeared to produce a more uniform pattern of myocardial blood flow. The limitation of the xenon washout technique is that it cannot differentiate between flow in subendocardial, medial, or

subepicardial layers and only measures transmural flow.

Fixed atherosclerotic stenotic segments, particularly of an eccentric nature, have been shown to be dilated by buccal nifedipine (Rafflenbeul & Lichtlen 1982). Presumably this is due to an effect on the vascular wall not involved by the atherosclerotic process. In addition to nifedipine's effect on fixed obstructive coronary lesions, it has recently been appreciated that nifedipine may ameliorate the excessive or inappropriate increases in coronary vasomotor tone that may accompany classic exertional angina. Mudge et al. (1976) demonstrated that patients with stable chronic exertional angina may develop a heightened coronary vasoconstrictive response to provocative measures performed at rest, such as a cold pressor test, and that these increases in coronary resistance and decreases in coronary blood flow may be associated with the development of angina. Nifedipine prevents these increases in coronary vasomotor tone induced by provocative manoeuvres such as the cold pressor test (De Servi et al. 1980; Goldberg et al. 1979; Gunther et al. 1981) and handgrip isometric exercise (Gunther et al. 1981).

In addition to the effects of nifedipine on the coronary vasculature in patients with classic exertional angina due to fixed atherosclerotic obstructions, the efficacy of nifedipine in preventing episodes of coronary vasospasm and Prinzmetal's variant angina has also been extensively studied. Waters et al. (1981) studied the efficacy of nifedipine and two other calcium antagonists, diltiazem and verapamil, in blocking ergonovine-induced coronary vasospasm in patients with documented Prinzmetal's variant angina. Both nifedipine 20mg 6-hourly and diltiazem 120mg 8-hourly were more effective than verapamil 160mg 8-hourly in either preventing the development of ST-segment changes produced by the maximal ergonovine dose (0.4mg), or increased the dose of ergonovine necessary to provoke ST-segment changes. The responses of these patients to calcium antagonists predicted the clinical responses of patients with variant angina during a 7-month follow-up period. The efficacy of nifedipine in the treatment of patients with Prinzmetal's variant angina has been confirmed in studies utilising either an unblinded design with open-label medication or a placebo-controlled, randomised, double-blind design (Antman et al. 1980; Schick et al. 1982).

1.5 Nifedipine in Combination with β-Adrenoceptor Blocking Agents

Additive antianginal actions of oral nifedipine in patients receiving propranolol or other β-blockers have been demonstrated by different investigators. Most agree that the negative intrinsic inotropic effect of nifedipine, seen in animal experiments and after direct intracoronary administration in humans, is not apparent when the drug is taken orally. However, the intrinsic negative inotropic effect of nifedipine may become apparent if the patients receive β-blockers concomitantly. Case reports of adverse haemodynamic interactions between nifedipine and β-blockers have indeed been published (Anastassiades 1980; Motte et al. 1980; Opie & White 1980; Robson et al. 1982; Staffurth et al. 1981) but in general, the combination has been shown to be beneficial rather than detrimental in controlled clinical studies.

Rowland et al. (1983) injected nifedipine 7.5 ng/kg intravenously in 9 patients who were already receiving atenolol 100 to 200mg daily orally. Nifedipine reduced both systolic blood pressure and left ventricular dP/dt transiently. Both values were significantly lower 5 and 10 minutes after infusion but were the same as the control at 20 minutes. LVEDP remained unchanged. Radionuclide angiography in patients taking the long term oral combination of atenolol and nifedipine for angina showed no change in ejection fraction compared with those taking atenolol alone, but there was a small increase in peak ejection rate. Resting blood pressure and heart rate were unchanged. Peak heart rate and systolic blood pressure with exercise were the same for the combination of nifedipine and atenolol as for atenolol alone. The absence of haemodynamic deterioration when oral nifedipine is combined with atenolol suggests that this combin-

ation can be used safely in patients with normal left ventricular function.

Joshi et al. (1981) administered 10mg nifedipine sublingually to 12 coronary artery disease patients who were at a constant atrial paced rate and were taking oral atenolol 400mg daily. They also 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 β-blockade.

Nifedipine reduced systemic vascular resistance, which was associated with decreases in systolic blood pressure and increases in left ventricular output, while LVEDP was unchanged. Koch (1980) gave 10mg nifedipine sublingually to patients with coronary artery disease pretreated with metoprolol. Stroke volume increased, and the LV filling pressure which had increased after metoprolol was reduced. Nelson et al. (1984a) investigated the haemodynamic effects of sublingual nifedipine 20mg and intravenous metoprolol 10mg singly and in combination in 20 patients with angina pectoris due to coronary artery disease. The reflex tachycardia which followed nifedipine and the fall in cardiac output and rise in left ventricular filling pressure after metoprolol were each to some extent offset when the drugs were used in combination.

Daly et al. (1982) evaluated the effects of adding nifedipine to long term propranolol therapy in patients with proven coronary artery disease. At rest, heart rate and cardiac output increased, while pulmonary artery diastolic pressure remained unchanged after adding nifedipine. During exercise, however, no increase in cardiac output was observed, while total peripheral resistance and arterial systolic pressure were lowered compared with the control period on propranolol alone. During exercise, when comparing the effect of acebutolol alone with combined therapy with nifedipine, Schmutzler et al. (1980) also did not observe increases in cardiac output. However, peripheral arterial resistance and arterial systolic pressure were lowered, and this, combined with an unchanged heart rate, resulted in a decrease in the rate-pressure product. This indicates that, at least in some patients with coronary artery disease, left ventricular work is further reduced after adding nifedipine to β-blockade, which implies lower myocardial oxygen requirements at a given level of physical activity. The haemodynamically beneficial interaction was further demonstrated by slight decreases in LVEDP and mean pulmonary artery pressure with combined therapy when compared with therapy with acebutolol alone.

Pfisterer et al. (1982) performed haemodynamic and radionuclide ejection fraction measurements at rest and during exercise, before treatment in patients with stable coronary artery disease, 1 hour after the administration of nifedipine or acebutolol, and again 1 hour after combined therapy. At rest, ejection fraction was lower and cardiac index was unchanged with combined therapy when compared with the control data. However, the depressant effects of short term β-blockade alone on cardiac index, resting ejection fraction and total peripheral resistance were clearly counterbalanced by nifedipine. During exercise, at the same level as achieved without drugs, additive beneficial effects of both drugs on the pressure-rate product were observed. Combined therapy limited the decrease of ejection fraction observed during exercise to a similar degree as did single therapy. Interestingly, no differences were seen between a subgroup of patients with a cardiac index at rest of less than 2.6 L/min/m^2 and the remaining patients.

Winniford et al. (1982) also observed an increase in cardiac output and ejection fraction, as measured by radionuclide ventriculography, after adding nifedipine to β-blocked patients. The addition of nifedipine produced no changes in left ventricular dP/dt (fig. 9). The addition of verapamil to the β-blocked patients was also studied and produced no change in ejection fraction but a fall in dP/dt.

The previous studies indicated that in patients with stable coronary artery disease, the reflex sympathetic nervous system activity after nifedipine administration can be offset by β-blockers. Thus, the intrinsic negative inotropic effect of nifedipine may become more apparent after β-blockade. Yet the vasodilatory effect of nifedipine still appears to predominate and thus a combination of the drugs

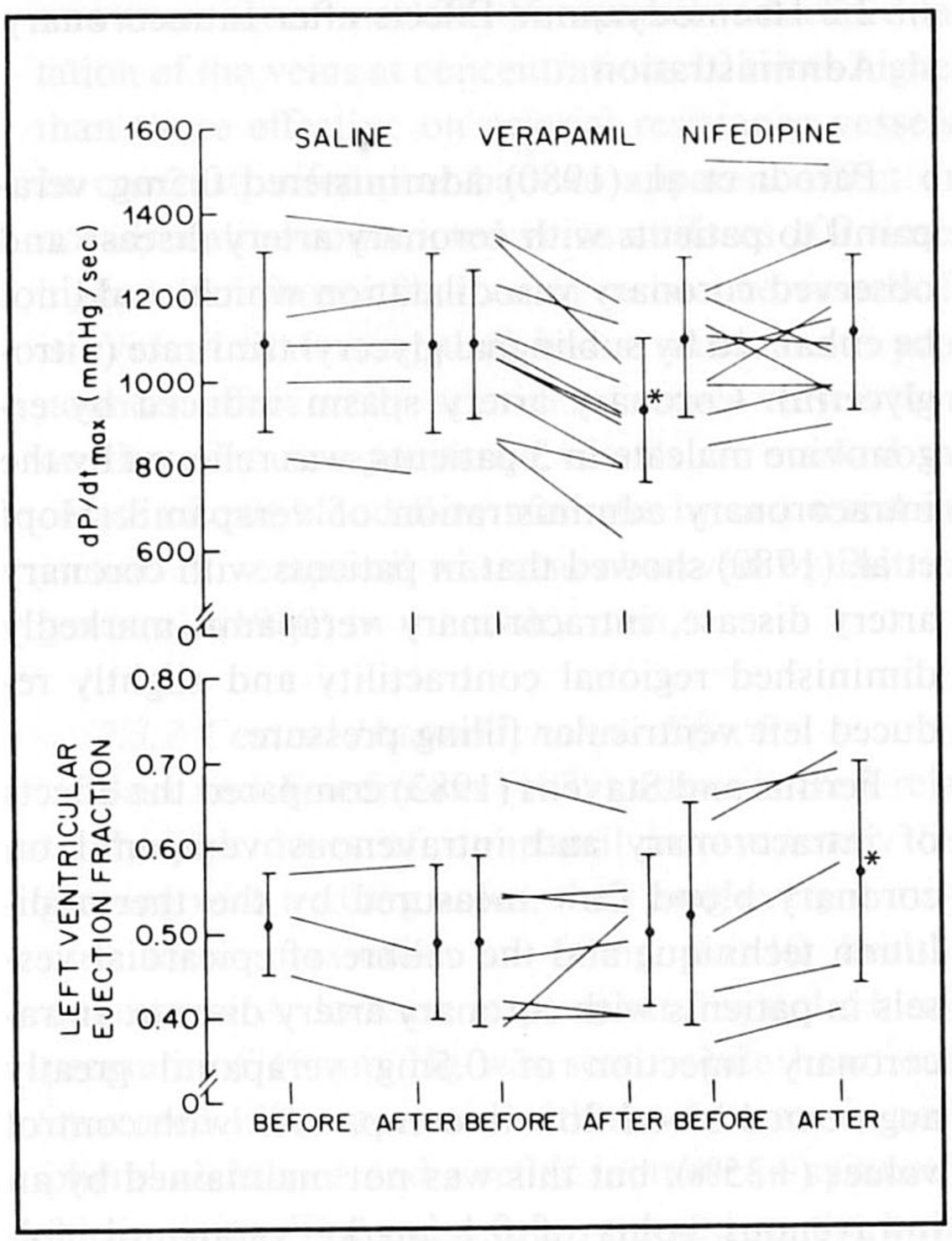


Fig. 9. Left ventricular maximal dP/dt and left ventricular ejection fraction, before and after the administration of saline solution, verapamil or nifedipine to β-blocked patients. Left ventricular dP/dt was reduced by verapamil; ejection fraction increased after administration of nifedipine. Asterisks indicate $p < 0.05$ in comparison with the same pharmacological agent before drug administration (from Winniford et al. 1982; with permission).

appears attractive, particularly as cardiac output is maintained with a lower heart rate and afterload.

In patients with unstable angina pectoris who remained symptomatic after maximal treatment with nitrates and β-blockers, the haemodynamic effect of adding 10mg nifedipine sublingually has been studied by Serruys et al. (1980a). No major haemodynamic changes were observed after adding nifedipine to the treatment while the drug proved to be highly effective in relieving angina. This suggests that the known peripheral haemodynamic effects of nifedipine are not the major cause of the relief of angina pectoris in this group of patients. The effectiveness of the drug appears to be related to its capacity to counteract the increased vasomotor tone of the coronary arteries, one of the main disturbances in unstable angina.

There is generally a lack of information on the haemodynamic effects of the long term use of nifedipine in combination with β-blockers. The possibility of diminishing sympathetic tone with continued β-blocker usage and the unmasking of the intrinsic negative inotropic effect of nifedipine should be considered.

2. Verapamil

2.1 Clinical Pharmacology

The electrophysiological effects of verapamil occur preferentially, with the result that atrioventricular block is likely to occur before substantial haemodynamic toxicity is manifest (Hamann et al. 1986; Manglardi et al. 1978). The plasma concentration-effect relationships for verapamil are complex. McAllister et al. (1982) administered 10mg intravenously and 80mg orally in single doses and observed the relationship between the change in P-R interval on the ECG and plasma verapamil concentration. Linear relationships between concentration and effects on atrioventricular conduction were seen. After oral administration, plasma concentrations required for specific effects on atrioventricular conduction were 2- to 3-fold higher than after intravenous administration, a difference which may be due either to differing tissue distributions after the oral as opposed to the intravenous route, or to preferential first-pass hepatic extraction of the more active L-isomer of verapamil (Eichelbaum et al. 1981). Due in part to this latter first-pass extraction, plasma concentrations after the administration of the same oral dose to different subjects vary more than 10-fold (McAllister et al. 1985), making the measurement of plasma concentrations of little clinical importance, except to demonstrate non-compliance or abnormal drug handling.

The correlation between plasma verapamil concentrations and cardiac output during constant intravenous infusion has been studied in dogs, demonstrating that with lower concentrations,

vasodilatation occurs with an increased cardiac output, while at higher concentrations, negative inotropic effects become evident and cardiac output decreases progressively (Hamann et al. 1986) [fig. 10]. When basal left ventricular function is impaired, negative inotropic effects are manifested at lower drug plasma concentrations (Chew et al. 1981).

Recommended daily dosages of verapamil range from 240 to 480mg administered in 3 to 4 divided doses. Total dosages as high as 720 mg/day have been used without adverse effects. The most commonly encountered side effects are bradycardia, atrioventricular block, hypotension, headache, dizziness and reduced intestinal smooth muscle motility leading to constipation. The overall incidence of adverse effects is 9 to 10%, but severe reactions requiring discontinuation of the drug occur in only 1% of patients (Singh et al. 1980).

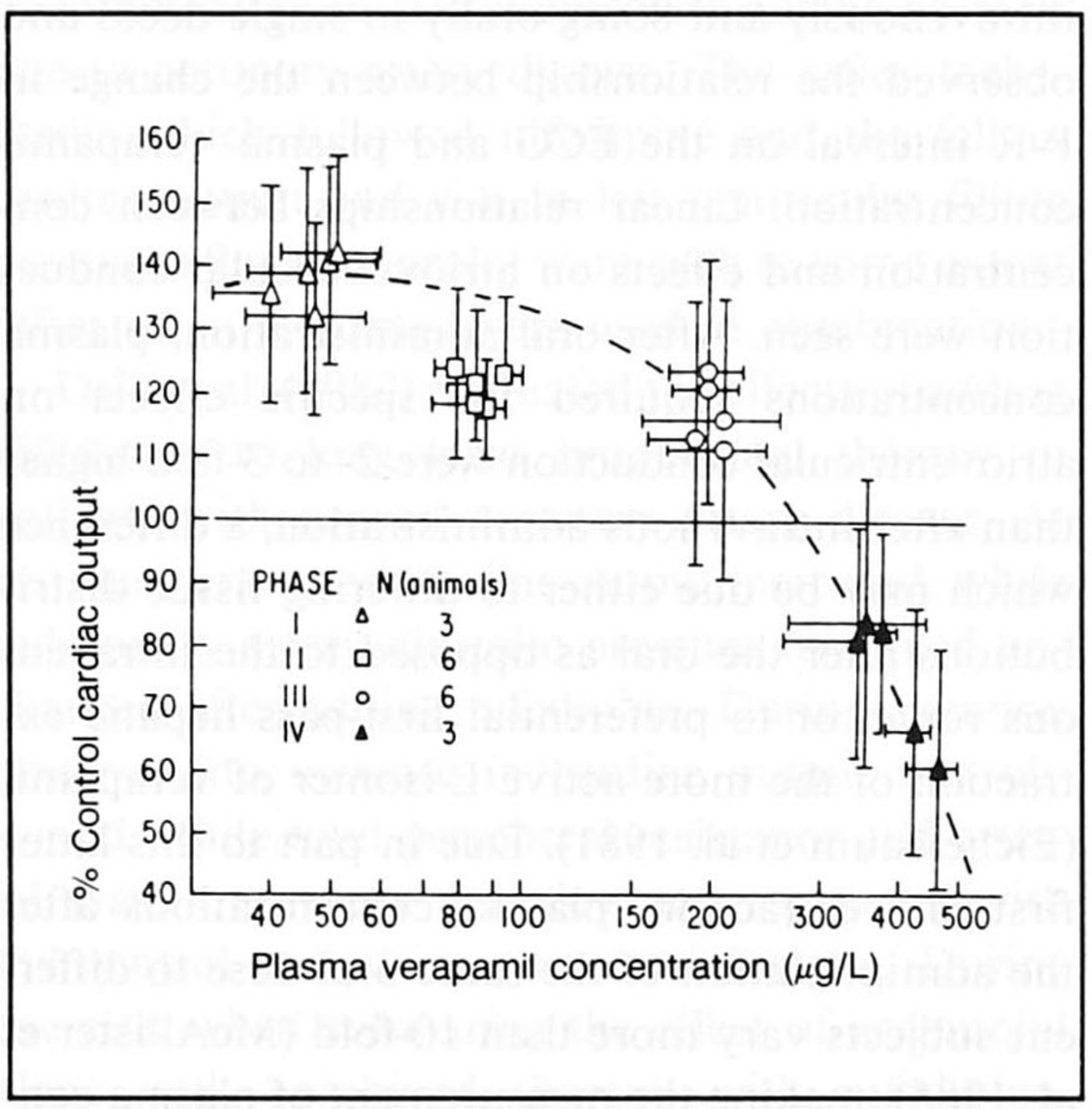


Fig. 10. Correlation between plasma concentrations of verapamil during constant intravenous infusions and percentage change in cardiac output from control concentrations in mongrel dogs. Data points reflect means of observations made at 20, 30, 40, 50 and 60 minutes after beginning verapamil administration. At concentrations of about 250 μg/L, direct negative inotropic effects of verapamil begin to become apparent (from McAllister et al. 1985; with permission).

2.2 Haemodynamic Effects after Intracoronary Administration

Parodi et al. (1980) administered 0.5mg verapamil to patients with coronary artery disease and observed coronary vasodilatation which could not be enhanced by sublingual glyceryl trinitrate (nitroglycerin). Coronary artery spasm induced by ergonovine maleate in 3 patients, was relieved by the intracoronary administration of verapamil. Hopf et al. (1980) showed that in patients with coronary artery disease, intracoronary verapamil markedly diminished regional contractility and slightly reduced left ventricular filling pressure.

Ferlinz and Stavens (1983) compared the effects of intracoronary and intravenous verapamil on coronary blood flow measured by the thermodilution technique and the calibre of epicardial vessels in patients with coronary artery disease. Intracoronary injection of 0.5mg verapamil greatly augmented blood flow in comparison with control values (+35%), but this was not maintained by an intravenous bolus of 0.1 mg/kg verapamil, followed by an 0.005 mg/kg/min infusion. To determine whether epicardial coronary arteries dilate preferentially during intracoronary injection, 20 patients were studied with selective left coronary cineangiography. The respective magnified cine frames did not show alterations in the calibre of normal and abnormal segments of the coronary artery. The authors therefore concluded that the changes in coronary blood flow, induced by verapamil after intracoronary injection, are due to changes in the coronary microcirculation.

2.3 Haemodynamic Effects after Intravascular Administration

2.3.1 Peripheral Effects

Verapamil's effect on peripheral blood vessels is similar to but not identical to that of nifedipine (Robinson et al. 1979). On a molar basis, verapamil was 3 times less potent than nifedipine in dilating the forearm resistance vessels (fig. 6) or potassium-constricted veins. On noradrenaline-constricted veins, the difference between the 2 drugs

was even more marked. Verapamil induced dilatation of the veins at concentrations 10 times higher than those effective on arterial resistance vessels. In contrast, nifedipine had no apparent effect on noradrenaline-constricted veins at doses 100 times higher than those effective on resistance vessels. It is evident that verapamil has a much more pronounced effect on the arterial resistance vessels than on the venous capacitance vessels. A marked increase of calf blood flow after the intra-arterial injection of verapamil was also observed by Brittinger et al. (1980) in 4 healthy men.

2.3.2 Central Haemodynamic Effects

Bass and Friedmann (1971) administered relatively high doses of verapamil intravenously beginning with a 10mg bolus, then 5mg every 4 minutes to a maximum of 60mg, to 10 healthy volunteers. A decrease in peripheral systolic blood pressure of 13mm Hg was seen, while heart rate increased 15% associated with the decrease in peripheral resistance and a reflex increase in sympathetic activity. The pulse rate returned to the basal values in 45 minutes. Similarly, Vincenzi et al. (1976) observed that an average dose of 10mg in 7 healthy controls resulted in a significant increase in heart rate and cardiac output within 4 minutes, together with a decrease in peripheral resistance and blood pressure.

Brittinger et al. (1980) reported an increase in heart rate by 13% without any significant effect on blood pressure after 5mg intravenously, while Atterhog and Ekelund (1975) injected a bolus of 0.1 mg/kg over 2 minutes followed by continuous infusion of 0.007 mg/kg/min in 8 asymptomatic men (some of whom had elevated pulmonary or systemic arterial pressures) and observed a slight decrease in systemic arterial pressure with an increase in heart rate. At rest, pulmonary capillary venous pressure was slightly elevated. All these data indicate that in subjects without heart disease, intravenous administration of verapamil leads to a decrease in vascular resistance, which by means of the baroreceptor reflex mechanism, gives rise to an increase in heart rate.

In patients with coronary artery disease, Seabra-Gomes et al. (1976) observed a reduction in left ventricular dP/dt after an intravenous dose of 0.1 mg/kg verapamil when the heart rate was fixed by atrial pacing. There were no changes in echocardiographic ventricular dimensions, systemic vascular resistance, or aortic pressure. Ferlinz et al. (1979) demonstrated in 20 coronary artery disease patients without heart failure that the vasodilatory effects of the drug compensated for any decrease in left ventricular contractility. Most indices of left ventricular performance were improved after an intravenous bolus of 0.1 mg/kg and an 0.005 mg/kg/min infusion of verapamil. Cardiac index, ejection fraction, and mean Vcf increased, but heart rate remained the same. LVEDP increased but there was no change in end-diastolic volume, indicating a verapamil-induced decrease in left ventricular compliance. In the same study, mean aortic pressure and systemic vascular resistance decreased by 12mm Hg and 30%, respectively. Overall, 70% of all ventricular asynergic segments improved or remained the same after verapamil, while 30% deteriorated further, as judged from hemiaxial shortening on left ventricular angiograms.

Differing results have been reported by Vlietstra et al. (1983). In spite of a marked reduction in systemic vascular resistance in 13 patients given 0.2 mg/kg verapamil over 10 minutes, no evidence of improved regional wall dynamics was present in portions of the left ventricle considered to be hypokinetic as a result of myocardial ischaemia. Furthermore, a small increase in the left ventricular end-diastolic volume index was observed without significant changes in the end-systolic volume index (fig. 11). According to the authors, the small but significant increase in end-diastolic volume probably represents a negative inotropic effect of verapamil, necessitating a larger end-diastolic volume to accomplish the increase in cardiac index associated with peripheral vasodilatation.

In their study, Chew et al. (1981) showed that the intrinsic depressant effect of verapamil is almost completely offset by its vasodilator properties in patients with a mild to moderate decrease in left ventricular ejection fraction with a normal or mildly elevated mean PCWP. Only a small increase in left

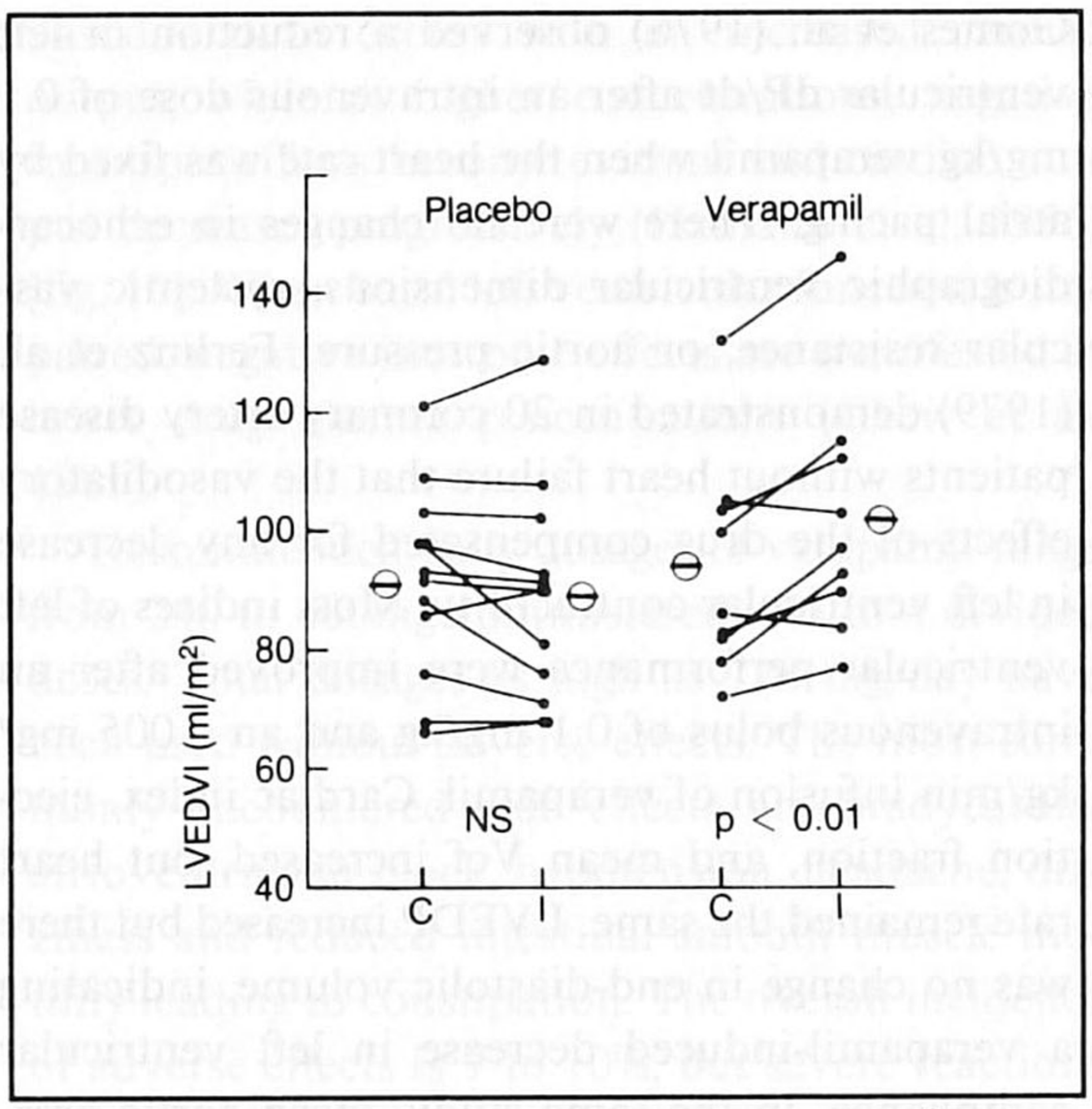


Fig. 11. Left ventricular end-diastolic volume index (LVEDVI) in patients after placebo and after verapamil. A significant increase was seen in patients treated with verapamil (C = control; I = intervention; NS = not significant) [from Vlietstra et al. 1983; with permission].

ventricular filling pressure was observed and with gated blood pool scanning, no decrease in ejection fraction was seen following verapamil. In a study using equilibrium gated radionuclide ventriculography, Klein et al. (1983) demonstrated that intravenous verapamil induces rapid and transient changes in the circulatory system in the first few minutes after its injection. They observed that the short term effect of verapamil is time-related, dose-dependent and related to the baseline functional reserve of the left ventricle. In 20 patients with ejection fraction > 35%, 0.1 mg/kg verapamil over 60 to 90 seconds had a biophasic effect: an initial, transient decrease in ejection fraction, accompanied by increased left ventricular volumes and cardiac output. Subsequently there was an overshoot of ejection fraction above control values, accompanied by a decrease in peripheral vascular resistance and marked decreases in left ventricular volumes, while cardiac output remains slightly elevated. Interestingly, in a smaller group of patients with ejection fraction < 35%, only the first effect on ejection fraction was seen. In 10 patients with ejection fraction > 35%, verapamil 0.06 to 0.075 mg/kg exerted qualitatively similar but milder effects on haemodynamic parameters. Finally, verapamil 0.1 mg/kg given more slowly, over 120 to 150 seconds, produced no significant changes in ejection fraction or left ventricular volumes in another 8 patients. The authors concluded that verapamil in the doses and duration of injection used commonly in various clinical situations, indeed depresses left ventricular function. Administration of a bolus is followed by a series of interrelated and varying haemodynamic results, which depend in part on the underlying cardiovascular state of the patient. The most important overall effect of verapamil on the vascular system as a whole appears to be an improvement in function, brought about by afterload reduction and by a sympathetically mediated increase in myocardial contractility. The earlier concepts which maintained that administration of verapamil produces pronounced negative inotropic effects even in normal hearts have been largely abandoned in view of later extensive evidence to the contrary.

It is still believed that the drug should be given with great caution to patients with a significantly impaired left ventricular function. However, preliminary reports have indicated that congestive heart failure is not an absolute contraindication to verapamil use, certainly when it occurs in the setting of supraventricular tachycardias. Ferlinz and Citron (1983) have studied the effect of intravenous verapamil in 14 patients with congestive heart failure at doses of 0.1 mg/kg as a bolus and 0.005 mg/kg/min as an infusion. Ejection fraction increased from 29 to 37% and Vcf from 0.45 to 0.64 circ/sec (fig. 12). No evidence was found that verapamil exacerbates left ventricular asynergy, with 89% of all asynergic segments improving or remaining the same after its administration and only 11% deteriorating further (fig. 13). Concomitantly, verapamil markedly lowered mean aortic pressure and systemic vascular resistance, without significant changes in heart rate, LVEDP or PCWP. Thus, the authors concluded that the intrinsic negative inotropic effect of intravenous verapamil in ther-

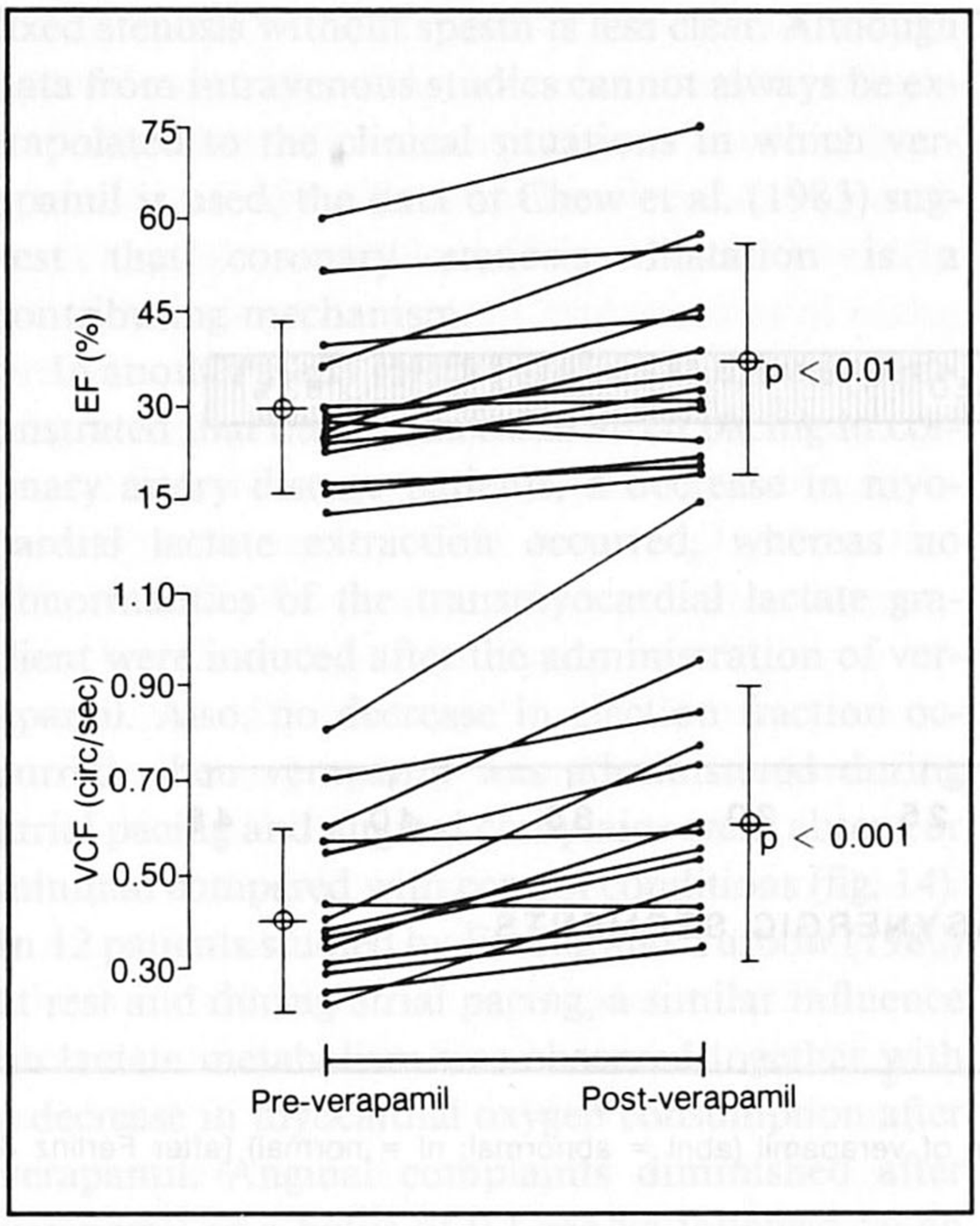


Fig. 12. Effect of verapamil on left ventricular ejection fraction (EF) and mean velocity of circumferential fibre shortening (Vcf) in patients with congestive heart failure (from Ferlinz & Citron 1983a; with permission).

apeutic doses generally does not represent a serious drawback, even in patients with congestive heart failure. Its potent unloading vasodilatory properties more than compensate for any intrinsic decrease in left ventricular contractility, and can actually improve overall cardiac function. At higher doses of verapamil, i.e. 0.145 mg/kg as a bolus followed by 0.005 mg/kg/min as an infusion, Chew et al. (1981) found in 3 patients with coronary artery disease that the mean arterial pressure decreased markedly together with the stroke volume index and that the PCWP abruptly increased. All of these patients had a PCWP > 20mm Hg prior to the administration of verapamil, and each developed clinical heart failure once the drug was injected. This last observation stresses the fact that higher doses of verapamil must be employed with great caution. Further investigations need to be performed to determine at which dosage verapamil can be safely administered to patients with overt congestive heart failure.

2.3.3 Effects During Exercise and Pacing Stress Tests

Verapamil, like diltiazem but unlike nifedipine, has a powerful depressant effect on atrioventricular nodal conduction. This has constituted a technical problem for studies attempting to investigate anti-anginal effects of verapamil by atrial pacing. In 8 patients, Hecht et al. (1981) using radionuclide ventriculography demonstrated that regional wall motion abnormalities and a reduced ejection fraction which appeared during angina pectoris induced by atrial pacing, could be prevented by the administration of intravenous verapamil. Verapamil in an intravenous bolus of 0.145 mg/kg followed by an infusion of 0.005 mg/kg/min also prevented the exercise-induced increase in PCWP. Using a similar intravenous verapamil regimen, Zygelman et al. (1981) observed lower arterial blood pressure and systemic vascular resistance and a diminished maximal dP/dt during spontaneous rhythm as well as during atrial pacing in 8 patients. LVEDP became slightly elevated during sinus rhythm after the administration of verapamil but remained unchanged during pacing, as did the cardiac output. Patton et al. (1984) administered a total of 0.2 mg/kg using a 0.1 mg/kg bolus followed by an infusion of 0.01 mg/kg/min and found no effect on exercise-induced increases in LVEDP or cardiac index in patients with coronary artery disease undergoing mild exercise. In 13 patients with stable effort angina, Sadick et al. (1982) studied the effect of intravenous verapamil, 0.1 mg/kg as a bolus followed by a 0.005 mg/kg/min infusion, on exercise haemodynamics and left ventricular function. Radionuclide ventriculography and haemodynamic measurements were performed at 50% (level 1) and 80% (level 2) of the patients' maximal exercise capacity. No patient had angina during level 1 and all patients had angina at level 2 during the control exercise test. During exercise, at identical workloads, verapamil increased cardiac index and decreased PCWP and systemic vascular resistance at level 1 and level 2. Left ventricular ejec-

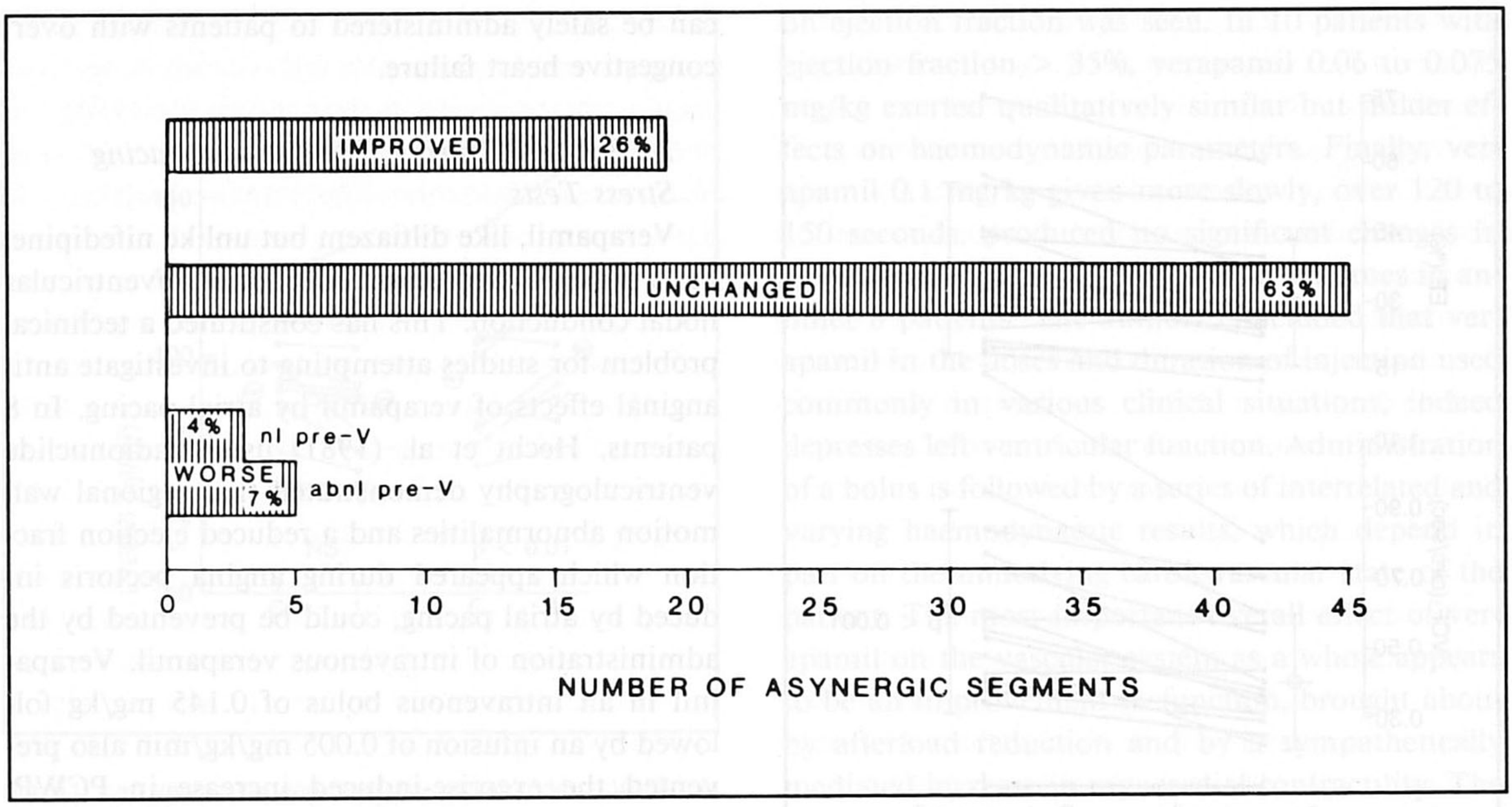


Fig. 13. Changes in left ventricular contractility after administration of verapamil (abnl = abnormal; nl = normal) [after Ferlinz & Citron 1983; with permission].

tion fraction was the same at level 1 of both the control exercise test and the exercise test during verapamil administration, but increased from 55% to 64% at level 2. Since the end-diastolic volume remained unchanged, this important beneficial effect was essentially due to a reduction of exercise-induced increase in end-systolic volume. The authors concluded that verapamil partially prevents the disproportionate rise in end-systolic volume observed during ischaemia.

2.3.4 Coronary Haemodynamic Effects

Luebs et al. (1966), using myocardial clearance of rubidium as an index of coronary blood flow, found that intravenous verapamil increased coronary blood flow in patients without coronary artery disease but not in patients with coronary artery disease. More recently, Chew et al. (1983) studied the effect of intravenous verapamil on coronary haemodynamics and on coronary artery calibre with particular reference to changes in large vessel cross-sectional area and stenosis flow resistance as measured by quantitative coronary angiography. After the administration of 0.145 mg/kg verapamil as an intravenous bolus followed by an infusion of 0.005 mg/kg/min, coronary vascular resistance decreased by 24% together with a small but non-significant increase in coronary sinus blood flow. No significant change in myocardial oxygen consumption was found. 50% of normal as well as diseased coronary segments dilated significantly after verapamil. Stenosis dilatation resulted in an average 14% reduction in estimated flow resistance. In a subgroup of patients, the luminal changes induced by verapamil were compared with those induced by sublingual glyceryl trinitrate. Glyceryl trinitrate induced a significantly greater increase in coronary calibre in both normal and diseased segments. Estimated stenosis flow resistance decreased 28% with glyceryl trinitrate compared with 14% with verapamil. The finding that intravenous verapamil reduces coronary vascular resistance and dilates both diseased and normal coronary vessels probably explains its beneficial effects in patients with vasospastic disorders. The mechanism of its beneficial action in patients with angina due to a

fixed stenosis without spasm is less clear. Although data from intravenous studies cannot always be extrapolated to the clinical situations in which verapamil is used, the data of Chew et al. (1983) suggest that coronary stenosis dilatation is a contributing mechanism.

In another study (Hecht et al. 1981), it was demonstrated that during maximal atrial pacing in coronary artery disease patients, a decrease in myocardial lactate extraction occurred, whereas no abnormalities of the transmyocardial lactate gradient were induced after the administration of verapamil. Also, no decrease in ejection fraction occurred when verapamil was administered during atrial pacing and anginal complains were absent or minimal compared with control conditions (fig. 14). In 12 patients studied by Ferlinz and Turbow (1980) at rest and during atrial pacing, a similar influence on lactate metabolism was observed together with a decrease in myocardial oxygen consumption after verapamil. Anginal complaints diminished after verapamil as a bolus of 0.1 mg/kg followed by an infusion of 0.005 mg/kg/min although coronary sinus blood flow at rest, and during pacing, had decreased.

Zygelman et al. (1981) observed no change in coronary blood flow at rest but a decreased flow during atrial pacing with verapamil at 0.10 or 0.17 mg/kg as a bolus and 0.005 mg/kg/min as an infusion. Myocardial oxygen consumption was reduced at rest and during atrial pacing. After verapamil administration, an increased extraction of lactate was found during pacing. Despite different doses of verapamil, the data from these authors indicate that intravenous administration usually decreases myocardial oxygen consumption with or without a consistent decrease in coronary sinus blood flow.

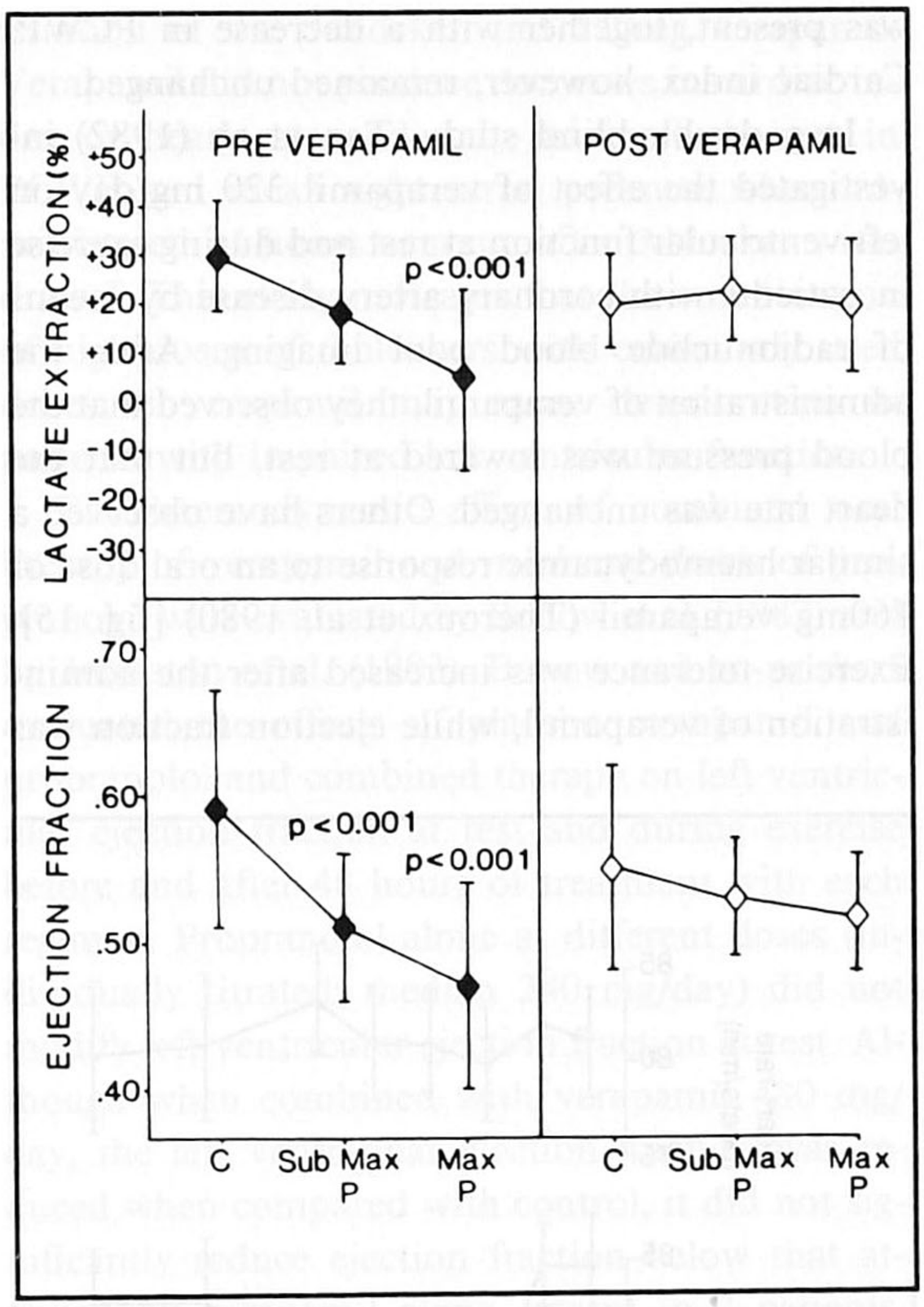


Fig. 14. Comparison of the changes (mean ± SD) in myocardial lactate extraction in left ventricular function before and after verapamil infusion during coronary sinus pacing in patients with coronary artery disease. Verapamil abolishes the abnormalities of lactate extraction and prevents the significant reduction of the ejection fraction at submaximal as well as maximal coronary sinus pacing rates: Max P = maximal pacing; Sub Max P = submaximal pacing (from Hecht et al. 1981; with permission).

2.4 Haemodynamic Effects after Oral Administration (Central and Systemic)

Rouleau et al. (1983) evaluated the influence of a single oral dose of verapamil on left ventricular function in coronary artery disease patients. There was no significant change in heart rate, PCWP or cardiac index at 75 to 90 minutes after doses of 80 or 120mg verapamil. Mean arterial pressure and stroke work index decreased after both doses. Systemic vascular resistance and arterial diastolic pressure decreased significantly only after the 120mg dose. During pacing at heart rates of 90 and 110 beats/min, no major changes in systemic haemodynamics were observed after 80mg verapamil, except for a lower arterial pressure at 90 beats/min and a lower stroke work index at 110 beats/min. Changes were more pronounced after 120mg verapamil. A significant decrease in arterial pressure at pacing rates of 90 and 110 beats/min

was present, together with a decrease in PCWP. Cardiac index, however, remained unchanged.

In a double-blind study, Tan et al. (1982) investigated the effect of verapamil 320 mg/day on left ventricular function at rest and during exercise in patients with coronary artery disease by means of radionuclide blood pool imaging. After the administration of verapamil, they observed that the blood pressure was lowered at rest, but that the heart rate was unchanged. Others have observed a similar haemodynamic response to an oral dose of 160mg verapamil (Theroux et al. 1980) [fig. 15]. Exercise tolerance was increased after the administration of verapamil, while ejection fraction was maintained at the resting level. In contrast, the control group experienced a fall in ejection fraction together with an increase in end-systolic volume during exercise. Josephson et al. (1981) studied the effects of verapamil 480 mg/day on resting and exercise left ventricular function and observed that verapamil reduced the number of exercise-induced regional wall motion abnormalities and the degree of exercise-induced reduction in ejection fraction. In contrast, Leon et al. (1980) observed a decrease in resting ejection fraction from 48% to 44% after the same dose of verapamil, although the placebo treated patients behaved similarly. The same group (Bonow et al. 1982) also studied the influence of oral verapamil on left ventricular diastolic filling in patients with coronary artery disease. Heart rate and ejection fraction decreased after verapamil administration, although the peak filling rate increased. They postulated that the improvement in left ventricular diastolic filling may be partly responsible for the symptomatic improvement during verapamil therapy.

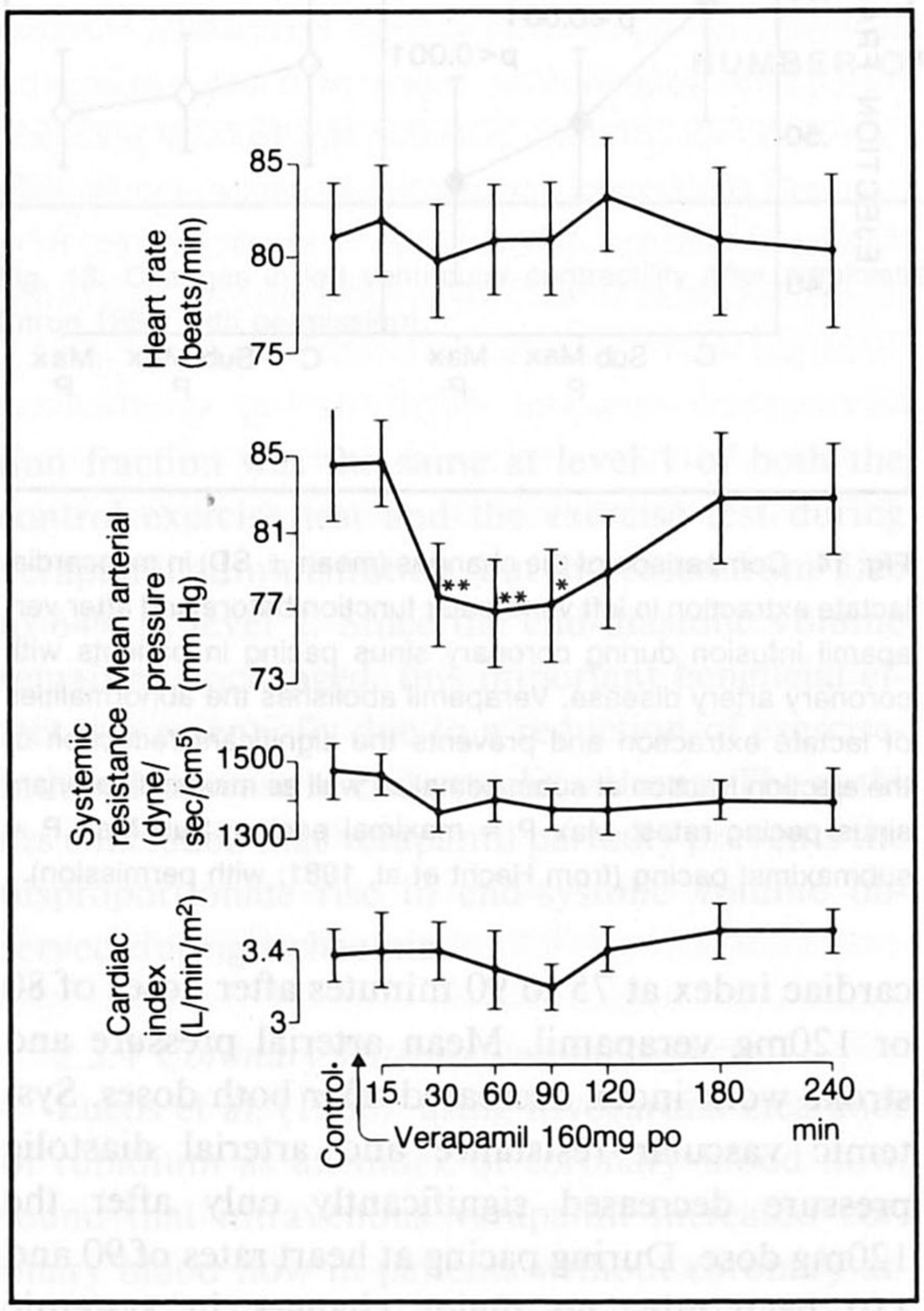


Fig. 15. Mean haemodynamic effects (± SEM) of 160mg verapamil in 10 patients. Heart rate decreases by 2% (NS) while mean arterial blood pressure decreases by 9% ($p < 0.01$). Cardiac index is unchanged and systemic vascular resistance decreases by 7% (NS). The p value was calculated by Student's t-test modified for multiple comparisons: * $p < 0.05$; ** $p < 0.001$ (from Theroux et al. 1980; with permission).

2.5 Haemodynamic Effects of Verapamil in Combination with β-Adrenoceptor Blockers

Seabra-Gomes et al. (1976) compared the effect of administering intravenous practolol, verapamil and a combination of the 2 drugs, both at doses of 0.1 mg/kg, in patients with coronary artery disease. With heart rate controlled by atrial pacing, administration of verapamil intravenously after practolol resulted in a decrease in maximal left ventricular dP/dt and cardiac index. Practolol alone did not influence haemodynamics when bradycardia was abolished by pacing, and the effect of verapamil alone was a reduction in maximal dP/dt. The authors therefore recommended caution with the combination of these drugs in patients with impaired myocardial function. In patients with supraventricular tachycardia, pronounced hypotension has occurred after intravenous verapamil in patients on long term β-blocker therapy. The additive depressant effect of verapamil and β-blockers on atrioventricular conduction must also be considered in the use of this combination.

Kieval et al. (1982) evaluated the haemodynamic effects of intravenous verapamil in 20 patients with chronic stable angina, all with ejection fractions greater than 40%, who had been treated with an average dose of 160mg propranolol daily. The patients received verapamil intravenously at doses of 0.025, 0.05 or 0.1 mg/kg given over 2 minutes followed by an infusion of 0.005 mg/kg/min for a maximum of 60 minutes. A substantial decrease in mean arterial pressure was accompanied by a significant reduction in systemic vascular resistance. Despite this unloading effect, simultaneous increases in cardiac index, mean Vcf and ejection fraction did not occur. Interestingly, maximal dP/dt also remained unchanged. In a similar study, Reddy et al. (1984) studied the short term effects of intravenous verapamil in patients undergoing cardiac catheterisation. All 19 patients had been on oral propranolol therapy and none had clinical evidence of left ventricular failure. In 6 patients, no evidence of organic heart disease was found. Similar doses of verapamil as used by Kieval and colleagues were given. Despite significant afterload reduction there was again no resultant increase in various indices of left ventricular function. This lack of improvement in the indices of left ventricular function suggests an interaction between the two drugs, which may be of importance in patients with evidence of depressed myocardial performance.

Several recent reports have investigated combined oral administration of verapamil and propranolol or metoprolol. Packer et al. (1982) described the haemodynamic effects of the oral administration of different doses of verapamil in 15 patients with severe angina pectoris pretreated with *high* doses of propranolol (mean 502 mg/day) or metoprolol (400 mg/day). At doses of 40 and 80mg, systemic vascular resistance, stroke volume index and mean PCWP showed no significant changes. With 120mg of verapamil, significant decreases in mean arterial pressure, cardiac index (-0.38 L/min/m^2) and heart rate were accompanied by a significant decline in stroke volume index and increases in PCWP. Two patients developed asymptomatic hypotension during administration of the β-blocker and 120mg verapamil. Verapamil did not produce decreases in cardiac index or heart rate and only minimal changes in PCWP and mean right atrial pressure when administered 24 hours or more after β-blocker withdrawal. This study indicates that the combination of high doses of β-blockers with commonly used doses of verapamil may cause deterioration in patients with impaired left ventricular function.

The haemodynamic effect of combined oral therapy of verapamil and *moderate* doses of propranolol were evaluated by Bonow et al. (1982) and by Johnston et al. (1983). Bonow and co-workers evaluated the effects of placebo, verapamil and propranolol and combined therapy on left ventricular ejection fraction at rest and during exercise before and after 48 hours of treatment with each regimen. Propranolol alone at different doses (individually titrated; median 240 mg/day) did not modify left ventricular ejection fraction at rest. Although when combined with verapamil 480 mg/day, the left ventricular ejection fraction was reduced when compared with control, it did not significantly reduce ejection fraction below that attained by verapamil alone, except in 2 patients. Verapamil and combined verapamil/propranolol treatment did reduce the magnitude of decrease in ejection fraction from rest to exercise. This study shows that changes in left ventricular function observed after verapamil treatment are not exaggerated when moderate doses of a β-blocker are used concomitantly.

However, it is apparent that in individual patients, left ventricular function can become significantly impaired during combined therapy. With the use of equilibrium radionuclide ventriculography, Johnston et al. (1983) compared the effects on left ventricular function of 360mg verapamil and 160mg propranolol alone and in combination in 18 patients with chronic exertional angina and normal or mildly impaired left ventricular function. Verapamil, but not propranolol, caused a reduction in myocardial contractility, as shown by an increase in end-systolic volume and a decrease in the peak systolic pressure/end-systolic volume index ratio. Combination therapy with moderate doses of pro-

pranolol and verapamil did not cause additive myocardial depressant effects. Using normalised regional ejection fraction, Johnston et al. (1983) also showed that both propranolol and the combination of verapamil and propranolol improved the function of hypokinetic LV segments at rest.

During exercise, a significant improvement in exercise-induced hypokinesis occurred only with the combination therapy and this was associated with a significant reduction in the rate-pressure product compared with propranolol alone. During exercise-induced ischaemia, a highly significant increase in end-systolic volumes was demonstrated in patients taking placebo. Only the combination therapy significantly improved exercise LV function, and in so doing appeared to be superior to therapy with verapamil and propranolol alone. Combination therapy was associated with an additional decrease in the rate-pressure product, implying a reduction in myocardial oxygen demand. While Johnston and colleagues noted that combined therapy may improve exercise left ventricular function, all previous studies indicate that, despite its vasodilating properties, verapamil does not improve cardiac performance at rest (as can usually be seen with nifedipine) when added to β-blocker treatment. However, only patients with relatively well preserved left ventricular function were included in the study.

Since Chew et al. (1981) showed that verapamil alone can cause deterioration in patients with impaired left ventricular function (ejection fraction below 30%, or PCWP higher than 20mm Hg), one must advise against the use of combined β-blocker/verapamil therapy in this subset of patients.

3. Diltiazem

3.1 Clinical Pharmacology

In an early study of diltiazem, Kinney et al. (1981) reported that 30mg of the orally administered drug produced barely measurable plasma concentrations while 60, 90 and 120mg doses resulted in progressively larger areas under the plasma drug concentration *versus* time curve. Preliminary studies in dogs (Browne et al. 1983) and humans (Taeymans et al. 1982) suggest that diltiazem plasma concentrations are related to both the haemodynamic and electrophysiological effects of the drug. Daily dosage of 180 to 360mg administered in 3 to 4 divided doses is recommended. In contrast to verapamil and nifedipine, its excretion is primarily hepatic. Adverse effects are uncommon and include headache, dizziness, flushing, gastrointestinal disturbances and skin rash.

3.2 Haemodynamic Effects after Intracoronary Administration

The effect of intracoronary diltiazem was analysed by Bertrand et al. (1982) in 12 patients with coronary artery disease. Five patients received 0.15 mg/kg diltiazem into the left coronary artery and 7 patients received 0.05 mg/kg. After the 0.15 mg/kg injection, heart rate was unchanged but mean aortic pressure immediately fell. Coronary sinus blood flow was augmented and remained increased for 10 minutes after the injection. Coronary vascular resistance fell significantly and remained lower until 5 minutes after injection. Myocardial oxygen consumption was decreased at 3 minutes but was unchanged at 5 and 10 minutes. The effects of 0.05 mg/kg diltiazem were less pronounced. Coronary sinus blood flow had already returned to the control value at 3 minutes. The maximal rise in coronary flow was only 23% after the low dose and 47% after the higher dose.

The effects of intracoronary injection of 1mg diltiazem on left ventricular pressures, echocardiographic fractional shortening, and coronary sinus saturation were studied by Kober et al. (1982) and compared with the intravenous effect of 10mg diltiazem. Intracoronary administration of the drug did not affect systolic and end-diastolic pressures. Peak positive dP/dt remained unchanged while peak negative dP/dt decreased transiently. The ejection phase indices derived from echocardiographic measurements were not influenced by the drug. A pronounced but short-lasting effect (5 minutes) on coronary sinus oxygen saturation was observed.

3.3 Haemodynamic Effects after Systemic Parenteral Administration

3.3.1 Central and Systemic Haemodynamic Effects

The findings of 5 studies are summarised in table I. Following intravenous infusion of diltiazem 0.03 mg/kg/min in patients with coronary artery disease, Bourassa et al. (1980) observed a slight but insignificant decrease in aortic pressure. Systemic vascular resistance, however, decreased 20%. 15 minutes after cessation of drug administration, the fall in blood pressure persisted and heart rate, which had remained unchanged during the infusion, began to decrease. LVEDP and cardiac index were unchanged during diltiazem administration.

At the end of a 5-minute infusion of 0.06 mg/kg/min in patients with coronary disease, Biamino et al. (1982) observed an increase in heart rate and cardiac output together with a sharp decrease in blood pressure and total peripheral resistance. Left ventricular filling pressure increased concomitantly and dP/dt/P was reduced. Following these initial changes, heart rate decreased below the initial values, while the reduction in blood pressure and peripheral resistance persisted over a 15-minute period. These authors concluded that the temporary increase in left ventricular filling pressure could reflect a negative inotropic effect of the drug. However, this effect was counterbalanced by a reduction in afterload. Increases in cardiac output combined with a fall in mean arterial pressure and systemic vascular resistance after 0.20 to 0.25 mg/kg intravenous diltiazem have been observed by others (Kenny et al. 1982; Koiwaya et al. 1982).

Serruys et al. (1984) studied the effect of intravenous diltiazem 0.1 mg/kg/min for 5 minutes on left ventricular volumes in patients with coronary artery disease. While the end-diastolic volume index remained unchanged, the end-systolic volume index decreased by 7%. Ejection fraction after diltiazem tended to increase, but the observed slight change was not significant. Circumferential fibre shortening rate remained unchanged, despite a reduction in peripheral vascular resistance by 23%.

In a recent study of 22 patients with coronary artery disease (Dash et al. 1985), 0.25 mg/kg diltiazem was given as a bolus followed by a continuous infusion of 0.0014 mg/kg/min increased as necessary to maintain a fall in mean arterial pressure of approximately 10% from baseline. Haemodynamics and left ventricular function during ventriculography were recorded. The decrease in blood pressure was accompanied by a decrease in heart rate (−6.8%) and increases in cardiac index (+8.8%) and global ejection fraction (+9.1%). Significant in-

Table I. Acute haemodynamic effects of intravenous diltiazem in patients with coronary artery disease

References	Dose	HR	MAP	SVR	CO
Biamino et al. (1982)	0.06 mg/kg/min for 5 min	↓	↓	↓	↓
Bourassa et al. (1980)	0.03 mg/kg/min for 10 min	↔	↔	↓	↔
Dash et al. (1985)	0.25 mg/kg followed by 0.0014 mg/kg[a]	↓	↓	↓	↓
Koiwaya et al. (1982)	0.2 mg/kg bolus	↔	↓	↓	↑
Serruys et al. (1982)	0.1 mg/kg for 5 min	↔	↓	↓	

a Increased as necessary to maintain 10% fall in MAP.

Abbreviations: HR = heart rate; MAP = mean arterial pressure; SVR = systemic vascular resistance; CO = cardiac output; ↑ = increase; ↔ = no change; ↓ = decrease.

creases in regional ejection fractions occurred in 53% of hypokinetic areas supplied by diseased arteries compared with 13% of normokinetic areas supplied by diseased arteries. The increase in regional ejection fraction did not occur at the expense of normokinetic areas as regional ejection fraction did not decrease in the latter. More rapid local left ventricular relaxation, afterload reduction and improvement of myocardial function in asynergic areas by changes in blood flow, calcium metabolism or ATP utilisation were considered as possible explanations for the findings. The beneficial effect of diltiazem was evidenced by a decrease in the time constant of relaxation by 14.3%. A negative inotropic effect was evidenced by an increase in LVEDP and left ventricular end-diastolic volume and a decrease in the left ventricular end-systolic pressure-volume ratio. The main conclusions were that diltiazem in a dose producing a plasma concentration of 154 ± 12 μg/L produced a negative chronotropic effect with improvement in regional wall motion abnormalities in coronary artery disease patients. The improvement was associated with improved left ventricular relaxation. Global indices of left ventricular systolic performance were favourably influenced, despite a mild negative inotropic effect.

Joyal et al. (1985) using the same bolus and infusion doses of diltiazem, but not increasing the infusion rate to maintain the fall in mean arterial pressure, achieved lower serum diltiazem concentrations of 136 ± 30 μg/L. They observed no change in heart rate and no negative inotropic effects in their 18 patients with angina pectoris, and found favourable alterations in indices of myocardial oxygen supply and demand.

3.3.2 Effects During Atrial Pacing

Joyal et al. (1983) studied 10 patients with exercise-induced angina using atrial pacing to control heart rate. Systolic blood pressure, heart rate, LVEDP and cardiac output were measured before and after diltiazem (0.25 mg/kg as a bolus and 0.0014 ng/kg/min as an infusion) at rest and during pacing-induced angina. At rest, diltiazem decreased heart rate by 4.5 beats/min and systolic blood pressure by 20mm Hg without altering LVEDP and cardiac output. At the angina threshold, before and after diltiazem, heart rate, LVEDP and cardiac output were not significantly altered, but systolic blood pressure and the pressure-heart rate product were both 10% lower after diltiazem.

Fernandez et al. (1983) observed that diltiazem prevented the pacing-induced increase in LVEDP. During the control pacing stress test, left ventricular volume remained unchanged, while a decrease in end-diastolic volume was observed after diltiazem.

3.3.3 Coronary Haemodynamic Effects

Bertrand et al. (1982) studied the coronary haemodynamic effects of an infusion of 0.15 mg/kg diltiazem over 2 minutes, followed by an infusion of 0.05 mg/kg over 8 minutes. A transient increase by 14% was noted in coronary blood flow during the first minute of the infusion. At 3.5 or 10 minutes, coronary blood flow was unchanged compared with baseline values. However, there was a significant fall in the calculated coronary vascular resistance during the first 5 minutes of the infusion. As expected, these changes were not as marked as those observed after intracoronary injection of an identical bolus dose of 0.15 mg/kg; after intracoronary injection, coronary blood flow increased by more than 20% together with a reduction in coronary vascular resistance of 40%.

Bourassa et al. (1980) observed a decrease in coronary vascular resistance without significant changes in coronary blood flow, following diltiazem 0.3 mg/kg/min as an infusion. Myocardial oxygen consumption, on the other hand, was not altered significantly since the product of coronary blood flow and left ventricular oxygen extraction did not change. Using the argon method for measuring coronary blood flow, Biamino et al. (1982) observed that intravenous diltiazem 0.3 mg/kg over 5 minutes produced a slight decrease in coronary blood flow which, when combined with a narrowed aortocoronary sinus oxygen difference, resulted in a significant reduction in myocardial consumption.

Fernandez et al. (1983) studied the coronary

haemodynamic effects of 0.2 mg/kg intravenous diltiazem in patients with coronary artery disease. Coronary blood flow and coronary vascular resistance remained unchanged after diltiazem administration as well at rest as during exercise. However, the aortocoronary sinus oxygen difference and hence myocardial oxygen consumption decreased, together with an increase in the aortocoronary sinus lactate difference. Joyal et al. (1983) did not observe changes in coronary blood flow at rest or at angina threshold in 10 patients with exercise-induced angina after intravenous diltiazem. Similar results were obtained by Serruys et al. (1984). 19 patients with chest pain were studied at the time of cardiac catheterisation. Measurements were performed in a control state before diltiazem and 2 minutes after infusion of 0.5 mg/kg diltiazem over 5 minutes. After diltiazem infusion, coronary sinus blood flow and great cardiac vein blood flow remained unchanged. As the mean aortic pressure decreased from 107 to 74mm Hg after diltiazem, the global and regional coronary vascular resistance diminished by 25% and 33%, respectively. A significant decrease in aortocoronary sinus oxygen difference without an increase in coronary sinus blood flow resulted in a significant decrease in myocardial oxygen consumption.

In patients with coronary artery disease, intravenous doses of 20 or 30mg diltiazem have both been shown in one study to dilate normal epicardial, atherosclerotic and spastic coronary arteries and collaterals (Bonzel et al. 1986). In another study, of 13 patients with coronary artery disease, a 0.25 mg/kg bolus followed by a 0.003 mg/kg/min infusion of diltiazem prevented the sympathetically-mediated constriction of normal and diseased epicardial coronary arteries in humans during isometric handgrip exercise (Hossack et al. 1984). This manoeuvre induces coronary vasoconstriction by an α-sympathetic effect and diltiazem probably prevents this by blockade of receptor-activated calcium slow channels.

From the above investigations it can be concluded that diltiazem tends to decrease myocardial oxygen consumption. Increased oxygen delivery appears to be of less importance in the prevention of exercise-induced angina by diltiazem.

3.4 Haemodynamic Effects after Oral Administration

3.4.1 Central and Systemic Effects

The haemodynamic effects of oral diltiazem (120mg) were investigated in 6 volunteers at rest, in various orthostatic conditions, and while under psychological stress (Magometschnigg et al. 1981). Under all conditions diltiazem showed a vasodilating effect that was more pronounced on the arterial resistance vessels than on the pulmonary vessels.

Oral doses of diltiazem 30mg 3 times daily caused a significant decrease in stroke volume, cardiac output, and stroke work in patients with coronary artery disease (Kusakawa et al. 1977). Systemic vascular resistance and heart rate were not lowered. Because the decrease in end-diastolic volume occurred with a decrease in stroke volume in their radionuclide studies, Kusakawa et al. concluded that a decrease in venous return was responsible for the observed changes. In patients with coronary artery disease, Kinoshita et al. (1979) found a significant decrease in heart rate, blood pressure, cardiac work index, and rate-pressure product 90 minutes after a 60mg oral dose of diltiazem, while total systemic resistance was not altered. These changes, however, were not present during exercise. In patients with coronary artery disease, Rosenthal et al. (1980a) observed only a decrease in diastolic blood pressure of 9mm Hg at 6 hours after a dose of 120mg.

Theroux et al. (1980) administered a single oral dose of 120mg to patients following an acute myocardial infarction and observed that heart rate and mean arterial pressure decreased significantly, although there was no significant change in cardiac index or systemic vascular resistance (fig. 16). Hossack & Bruce (1981) administered diltiazem to 10 patients with coronary disease and found that it was effective in increasing the total duration of exercise and the time to the onset of angina. These effects were most marked with a dose of 240 mg/

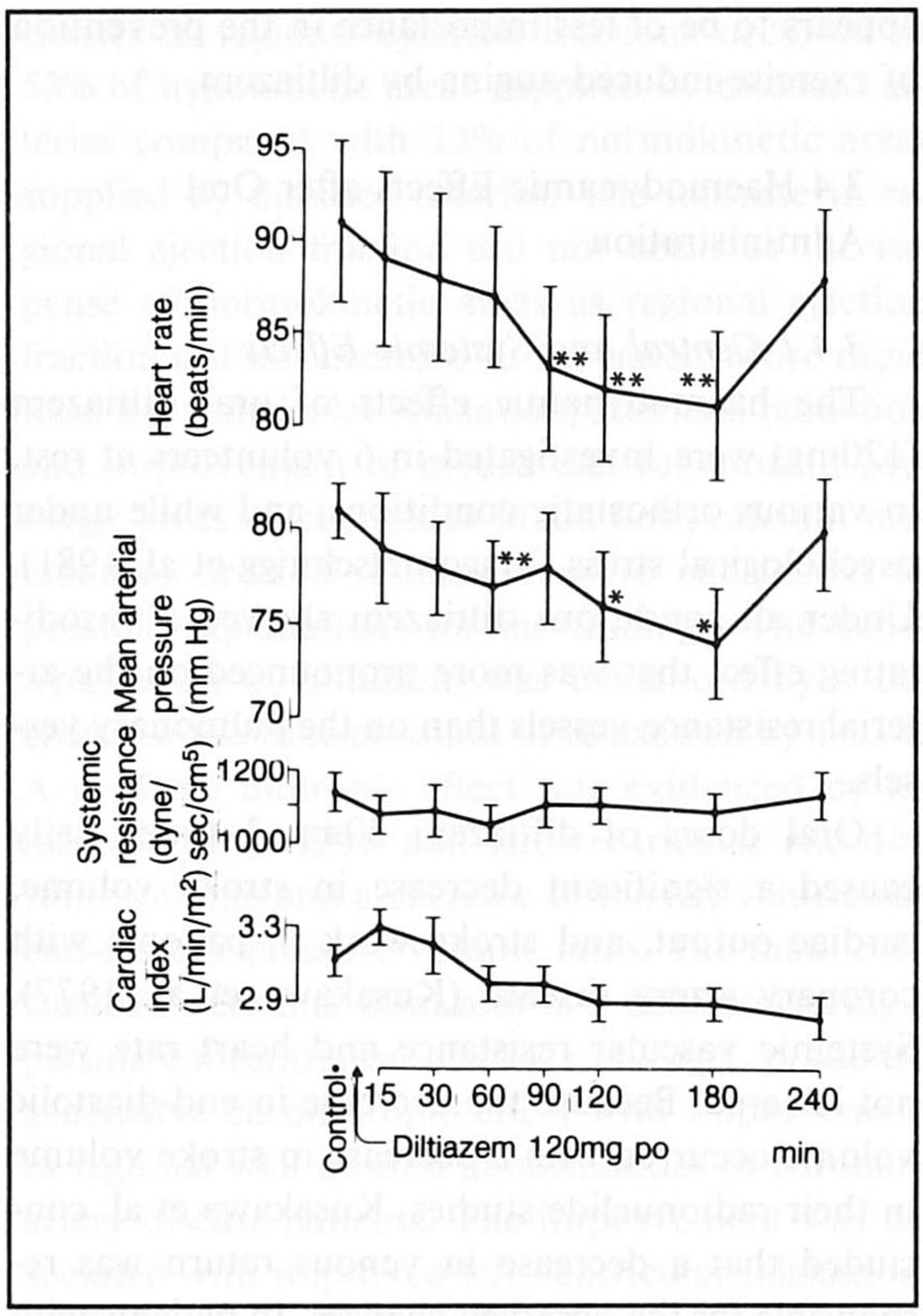


Fig. 16. Mean haemodynamic effects (± SEM) of 120mg diltiazem in 12 patients. Heart rate decreases by 10 % ($p < 0.01$) while mean arterial blood pressure decreases by 7% ($p < 0.01$). Cardiac index decreases by 6% (NS) and systemic vascular resistance decreases by 7% (NS). The p value was calculated by Student's t-test modified for multiple comparison: $*p < 0.05$, $**p < 0.001$ (from Theroux et al. 1980; with permission).

day. Heart rate was reduced at rest and during submaximal exercise. There was no change in systolic blood pressure, while diastolic pressure was reduced during submaximal exercise but not at maximal exercise. Similar effects of diltiazem on exercise performance were reported by Low et al. (1981). These authors used doses of 120, 180 and 240mg in a placebo-controlled crossover trial. They observed a fall in heart rate with diltiazem but no change in the rate-pressure product. Nevertheless, diltiazem had a clear antianginal effect which was accompanied by a greater ejection fraction at rest during treatment when compared with placebo.

3.4.2 Coronary Haemodynamic Effects

Oral diltiazem, 120mg every 8 hours, has been shown angiographically to either prevent ergonovine-induced coronary vasospasm or to increase the dose of ergonovine necessary to provoke vasospasm in 22 of 27 patients with documented Prinzmetal's variant angina (Waters et al. 1981). Furthermore, the ability of diltiazem to reduce provocable vasospasm during angiography was effective in predicting the subsequent clinical efficacy of the drug in these patients. Others have demonstrated that oral diltiazem is effective in preventing episodes of vasospasm both in patients with Prinzmetal's variant angina (Pepine et al. 1981; Rosenthal et al. 1980b) and in patients with exercise-induced vasospasm (Yasue et al. 1978, 1979).

3.5 Haemodynamic Effects of Diltiazem in Combination with β-Adrenoceptor Blockers

Hung et al. (1983) compared the effect of oral diltiazem and propranolol, alone and in combination, on exercise performance and left ventricular function in 12 patients with stable effort angina. Patients performed a symptom-limited exercise test while undergoing equilibrium-gated radionuclide scanning after 2-week periods of 90mg diltiazem 4 times daily, 60mg propranolol 4 times daily, a combination of 90mg diltiazem and 60mg propranolol 4 times daily, and placebo. Compared with placebo, heart rate and rate-pressure product at a fixed submaximal workload were decreased after diltiazem but were unchanged at peak effort. Heart rate and the rate-pressure product at both submaximal and peak effort were decreased by propranolol and were decreased further by the combination of diltiazem and propranolol. Diltiazem or propranolol alone and in combination significantly increased exercise duration. The mean resting left ventricular ejection fraction during placebo was 59%. The mean exercise left ventricular ejection fraction was higher during diltiazem (59%) than during placebo (52%), propranolol (53%) or the combination of diltiazem and propranolol (55%), and the difference was most significant at the submaximal exercise stage (placebo 55% *vs* diltiazem

64%). The study demonstrated that high-dose diltiazem does not produce significant left ventricular dysfunction and may actually improve systolic function. The combination of diltiazem and propranolol did not produce any clinically significant left ventricular dysfunction and the resting and exercise ejection fractions were in fact similar to those seen after propranolol alone. It must be stressed that patients with heart failure were excluded and that the combination of both drugs led to significant bradyarrhythmias or hypotension in 4 of the 12 patients.

Another study of diltiazem and propranolol was conducted as a crossover trial and investigated the frequency of angina attacks and maximal exercise duration (Strauss & Paris 1985). The combination of the maximally tolerated dose of diltiazem (up to 360mg daily) with propranolol in a dose to produce β-blockade was found to be superior to monotherapy with either drug. It is important to note that 1 patient who had tolerated both drugs alone developed congestive heart failure with combination therapy.

11 male patients taking various β-blockers were given an intravenous bolus of 0.25 mg/kg diltiazem over 2 minutes followed by an infusion of 0.005 mg/kg/min in a study by Kenny et al. (1985). All patients had coronary artery disease. Systemic vasodilatation and a reduction in heart rate resulted. During pacing-induced ischaemia, myocardial oxygen consumption was reduced and the pacing time to angina was prolonged with an improvement in myocardial lactate extraction. Patients with cardiac failure were again excluded. The authors concluded that diltiazem could be administered to patients receiving long term oral β-blockers without adverse haemodynamic effects and that combination therapy has significant beneficial effects in coronary artery disease. The reverse situation, in which intravenous propranolol 0.1 mg/kg was given to 12 patients on long term oral diltiazem (mean 243 mg/day), was studied by Wolfe et al. (1985). A control group of 10 patients who were not receiving diltiazem were also studied. Cardiac index, left ventricular peak dP/dt fell and LVEDP increased similarly in both the diltiazem and the control groups. Mean arterial pressure was unchanged. Coronary sinus blood flow, as assessed by thermodilution, decreased slightly in the diltiazem group and was unchanged in the control. Similar falls in heart rate and increases in atrio-His conduction occurred in both groups.

Thus diltiazem when added to the treatment of patients on β-blockers, unlike nifedipine, does not improve the indices of left ventricular function and may induce significant bradyarrhythmias and hypotension. Its use in combination with β-blocking agents requires further evaluation.

4. Conclusions: Comparative Haemodynamic Effects

This review of the recent literature on the calcium antagonists nifedipine, verapamil and diltiazem places particular emphasis on their haemodynamic actions, especially in patients with coronary artery disease. Between the 3 calcium antagonists, major differences in potency and tissue specificity are present in isolated tissue preparations (table II) and in the clinical setting in man (table III). This may indicate the existence of different types of slow channels or perhaps different surface binding properties of the drugs determining the extent to which each calcium antagonist antagonises slow channel calcium ion transport. Cal-

Table II. Relative potencies of nifedipine, verapamil and diltiazem on various cardiovascular functions studied in isolated tissue preparations[a]

	Nifedipine	Verapamil	Diltiazem
Negative chronotropic action	1	1	1/3
Negative inotropic action	1	1/13	1/40
Negative dromotropic action	1	1/2	1/2
Vasodilator action	1	1/12	1/26

a Ascertained from the addition of equimolar doses of the different Ca^{++} channel antagonists to isolated tissue preparations (from Ono et al. 1979; with permission).

Table III. Haemodynamic effects at rest of intravenous or sublingual nifedipine and intravenous verapamil and diltiazem[a]

	Nifedipine	Verapamil	Diltiazem
Heart rate	↑	↑/↔	↔/↓
Contractility	↑	↓	↔/↓
Preload	↔	↔	↔
Afterload	↓	↓	↓
Cardiac output	↑	↑/↔	↑/↔
Left ventricular ejection fraction	↑	↑/↔	↔
Coronary blood flow	↑	↔/↓	↔
Coronary vascular resistance	↓	↓	↓
Myocardial oxygen consumption	↔/↓	↓	↓

a Notations indicate most commonly reported changes *versus* control: ↑ = increase; ↓ = decrease; ↔ = no change. The first mentioned change is the one most commonly observed.

cium antagonists can influence cardiovascular haemodynamics by 3 primary actions: a direct negative inotropic effect; peripheral arterial vasodilatation; and coronary arterial vasodilatation. The net haemodynamic and electrophysiological effects of a given calcium antagonist are further influenced by reflex-mediated adrenergic activity.

Nifedipine appears to be the most potent arterial vasodilator of the currently available calcium antagonists. It causes profound afterload reduction of the left ventricle, resulting in increases in cardiac output and left ventricular ejection fraction. Furthermore, coronary blood flow has generally been found to increase at rest after nifedipine administration, contrasting with the changes found in coronary flow following verapamil and diltiazem. The intense reflex adrenergic activity induced by nifedipine masks its *direct* inhibitory effects on contractility. Increases in heart rate from stimulation of the sympathetic nervous system after nifedipine can in part be blocked by β-adrenoceptor blockers. After β-blockade, the intrinsic negative inotropic effect of nifedipine may become apparent but in most cases the cardiac output is maintained. This vasodilatation with maintenance of cardiac output at a lower heart rate makes the combination of nifedipine and β-blocking agents an attractive one in the treatment of coronary artery disease.

Although *verapamil* is also a potent vasodilator, its negative inotropic and dromotropic properties are more apparent than those of nifedipine in therapeutically used dosages. When used alone, reflex sympathetic activity usually offsets to a certain extent the negative inotropic effects of the drug, with no resultant change in cardiac output or ejection fraction. Associated decreases in peak dP/dt and increases in ventricular filling pressures occur which indicate some depressant effect on cardiac performance. Verapamil must therefore be employed with great caution in patients with congestive heart failure. A combination of verapamil and β-blockade, although providing more symptomatic relief than therapy with β-blockers or verapamil alone in some patients with angina pectoris, may be hazardous because of potential additive effects on myocardial contractility and sinoatrial and atrioventricular nodal function. The adverse effect on ventricular function is of particular importance in those with pre-existent impairment of left ventricular function. The data of different authors indicate that, at least after intravenous administration, a decrease in myocardial oxygen consumption with or without a decrease in coronary sinus blood flow is observed. Reduced oxygen demand after verapamil, as reflected in decreases in rate-pressure product in most studies after oral administration, appears to be a major mechanism of its antianginal effect. The rate-pressure product is decreased both by the fall in arterial pressure and by the decrease in heart rate induced by the effect of verapamil on cardiac pacemaker and conduction tissues.

The haemodynamic and electrophysiological effects of *diltiazem* appear to resemble those of verapamil more than those of nifedipine. Like verapamil, it inhibits sinoatrial and atrioventricular nodal function in clinically employed doses. The

effects on sinoatrial function seem even more pronounced than those observed after verapamil, since despite reflex-mediated adrenergic activity following a decrease in peripheral vascular resistance, a decrease in heart rate is often observed after intravenous administration of diltiazem – a finding infrequently seen after intravenous verapamil. Thus, a decrease in the rate-pressure product is observed after diltiazem, making decreased oxygen demand a likely and important mechanism of action in relieving angina pectoris. Like verapamil but unlike nifedipine, diltiazem does not appear to cause significant increases in coronary blood flow. Usually there is no improvement in ejectional and isovolumic indices of myocardial contraction after diltiazem administration, reflecting the intrinsic negative inotropic effect of the drug. This is presumably nullified by the salutary effect of afterload reduction.

Even though the current 'generation' of calcium antagonist drugs have varying effects on myocardial contractility, vasodilatation, and electrophysiological properties, they are all relatively nonspecific in their effects on the calcium channels of different tissues. This non-specificity often complicates their clinical utility in that the desired clinical effect may be compounded by an untoward physiological effect. There is a great deal of research in progress to synthesise newer, more selective, calcium antagonists that may affect the calcium channels in only one tissue type. In the next few years we will undoubtedly witness the introduction of a variety of new calcium antagonists with such specificity that will further improve the treatment of patients with cardiovascular disorders.

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