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Nifedipine effects in severe myocardial ischaemia in the dog due to left anterior descending coronary occlusion with left circumflex coronary artery constriction

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1 The effects of nifedipine were studied in a model of local myocardial ischaemia, comprising anaesthetized thoracotomized dogs in which a critical constriction of the left circumflex coronary artery (LCX) was combined with sudden occlusion of the left anterior descending coronary artery (LAD). Since more than one coronary artery is involved in ischaemic heart disease, the model seems to reflect the clinical situation very closely.

2 In this model, infusion of 1 $\mu g\,kg^{-1}\,min^{-1}$ nifedipine increased myocardial blood flow within the stenosed area served by the LCX as well as in the myocardial region supplied by the LAD, mainly in the subepicardium. Accordingly, the drug reduced ischaemic ST-segment elevation only in the epicardium.

3 It is suggested that nifedipine directed flow to the sub-epicardium of the ischaemic area by improving the collateral circulation. This redistribution of flow resulted in a decrease in the endo/epicardial flow ratio.

4 Nifedipine did not change the inhomogeneity of electrical activation indicating that it has no effect on the ischaemia-induced conduction delay. At the same time nifedipine was not able to reduce either the number of extrasystoles appearing in the early postocclusion and reperfusion phase or the incidence of ventricular fibrillation occuring mainly during reperfusion.

Introduction

The dihydropyridine derivative nifedipine is a potent coronary and systemic vasodilator in both isolated arteries and intact animals (Ekelund, 1978; Jolly *et al.*, 1981). It may also depress myocardial contractility and exert a negative chronotropic effect *in vitro* (Fleckenstein, 1977; Perez *et al.*, 1982). The action of the drug is attributed to an inhibition of the calcium influx into vascular smooth muscle cells and myocardial cells (Fleckenstein, 1977). However, in man and in conscious animals the cardio-depression is compensated by increased autonomic nervous system activity triggered by the activation of hypotension-induced baroreflexes (Nakaya *et al.*, 1983).

On the basis of these results, nifedipine is widely used in therapy of the harmful consequences of ischaemic heart disease, e.g. in vasopastic angina, in classical effort angina and in unstable angina (Johansson, 1978; Henry, 1980). The antianginal action of nifedipine is a complex phenomenon which may include: (1) dilatation of the large coronary arteries (Henry *et al.*, 1978; Jolly *et al.*, 1981) increasing blood and oxygen supply to the jeopardized myocardium. (2) Reduction in myocardial oxygen requirement by a direct negative inotropic effect. (3) Reduction in the afterload due to dilatation of peripheral resistance vessels (Jolly *et al.*, 1981). (4) Protection of the ischaemic myocardium from hypoxia by preventing influx of excess calcium, hence preserving mitochondrial integrity (Nayler *et al.*, 1980). However, a too extensive vasodilatation with higher doses may reduce arterial blood pressure unduly and thus diminish the coronary perfusion pressure, the driving force for collateral flow to the ischaemic zone.

It is well known that most cases of acute myocardial ischaemia are complicated by ventricular arrhythmias arising mainly as a result of ischaemia-induced electrical instability. In contrast with the other calcium antagonists, such as diltiazem or verapamil, nifedipine appears to have no direct antiarrhythmic effect (Ellrodt *et al.*, 1980; Ribeiro *et al.*, 1981). Coker & Parratt (1985) and Sheehan & Epstein (1982) have found no protection against reperfusion ventricular fibrillation after nifedipine treatment in anaesthetized open chest dogs. In anaesthetized pigs, Bergey *et al.* (1984) showed that although nifedipine produced a slight dose-dependent decrease in the incidence of

ventricular fibrillation, this protection was accompanied by a significant increase in ectopic activity.

On the basis of these results nifedipine seems to be a potent and useful anti-ischaemic agent without any effect on cardiac arrhythmias. In earlier experiments (Szekeres *et al.*, 1985) we described a new model of local myocardial ischaemia in dogs more closely related to the clinical situation in ischaemic heart disease. Here the single vessel disease is a rarity and usually more than one vessel is involved in the sclerotic narrowing. In our model a critical constriction of the left circumflex branch (LCX) was combined with sudden occlusion of the left anterior descending coronary artery (LAD). As a result the ischaemia induced by coronary occlusion became more severe; accordingly, extrasystolic activity and the incidence of ventricular fibrillation increased. The present investigations were intended to elucidate, firstly, the mechanism by which nifedipine proved to be effective in different forms of local myocardial ischaemia; and secondly, whether or not by reducing ischaemia, it is possible to moderate arrhythmias arising from elevated myocardial instability due to increased myocardial ischaemia.

Methods

General preparation

Adult mongrel dogs of either sex, weighing 14–25 kg were anaesthetized with sodium pentobarbitone (Nembutal, Serva, 30 mg kg^{-1}, i.v.) and ventilated (respirator, RO-5, Soviet Union) with room air at 10–15 strokes min^{-1} and 15 ml kg^{-1} volume. Arterial blood pH and P_{O_2} were monitored at selected intervals by means of a blood gas analyser (Astrup, OP-2102) and maintained respectively at 7.4 ± 0.2 and between 79–90 mmHg. Body temperature was monitored from a temperature probe in the oesophagus and maintained at 37 ± 0.5°C by a heated pad.

Haemodynamics

Mean arterial blood pressure (MAP) was recorded by means of a catheter inserted into the right femoral artery attached to a pressure transducer (Statham P23Db) and registered on a Hellige pressure recorder, while left ventricular systolic (LVSP) and end-diastolic (LVEDP) pressures were measured by means of a catheter introduced through the left carotid artery into the left ventricle and attached to a pressure transducer (Statham P23Db) and an electromanometer. The LVSP pulse was electronically differentiated to obtain a measure of a left ventricular contractility (dP/dt). The differentiator was calibrated by means of a triangular wave form of known slope. These parameters were recorded on a Watanabe recorder. The right femoral vein was prepared and cannulated for administration of drugs.

Coronary flow, stenosis and occlusion

The experimental arrangements were similar to those already described (Szekeres *et al.*, 1985). Thoracotomy was performed in the fifth intercostal space, the LAD and LCX coronary arteries were dissected free and silk threads loosely placed around them. LCX flow was measured by means of a flow probe (AS Nycotron 376, Type 1613, size: 1.8–2.0 mm). Distal to the flow probe a hydraulic occluder was placed around the LCX in order to produce a critical stenosis. Stenosis was termed 'critical' when complete occlusion of the artery for 20 s was no longer followed by a hyperaemic response. The degree of critical stenosis was determined in each dog individually.

In the area supplied by the LAD, peripheral coronary perfusion pressure was measured in a small branch of the LAD distal to the site of occlusion by means of a catheter filled with heparinized saline. This catheter was attached to a pressure transducer (Gould-Statham P23Db). Mean peripheral coronary perfusion pressure was registered on a 6NEK4-six channel recorder.

ST-segment and electrical inhomogeneity

In order to follow the ischaemia-induced inhomogeneity in electrical activation, a composite electrode (Williams *et al.*, 1974) was sutured onto the epicardial surface in the regions supplied by both the LAD and LCX. In this way it became possible to obtain a summarized picture of the R waves from 30 epicardial measuring points. The records so obtained were filtered in the range between 40–200 Hz. Widening and fractionation of this summarized picture of R waves following occlusion indicated that adjacent fibres were not simultaneously activated because of an inhomogeneous conduction of impulses. Inhomogeneity of activation was expressed as the greatest delay in activation (in ms) between the first and the last burst (for the method in detail see: Szekeres *et al.*, 1985). Changes in the epicardial ST-segment were recorded by two unipolar electrodes built separately into the composite electrode. Changes in the endocardial ECG were registered from two sites in the area supplied by LAD. Both epicardial and endocardial ECGs were recorded on a 6NEK4-six channel recorder.

Local myocardial contractility and blood flow

Local myocardial contractility was measured by strain-gauge arches placed on areas supplied by the LAD and LCX respectively, and on the border zone.

The arches were calibrated by means of 2, 5, 10 and 20 g weights at the beginning and end of the experiment. The deflections were registered on a Watanabe recorder.

Myocardial tissue blood flow (MBF) was measured by means of a modification (Juhász-Nagy *et al.*, 1974) of the heat clearance technique allowing only the estimation of percentage changes. Flexible copper-constantan thermocouples were inserted atraumatically into two different layers (subendocardial and subepicardial) of the area supplied by the LAD and into one layer (midmyocardial) of the area supplied by the LCX. The probes were fixed by epicardial sutures. Separate ECG leads were attached to each probe to localize the site of the probes (for details see Szekeres *et al.*, 1985). The MBF from each site was registered continuously on a Kipp & Zonen BD6 recorder. The magnitudes of the blood flow changes were expressed as percentages of the flow value recorded at the beginning of the experiment which was arbitrarily taken as 100% and the value at death as 0%.

Experimental protocol

After control recordings, repeated 5 min occlusions of the LAD were performed at 30 min intervals. After the second LAD occlusion (which was considered as control) the LCX was subjected to a critical constriction (i.e. until the disappearance of the postocclusion hyperaemic reaction). The LAD occlusion was then repeated. After release of the LAD occlusion, a nifedipine infusion of 1 $\mu g\,kg^{-1}\,min^{-1}$ was given for 10 min. This was followed by a further occlusion of the LAD during which the infusion of nifedipine was continued. After release of this occlusion the infusion was stopped; 5 min later the constriction of the LCX was removed.

Drugs

Nifedipine (Bayer) was dissolved in ethanol to give a stock solution of 1 $mg\,ml^{-1}$. Immediately before the experiments, an aliquot of this solution was diluted with 0.9% (w/v) NaCl solution without exposure to light. The final concentration of ethanol was less than 10% (v/v). This solution was administered in the form of an intravenous infusion. All solutions containing nifedipine and the infusion system were covered with aluminium foil to prevent inactivation of the drug by light.

Statistics

Values are exressed as means ± s.e.mean of 14 experiments. Differences were compared by two-way analysis of variance (no replication) and a least significance difference test. When extrasystolic activity values were compared during occlusion and reperfusion, one-way analysis of variance and a least significance difference test were used. Differences between interventions were considered significant when $P < 0.05$.

Results

Haemodynamics

After occlusion of the LAD alone, MAP decreased slightly but not significantly while there were considerable declines in peripheral coronary perfusion pressure and left ventricular dP/dt_{max} (Figure 1). These changes were more pronounced in the presence of a constricted LCX. During nifedipine infusion MAP significantly decreased while left ventricular dP/dt_{max} and peripheral coronary perfusion pressure remained unchanged. Following LAD occlusion MAP and dP/dt_{max} were similar to the values recorded in the absence of the drug, whereas peripheral coronary perfusion pressure significantly improved. Heart rate did not change during the experiment.

Control LAD occlusion caused a significant increase in the LVEDP which was more pronounced when the LCX was critically constricted. During nifedipine infusion and subsequent LAD occlusion LVEDP was essentially unchanged.

LCX inflow markedly increased following LAD occlusion alone, compensating for the lack of circulation within the occluded area. However, this compensation was abolished when the LAD occlusion was repeated in the presence of a critically constricted LCX. Nifedipine significantly augmented the blood flow to the area supplied by the narrowed LCX artery resulting in the return of circulatory compensation on repeated LAD occlusion.

Local myocardial contractility

In Table 1 we termed the area supplied by the LCX as 'normal' because, after critical constriction of this artery, this party of the myocardium was not, or was relatively less, ischaemic (since the resting flow did not change significantly after LCX constriction) than the 'real' ischaemic area which was supplied by the completely occluded LAD. It can be seen from Table 1 that in the heart with intact coronary circulation, control occlusion of the LAD caused a compensatory increase in contractility of the area supplied by the LCX (Table 1). This compensatory increase became more and more accentuated as the ischaemic area was approached and was maximal around the border zone. At the same time contractility in the centre of the ischaemic area decreased considerably. In the presence

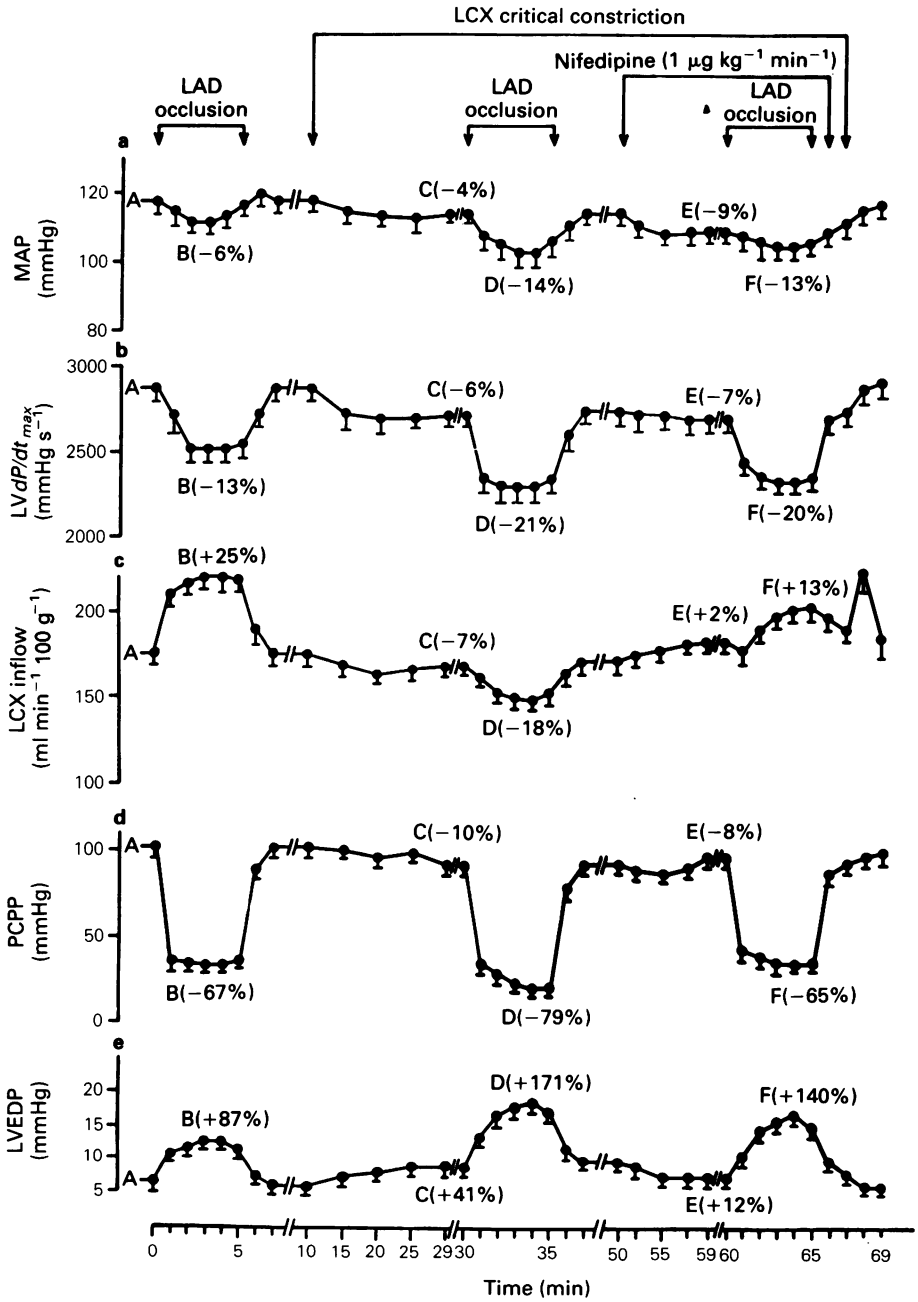

Figure 1 Haemodynamic effects of nifedipine. MAP = mean arterial blood pressure; LV dP/dt_{max} = left ventricular contractility; LVEDP = left ventricular end-diastolic pressure; PCPP = peripheral coronary perfusion pressure; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; $n = 14$. Results relate to the 14 dogs surviving the whole experiment out of 21. Values are mean with vertical lines representing s.e.mean. Numbers in parentheses as % = difference from the control value. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; NS = not significant. Statistical analysis was carried out by two-way analysis of variance. Differences were as follows: in (a) MABP: A vs B NS; A vs C NS; B vs D*; C vs E*: D vs F NS. In (b) LV$dP/dt_{max}$: A vs B**, A vs C NS; B vs D**; C vs E NS; D vs F NS. In (c) LCX inflow: A vs B***: A vs C NS; B vs D***; C vs E**; D vs F***. In (d) PCPP: A vs B***; A vs C NS; B vs D*; C vs E NS; D vs F**. In (e) LVEDP: A vs B***; A vs C*; B vs D***; C vs E*; D vs F NS.

Table 1 Changes in the local myocardial contractility (g) after nifedipine treatment on the areas supplied by the LAD and LCX coronary arteries and on the border zone

			LCX critical constriction			
					Nifedipine (1μg kg⁻¹min⁻¹)	
Site of estimation of local myocardial contractility	*Control* (A)	*LAD occlusion* (B)	*20 min* (C)	*LAD occlusion* (D)	*10 min* (E)	*LAD occlusion* (F)
Area supplied by LCX (normal) ($n = 7$)	7.00 ± 0.41	9.15 ± 0.72 (+ 31%) A-B**	6.40 ± 0.51 (− 9%) A-C^{NS}	7.28 ± 0.42 (+ 4%) B-D*	7.40 ± 0.24 (+ 6%) C-E*	8.24 ± 0.44 (+ 18%) D-F**
Border zone ($n = 7$)	7.63 ± 0.52	13.69 ± 0.49 (+ 79%) A-B***	8.30 ± 1.02 (+ 9%) A-C^{NS}	11.4 ± 0.64 (+ 49%) B-D*	8.95 ± 0.42 (+ 17%) C-E*	13.56 ± 0.63 (+ 77%) D-F*
Area supplied by LAD (ischaemic) ($n = 7$)	7.45 ± 0.92	5.40 ± 0.58 (− 28%) A-B***	7.30 ± 0.44 (− 2%) A-C^{NS}	3.35 ± 0.46 (− 55%) B-D**	7.80 ± 0.65 (+ 5%) C-E*	4.85 ± 0.26 (− 35%) D-F**

Values shown are mean ± s.e.mean. Numbers in parentheses as % = difference from the control value; $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; NS = not significant. Statistical analysis was carried out by one-way analysis of variance. LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; n = number of animals. Results relate to the 7 dogs out of the surviving 14 in which local myocardial contractility was measured.

of a stenosed LCX, repeated LAD occlusion resulted in a reduced compensation in the border zone. In the area supplied by the LCX the compensation was abolished and in the centre of the ischaemic area the contractility was almost completely absent. During nifedipine infusion, local myocardial contractility was significantly increased in all areas but especially in the border zone. Repeated LAD occlusion evoked a more intensive compensation both in the border zone and in the area supplied by the LCX. Even in the ischaemic area the fall in contractility was less marked than that before nifedipine treatment.

Local myocardial blood flow

After occluding the LAD alone, myocardial blood flow (MBF) declined suddenly and markedly in the region supplied by this vessel (Figure 2). The decline was somewhat more pronounced in the subendocardium than in the subepicardium, thus the arbitrary calculation of endo/epi flow ratio was 0.80. At the same time a compensatory increase in MBF was observed in the area supplied by the LCX. During critical constriction of the LCX, MBF decreased, mainly in the area supplied by this vessel. In addition a slight fall in MBF – despite the expected compensatory increase – was observed in the region supplied by the now intact LAD, especially in the subepicardium. Thus the endo/epi flow ratio increased to 1.06. In the presence of a critical stenosis, ischaemia produced by subsequent LAD occlusion became more severe; MBF in the ischaemic area decreased further, mainly in the subepicardium. In the region supplied by the LCX the compensation was abolished and a fall in the MBF was observed.

As previously found (Szekeres *et al.*, 1985), during control occlusion of the LAD the subendocardial vessels seem to be maximally dilated since no further dilatation could be observed during LCX constriction and repeated LAD occlusion. At the same time the subepicardium was less affected by the occlusion, in such a case a critical constriction of LCX may exhaust the subepicardial reserve of the ischaemic area.

In this model of severe myocardial ischaemia, due to LAD occlusion in the presence of LCX constriction, nifedipine significantly increased the MBF both in the area served by LCX and in the ischaemic LAD region, primarily in the subepicardium. Since in the occluded area only the reduced subepicardial circulation due to the critical constriction of LCX was increased and the MBF in the subendocardium was unchanged, the endo/epi flow ratio decreased to 0.93. The enhanced blood supply moderated the diminution of MBF following LAD occlusion both in the LCX area and in the subepicardium of the LAD region, but not in the subendocardium of the occluded area. Thus the endo/epi flow ratio further decreased to 0.79, indicating that nifedipine was able to alter the distribution of flow within the ischaemic area, increasing the blood supply in the ischaemic subepicardium but not in the subendocardium.

Electrophysiological parameters and extrasystolic activity

Table 2 shows the changes at the unipolar and multipolar electrode sites recorded from both areas served by LAD and LCX. Inhomogeneity of electrical

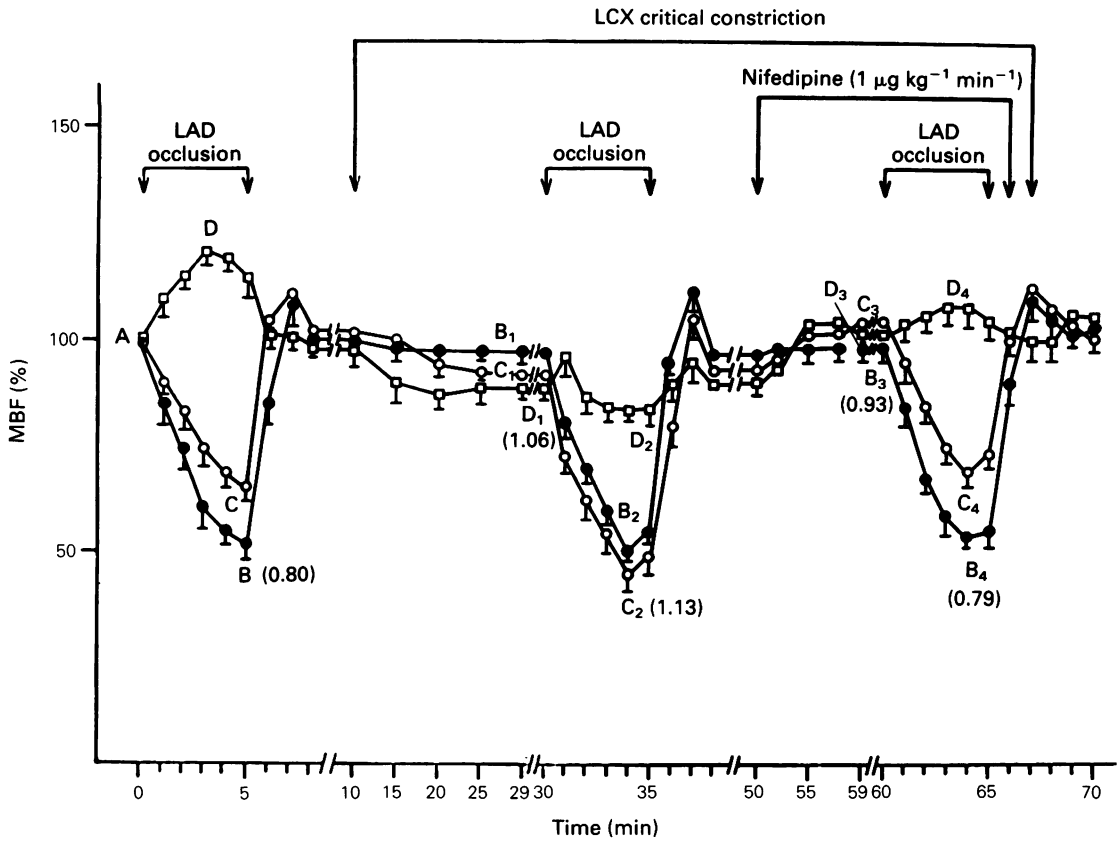

Figure 2 Changes in regional myocardial blood flow (MBF) of both the subepicardial (○) and subendocardial (●) layers of the ischaemic area as well as of the area served by the left circumflex branch (LCX; □) after occlusion of the left anterior descending coronary artery (LAD), LCX constriction and nifedipine treatment. Values are mean with s.e.mean shown by vertical lines. $n = 7$. B, C, D; B_1, C_1, D_1; etc. indicate the sites of MBF changes where signficance of differences between values was calculated. Level of significance; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; NS = not significant. Statistical analysis was carried out by two-way analysis of variance. Differences were as follows: A vs B***; A vs C***; A vs D***; A vs B_1 NS; A vs C_1*; A vs D_1*; B vs B_2 NS; C vs C_2**; D vs D_2***; B_1 vs B_3 NS; C_1 vs C_3*; D_1 vs D_3*; B_2 vs B_4 NS; C_2 vs C_4**; D_2 vs D_4**. The numbers in parentheses represent the endo/epi ratio at that point.

activation increased following LAD occlusion, i.e. there was an increase in the delay of activation between the first and last deflection appearing in the composite electrogram. At the same time there was an ST-segment elevation of 12 mV (endocardium) and 10 mV (epicardium). In the presence of a critical stenosis of the LCX, occlusion of the LAD increased both ventricular inhomogeneity in areas served by the LCX and ST-segment elevation in the ischaemic area, especially in the epicardium. Nifedipine infusion slightly moderated this inhomogeneity in the area supplied by the LCX but not in the LAD region. At the same time ST-segment elevation was reduced only in ischaemic epicardium, the endocardial ST-segment remained unchanged as compared with the situation in the absence of nifedipine.

Figure 3 shows the effect of the above interventions on the development of ST-segment elevation compared with the extrasystolic activity (calculated over 5 min intervals) and the incidence of ventricular fibrillation (VF).

In the presence of an otherwise intact coronary circulation, LAD occlusion caused moderate myocardial ischaemia with only slight extrasystolic activity but a significant increase in the ST-segment elevation. Only 1 animal out of 21 died during reperfusion. In the presence of a stenosed LCX, LAD occlusion led to a more severe ischaemia and an enhanced elevation of

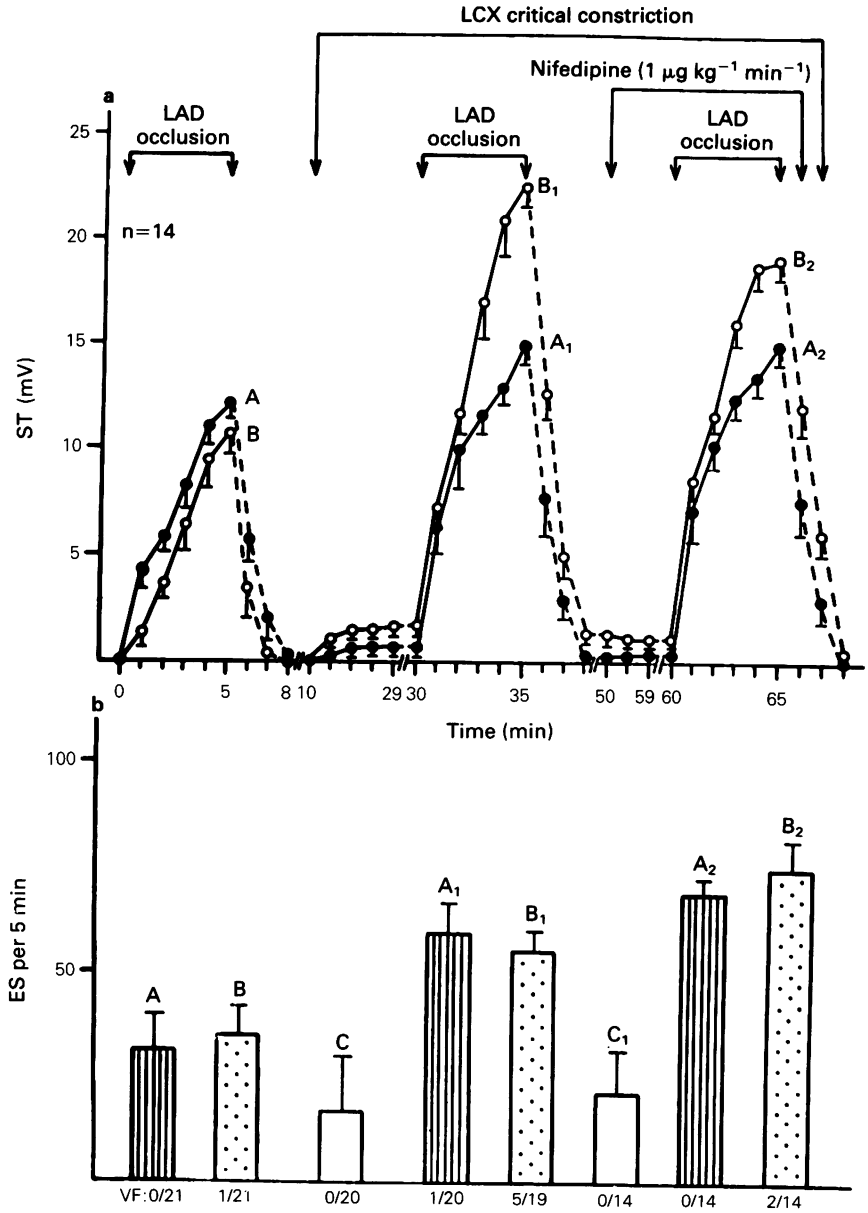

Figure 3 (a) Changes in the ST-segment elevation of the epicardial (○) and endocardial (●) ECG leads of the ischaemic area. Values are the means with s.e.mean shown by vertical lines. A, B, A_1, B_1 and A_2, B_2 mean maximal values of ST-segment elevation used for comparison and calculation of statistical significance. Level of significance: $*P<0.05$; $**P<0.01$; $***P<0.001$; NS = not significant. Statistical analysis was carried out by two-way analysis of variance. Differences were as follows: A vs B*; A_1 vs B_1***; A_2 vs B_2***; A vs A_1*; B vs B_1***; B_1 vs B_2**; A_1 vs A_2 NS. (b) Number of extrasystoles (ES) and the incidence of ventricular fibrillation (VF) in the presence of left anterior descending coronary artery (LAD) occlusion alone, left circumflex branch (LCX) constriction alone and combined with LAD occlusion, also the effects of nifedipine treatment. Time scale and intervention as indicated in (1). Hatched columns indicate the number of extrasystoles during LAD occlusion (A, A_1, A_2), stippled columns the number of extrasystoles during reperfusion (B, B_1, B_2) and open columns the number of extrasystoles during critical constriction of LCX (C, C_1, C_2). Values are mean with s.e.mean shown by vertical lines. Levels of significance and statistical analysis as in (a). Differences were as follows: A vs A_1***; B vs B_1***; C vs C_1 NS, A_1 vs A_2 NS, B_1 vs B_2*. VF below horizontal line = number of animals developing ventricular fibrillation following the different interventions indicated by the columns.

Table 2 Electrophysiological effects of nifedipine in the presence of LAD occlusion and of a critical constriction of the left circumflex (LCX) artery

			LCX critical constriction			
					Nifedipine (1 μg kg⁻¹min⁻¹)	
Site of estimation	*Control* (A)	*LAD occlusion* (B)	*20 min* (C)	*LAD occlusion* (D)	*10 min* (E)	*LAD occlusion* (F)
		Inhomogeneity electrical activation (ms)				
Ischaemic area ($n = 7$)	40 ± 2	121 ± 8 (+ 203%) A-B***	49 ± 3 (+ 23%) A-C^{NS}	162 ± 9 (+ 305%) B-D***	50 ± 3 (+ 25%) C-E^{NS}	147 ± 11 (+ 268%) D-F^{NS}
Normal area ($n = 7$)	45 ± 4	47 ± 6 (+ 4%) A-B^{NS}	58 ± 12 (+ 29%) A-C^{NS}	75 ± 8 (+ 67%) B-D**	48 ± 4 (+ 7%) C-E^{NS}	56 ± 8 (+ 24%) D-F**
		St-segment elevation (mv)				
Endocardial ischaemic area ($n = 14$)	0	12.0 ± 0.8 A-B***	1.0 ± 0.5 A-C^{NS}	15.0 ± 2.0 B-D*	0.5 ± 0.2 C-E^{NS}	15.0 ± 1.0 D-F^{NS}
Epicardial ischaemic area ($n = 14$)	0	10.7 ± 1.2 A-B***	1.8 ± 0.5 A-C^{NS}	22.4 ± 1.3 B-D***	1.0 ± 0.5 C-E^{NS}	19.0 ± 1.6 D-F**
Normal area ($n = 14$)	0	0 A-B^{NS}	1.8 ± 0.2 A-C^{NS}	2.0 ± 0.5 B-D^{NS}	0 C-E^{NS}	0 D-F^{NS}

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; n = number of animals. Results relate to the 7 dogs out of the surviving 14 in which inhomogeneity of electrical activation and ST-segment elevation, using 2 unipolar electrodes in each dog, were measured. Values shown are mean ± s.e.mean. Numbers in parentheses as % = difference from the control value; $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; NS = not signficant. Statistical analysis was carried out by one-way analysis of variance.

the ST-segment. The incidence and severity of arrhythmias increased significantly and ventricular fibrillation occurred both during the occlusion (1/20) and after its release (5/19).

Nifedipine significantly reduced ST-segment elevation only in the epicardium of the occluded area but did not reduce the number of extrasystoles either during the occlusion or after its release; the number of extra beats even slightly increased during reperfusion. No ventricular fibrillation occurred after LAD occlusion whereas 2 dogs out of the remaining 14 died during reperfusion.

Discussion

This study describes the effects of nifedipine on haemodynamics, MBF and the incidence of arrhythmias in a model of myocardial ischaemia in which, in addition to a critical constriction of one of the major coronary arteries (LCX), the other main branch (LAD) was suddenly occluded. We assume that this model is more closely related to the clinical situation where multivessel coronary artery disease is a common finding, unlike the hitherto widely used single vessel occlusion in an otherwise healthy animal.

As described earlier (Szekeres *et al.*, 1985) the harmful consequences of myocardial ischaemia due to LAD occlusion were aggravated by simultaneous constriction of the LCX. This results in the compensatory increase in blood flow being absent in the area supplied by the LCX. In the area served by the LAD, the perfusion decreased mainly in the subepicardium and accordingly, ST-segment elevation was more marked in the epicardium. Ventricular fibrillation occurred in one-third of the animals either during LAD occlusion or after release of the occlusion.

In spite of the widespread application of nifedipine in therapy, the views on its effectiveness and mode of action are still contradictory. The most intensive investigation of nifedipine is directed towards its actions on the coronary collateral circulation. Both Henry *et al.* (1978) and Melin *et al.* (1984), in a conscious dog model, and Zyvoloski *et al.* (1982), in an acute and chronic coronary occlusion model, found an increase in collateral flow following administration of nifedipine, despite the systemic hypotension evoked by the drug. In these cases, the increase in collateral flow was limited to subepicardial regions both in the normal and the ischaemic areas. At the same time Jolly

et al. (1981), Lamping & Gross (1984) and Gross *et al.* (1984) revealed, in acute coronary occlusion experiments, that nifedipine was able to increase MBF in the normal area (primarily in the subepicardium) whereas it improved coronary collateral flow to the ischaemic myocardium only if the drug-induced hypotension was minimized. This indicates that collateral blood flow to the acutely ischaemic myocardium is dependent on arterial or aortic blood pressure (Jolly *et al.*, 1981; Gross *et al.*, 1984; Lamping & Gross, 1984). In their experiments nifedepine also increased collateral blood flow primarily to the ischaemic subepicardium.

Similar results were found in the chronic coronary occlusion model (Lamping *et al.*, 1984) in which a well-developed collateral circulation was found as soon as 8 weeks after coronary occlusion. In this model nifedipine increased MBF in the normal region, while MBF in the ischaemic myocardium was augmented primarily in the subepicardium. Subendocardial flow in the occluded area increased only when the aortic blood pressure was not allowed to change. Accordingly, nifedipine exerts a powerful vasodilator action on the large coronary arteries and collateral vessels in the subepicardium (Jolly *et al.*, 1981; Zyvoloski *et al.*, 1982; Gross *et al.*, 1984), whereas the lack of any increase in subendocardial perfusion of the ischaemic region supports the suggestion that nifedipine has no effect on large conductance vessels penetrating to the subendocardium (Lamping & Gross, 1984).

Contrary to these observations, Weintraub, *et al.* (1981, 1982) did not find any significant change in the circulation of the ischaemic zone after intracoronary or intravenous administration of nifedipine to anaesthetized dogs with severe coronary artery stenosis. Also Selwyn *et al.* (1979) demonstrated a decrease in collateral flow after administration of a high dose ($13\,\mu g\,kg^{-1}$, i.v.) of nifedipine. However, after a lower dose ($1\,\mu g\,kg^{-1}$, i.v.) they found an improved perfusion and limitation of the infarct size.

It is likely that the negative results of this latter group are due to differences in the dose and in the route of drug adminstration. In addition other contributory factors such as the experimental model used, the severity of myocardial ischaemia or infarction, and the development and actual capacity of the collateral circulation to the ischaemic myocardium may also be important.

In our study, as well as in those of Henry *et al.* (1978) and Melin *et al.* (1984), nifedipine exerted a distinctly protective effect at a relatively low flow. This low flow was produced in our experiments by LAD occlusion in the presence of a stenosed LCX. Despite severe myocardial ischaemia, nifedipine was able to improve myocardial blood flow in the LCX area which had restricted perfusion as well as in the ischaemic subepicardium, whereas the blood flow in the ischaemic subendocardium was unchanged.

The most likely mechanism for an increase in collateral blood flow is a direct dilatation of the larger arteries in the non-ischaemic or partially ischaemic area providing the source of collateral flow. Alternatively, according to Melin *et al.* (1984), nifedipine could dilate the collaterals themselves or the arteries within the ischaemic zone.

As shown here, critical constriction of the LCX caused a diminution of MBF not only in the LCX area but also in the subepicardium of the area supplied by a normally patent LAD. Nifedipine increased MBF in the area distal to the stenosed LCX as well as in the subepicardium of the LAD region and hence restored the circulation decreased by LCX constriction. Under these circumstances an additional occlusion of the LAD resulted in a smaller reduction in blood flow in these areas than in the absence of nifedipine.

On the basis of these results we assume that, in our model, improvement of the blood supply to the occluded area is probably due to the restored compensatory mechanism of myocardial circulation by nifedipine. The area supplied by the LCX, as a result of reopened collaterals, receives an enhanced blood supply from the large epicardial vessels probably dilated directly by nifedipine. This hypothesis is supported by the increased coronary blood flow through the constricted LCX and the improvement in peripheral coronary perfusion pressure in the occluded area.

At the same time local myocardial contractility increased in all myocardial regions. The fact that MBF was unchanged in the subendocardium after nifedipine and the endo/epi flow ratio decreased, could be due, at least in part, to the enhanced LVEDP which did not decrease after nifedipine. Similar results have been found by Lamping & Gross (1984) and Zyvoloski *et al.* (1982) with both acute and chronic coronary occlusion models. However, they assumed that nifedipine had no effect on large conductance vessels penetrating the subendocardium.

However, such a redistribution of blood flow after nifedipine is not unambiguously beneficial because it does not affect subendocardial ischaemia. In our experiments, nifedipine considerably reduced ST-segment elevation in the epicardium but not in the endocardium and it is well known that the subendocardium is the area which first becomes ischaemic during an anginal attack of the effort type (Winbury *et al.*, 1969).

Another important point is that nifedipine did not influence the ischaemic-induced electrical inhomogeneity of the myocardium, suggesting that this drug has little or no effect on the myocardial electrophysiological parameters (Ellrodt *et al.*, 1980; Ribeiro *et al.*, 1981; Millard *et al.*, 1982). Our observations on the failure of nifedipine to protect against early

postocclusion and reperfusion arrhythmias are in accordance with the above data.

As previously described (Szekeres *et al.*, 1985), in our model of myocardial ischaemia the number of extrasystoles and the incidence of ventricular fibrillation considerably increased both during LAD occlusion and after its release in the presence of a critical constriction of LCX. Nifedipine infusion failed to reduce either the number of extrasystoles, or the development of ventricular fibrillation during reperfusion. Coker & Parratt (1985) and Sheehan & Epstein (1982) have also found no protection by nifedipine against ventricular fibrillation occurring during reperfusion in anaesthetized open chest dogs. However, Bergey *et al.* (1984) showed that nifedipine produced a slight dose-dependent decrease in the incidence of ventricular fibrillation in anaesthetized pigs, but this protection was accompanied by a significant increase in ectopic activity.

On the basis of our results, we conclude that nifedipine is effective in the treatment of the harmful consequences of ischaemic heart disease such as angina pectoris, in which the myocardial ischaemia is not too severe and not complicated by arrhythmias

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