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Importance of myocardial blood flow changes in the protective action of diltiazem in a new model of myocardial ischaemia

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1 The effect of diltiazem was studied in a new model of myocardial ischaemia in which in addition to a critical constriction of the left circumflex branch (LCX), the left anterior descending coronary artery (LAD) was suddenly occluded. This model is probably more relevant to the clinical situation in which multivessel coronary artery disease is common.

2 In this model diltiazem exerted a beneficial effect, manifested by an increase in myocardial blood flow (MBF) within the stenosed area of the LCX; by a marked reduction of the enhanced preload (LVEDP); by a diminution of the inhomogeneity of electrical activation and by a decrease in ST-segment elevation. Diltiazem also caused a significant reduction both in the number of extrasystoles and in the incidence of ventricular fibrillation.

3 Increased MBF within the stenosed area was associated with enhanced blood flow to the ischaemic myocardium, i.e. diltiazem directed flow to the ischaemic zone by improvement of the collateral circulation.

4 The beneficial electrophysiological changes caused by diltiazem are probably at least partly due to the drug-induced improvement of myocardial blood supply to the ischaemic area.

Introduction

The pharmacological actions of diltiazem, a potent coronary vasodilator, were first described by Sato *et al.* (1971) and by Nakajima *et al.* (1975, 1976). Evidence has been provided that the drug belongs to the group of 'calcium antagonists' (Fleckenstein, 1977). Diltiazem has been successfully used in the therapy of angina pectoris (Ellrodt *et al.*, 1980; Schroeder *et al.*, 1980, Bertrand *et al.*, 1982) as have other calcium channel blocking agents such as nifedipine and verapamil (Ellrodt *et al.*, 1980).

As is well known, the clinical application of this group of agents extends to a wide range of indications. These include angina pectoris, hypertension and supraventricular arrhythmias. Experimentally, the three most widely studied calcium antagonists are verapamil, nifedipine and diltiazem. All three drugs possess a more or less expressed coronary dilatory effect (Henry *et al.*, 1978; Warltier *et al.*, 1981; Millard *et al.*, 1982) and at higher concentrations can to varying degrees reduce contractile force in isolated atria and ventricles. However, in the conscious animal, nifedipine increases, verapamil decreases and diltiazem has little effect on the inotropic state (Stone *et al.*, 1980; Millard *et al.*, 1982). In anaesthetized dogs only verapamil has been identified as being a negative inotropic agent (Warltier *et al.*, 1981). Among the three major calcium antagonists, verapamil has been the most extensively investigated with regard to arrhythmia. In patients, verapamil was shown to be effective particularly against supraventricular arrhythmias (Antman *et al.*, 1980; Braunwald, 1982). It has been reported that both verapamil and diltiazem (Nakaya *et al.*, 1980; Peter *et al.*, 1982) reduce the ischaemia-induced conduction delay in anaesthetized dogs. Ribeiro *et al.* (1981) have found that verapamil, in contrast to nifedipine, also decreases reperfusion ventricular arrhythmias in anaesthetized dogs. However, nifedipine appears to have no direct antiarrhythmic effect (Ellrodt *et al.*, 1980; Ribeiro *et al.*, 1981) but does protect the myocardium from ischaemia and reduces infarct extension (Henry *et al.*, 1978; Brückner *et al.*, 1980).

In contrast to the above agents, diltiazem is a more potent vasodilator and lacks a significant negative inotropic action (Franklin *et al.*, 1980; Millard, 1980; Nagao *et al.*, 1980; Nakamura *et al.*, 1980). It has been

found highly effective in the relief of anginal pain related to coronary arterial spasm (Stone *et al.*, 1980; Bertrand *et al.*, 1982).

In animal experiments diltiazem has a salutary effect on the ischaemic myocardium both through an increase in collateral circulation (Franklin *et al.*, 1980; Nakamura *et al.*, 1980) and also by direct actions on the myocardium (Millard, 1980; Nagao *et al.*, 1980; Bush *et al.*, 1981). Diltiazem can reduce or moderate the harmful effects of reperfusion on the severely ischaemic myocardium (Warltier *et al.*, 1981) and decreases the occurrence of early postocclusion arrhythmias (Nakamura *et al.*, 1980; Peter *et al.*, 1982).

The present study was undertaken to study the effect of diltiazem in a new model of myocardial ischaemia in which, in addition to a critical constriction of one of the major coronary arteries (left circumflex branch, LCX), the other main branch (left anterior descending coronary artery, LAD) was suddenly occluded.

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, SU) with room air at 10–15 strokes per min. Arterial blood pH and Po_2 were monitored at selected intervals by means of a blood gas analyser (Astrup, OP-2102), and maintained at 7.4 ± 0.2 and between 79–90 mmHg respectively. Body temperature was monitored from a temperature probe in the oesophagus and maintained at 37 ± 0.5°C by a heating pad.

Haemodynamics

Mean arterial blood pressure (MABP) 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. These parameters were recorded (together with the first derivative of LVSP) on a Watanabe recorder at a paper speed of 100 mm s^{-1}.

Coronary flow, stenosis and occlusion

Thoracotomy was performed in the fifth intercostal space, the LAD and LCX coronary arteries were dissected free and silk threads loosely placed around them. Left circumflex coronary flow (coronary blood flow, CBF) 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 constrictor screw was placed around the LCX in order to produce a critical stenosis of the LCX.

In the area supplied by the LAD, peripheral coronary perfusion pressure (PCPP) 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 PCPP was registered on a NEK4-six channel recorder.

ST-segment and electrical inhomogeneity

In order to follow the ischaemia-induced inhomogeneity in electrical activation, a composite electrode containing 30 bipolar electrodes connected with each other to give one single lead (Williams *et al.*, 1974) was sutured on the epicardial surface in both regions supplied by the LAD and LCX respectively. 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. In the adequately perfused and oxygenated myocardium all sites were activated simultaneously, resulting in a single large spike. However, 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 last burst. Changes in the epicardial ST-segment were recorded by a unipolar electrode built separately in 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 registered 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 at the end of the experiment. The deflections were registered on a Watanabe recorder. In addition left ventricular contractility was estimated as dP/dt.

Myocardial tissue blood flow was measured by means of the heat clearance technique (Juhász-Nagy *et al.*, 1974). Flexible copper-constantan thermocouples were inserted atraumatically in two different layers of the ischaemic area and in one layer of the area supplied

Table 1 Haemodynamic effects of diltiazem

			LCX critical constriction			
					Diltiazem (10 μg kg⁻ min⁻¹)	
Parameters	*Control* (A)	*LAD occlusion* (B)	20 min (C)	*LAD occlusion* (D)	30 min (E)	LAD occlusion (F)
MABP (mmHg) $n = 10$	114 ± 2.8	107 ± 2.2 −7% A–B*	105 ± 4.6 −8% A–C*	93 ± 5.5 −20% B–D**	101 ± 4.5 −12% C–E NS	95 ± 5.5 −17% B–F***, D–F NS
HR (beats min^{-1}) $n = 10$	140 ± 6.2	145 ± 4.3 +3% A–B NS	148 ± 2.5 +5% A–C NS	150 ± 2.5 +7% B–D NS	145 ± 2.2 +3% C–E NS	150 ± 3.2 +7% B–F NS, D–F NS
LVSP (mmHg) $n = 10$	135 ± 6.1	116 ± 4.3 −14% A–B**	119 ± 7.4 −12% A–C**	105 ± 7.1 −22% B–D**	121 ± 4.8 −11% C–E NS	103 ± 6.2 −23% B–F***, D–F NS
LVEDP (mmHg) $n = 10$	5.7 ± 0.6	11.3 ± 0.8 +98% A–B***	10.0 ± 0.5 +75% A–C***	13.5 ± 1.0 +136% B–D***	7.0 ± 2.1 +22% C–E***	11.3 ± 2.0 +98% B–F***, D–F***
dP/dt (mmHg s^{-1}) $n = 10$	1419 ± 117	1252 ± 117 −13% A–B***	1298 ± 119 −9% A–C**	982 ± 43 −31% B–D***	1308 ± 116 −8% C–E NS	1095 ± 115 −23% B–F***, D–F***
PCPP (mmHg) $n = 10$	102 ± 3.2	22 ± 2.7 −79% A–B***	94 ± 4.9 −10% A–C*	14 ± 2.0 −90% B–D***	95 ± 2.9 −9% C–E NS	19 ± 3.3 −81% B–F NS, D–F*
LCX inflow (ml min^{-1} 100 g^{-1}) $n = 10$	94 ± 13	119 ± 16 +26% A–B**	66 ± 11 +31% A–C*	61 ± 10 +36% B–D***	92 ± 8 −4% C–E*	77 ± 15 −19% D–F**

MABP = mean arterial blood pressure; HR = heart rate; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; PCPP = peripheral coronary perfusion pressure; dP/dt = left ventricular contractility; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; n = number of animals. Results relate to the 10 dogs surviving the whole experiment out of 16. Values are = mean ± s.e.mean; % = difference from the control value; $P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; NS = non significant

by LCX. The probes were fixed by epicardial sutures. Separate ECG leads were attached to each probe to localize the site of probes.

One thermojunction recorded the temperature of the tissue, while the other junction was heated continuously by a stabilized d.c. current through a separate thin constantan wire. An initial temperature difference of 1.5°C was established between the two junctions of the probe and the intensity of the heating current was maintained constant throughout the experiment.

The temperature difference (ΔT) between the heated and the reference junction, which is inversely proportional to the rate of blood flow perfusing the local tissue, was continuously registered on a Kipp-Zonen BD6 recorder. The magnitude of the blood flow changes was expressed as a percentage (the flow value at the beginning of experiment was arbitrarily taken as 100% and the value at death as 0%).

Experimental design

We examined the effect of diltiazem in severe myocardial ischaemia produced by occlusion of LAD in the presence of a critical stenosis of the LCX.

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

Results

Haemodynamics

After occlusion of the LAD alone, MABP, LVSP, PCPP and left ventricular *dP/dt* decreased slightly. These changes were more pronounced in the presence of the LCX constriction. Heart rate did not change significantly. During the diltiazem infusion HR, MABP, LVSP, *dP/dt* and PCPP were essentially unchanged, except at the beginning of the infusion (Table 1).

LAD occlusion alone caused a significant increase in the LVEDP which was more pronounced in the presence of the critical constriction of LCX. During diltiazem infusion the LVEDP was significantly reduced almost to the control level in spite of simultaneous LCX constriction; following additional occlusion of the LAD, there was only a moderate decline in LVEDP. LCX inflow was markedly increased following LAD occlusion alone, practically compensating

Table 2 Changes in the local myocardial contractility after diltiazem treatment on the ischaemic, non-ischaemic and border areas†

			LCX critical constriction		
Parameters	*Control* (A)	*LAD occlusion* (B)	20 min (C)	*LAD occlusion* (D)	*Diltiazem (10 μg⁻¹ min⁻¹)* 30 min (E)	LAD occlusion (F)
Normal area	6.07 ± 0.54	8.36 ± 0.93	5.46 ± 0.51	7.43 ± 0.40	7.6 ± 1.01	8.2 ± 0.85
		+37%	−8%	−22%	+25%	+35%
$n=7$		A–B***	A–C NS	B–D**	C–E***	D–F**
Border zone	7.3 ± 1.03	14.0 ± 1.25	7.88 ± 1.98	11.38 ± 0.94	8.75 ± 1.06	13.0 ± 0.88
		+91%	+7%	+55%	+19%	+78%
$n=6$		A–B***	A–C**	B–D**	C–E*	D–F*
Ischaemic area	8.25 ± 0.85	5.50 ± 0.68	8.33 ± 0.75	3.80 ± 0.71	8.50 ± 0.41	4.36 ± 0.35
		−34%	0%	−58%	+3%	−48%
$n=6$		A–B***	A–C NS	B–D**	C–E NS	B–F***, D–F*

Mean ± s.e.mean.
† Abbreviations and symbols as in Table 1.

for the lack of circulation within the occluded area. However, this compensation was abolished when the LAD occlusion was repeated in the presence of the LCX critical constriction. Diltiazem infusion augmented the blood flow to the area supplied by the LCX artery.

Local myocardial contractility

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 2). This 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 of a stenosed LCX, repeated LAD occlusions 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, contractility was almost completely abolished.

During diltiazem infusion, local myocardial contractility was slightly, but significantly increased both in the area supplied by the LCX artery and in the border zone, but not in the area supplied by the LAD. Repeated LAD occlusions evoked a more intensive compensation both in the border zone and in the area supplied by the LCX artery. Even in the ischaemic area the fall in contractility was less marked than before diltiazem.

Local myocardial blood flow

After occluding the LAD alone, MBF in the region supplied by this vessel suddenly and markedly declined (Figure 1.). The decline was somewhat more pronounced in the subendocardium than in the subepicardium. During LCX critical constriction, MBF also decreased in the region supplied by the

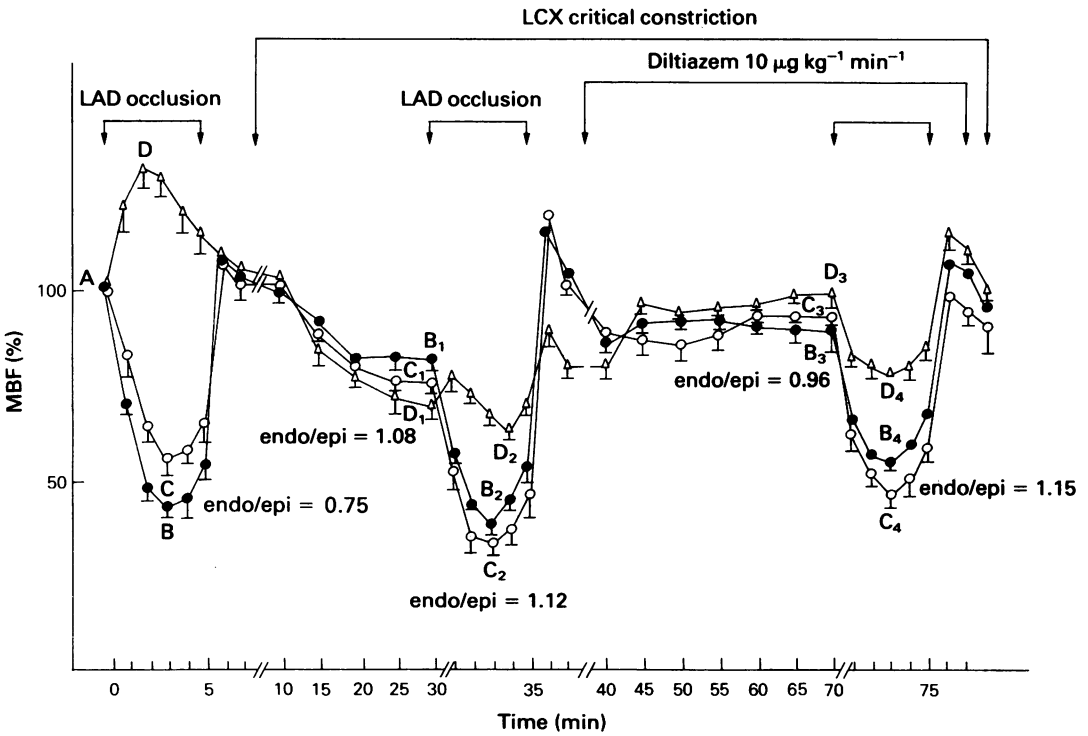

Figure 1 Changes in regional myocardial blood flow (MBF) of subendocardial (●) and subepicardial (○) layers of ischaemic area and also in the area served by left circumflex branch (LCX) (△) after left anterior descending coronary artery (LAD) occlusion, LCX constriction and diltiazem treatment. Abscissa scale: time (min). Ordinate scale: myocardial blood flow (% change). Values are mean with s.e.mean shown by vertical lines. $n=6$. B–C–D–, B_1–C_1–D_1 etc. Indicate the sites of MBF changes where significance of differences between values was calculated. Level of significance: $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$; NS = not significant. Differences were as follows: A–B***; A–C***; A–D***; B–C***; A–B_1***; A–C_1***; A–D_1***; B–B_2 NS; C–C_2**; D–D_2***; B_1–B_3**; C_1–C_3**; D_1–D_3**; B_2–B_4**; C_2–C_4**; D_2–D_4**.

Table 3 Electrophysiological effects of diltiazem in the presence of LAD occlusion and of a critical constriction of the left circumflex (LCX) artery†

Parameters		*Control* (A)	*LAD occlusion* (B)	*LCX critical constriction* 20 min (C)	*LAD occlusion* (D)	*Diltiazem (10μg kg^{-1} min^{-1})* 30 min (E)	LAD occlusion (F)
Inhomogeneity of electrical activation (ms)	Ischaemic area	69 ± 4	123 ± 8 +77% A–B***	81 ± 7 +17% A–C*	177 ± 15 +154% B–D***	70 ± 7 +1% C–E*	96 ± 12 +39% B–F***, D–F***
	Normal area	71 ± 4	80 ± 3 +2% A–B NS	89 ± 3 +25% A–C**	120 ± 8 +69% B–D***	79 ± 12 +11% C–E*	92 ± 6 +29% B–F* D–F***
ST-segment elevation (mV) Ischaemic area	Endocardial	0	14 ± 2.0 A–B***	1.5 ± 0.5 A–C NS	20 ± 2.0 B–D**	0 C–E NS	10.6 ± 2.0 B–F NS, D–F***
	Epicardial	0	11 ± 2.0 A–B***	2.0 ± 0.2 A–C NS	24 ± 2.0 B–D***	0 C–E NS	18.0 ± 3.0 B–F** D–F**
	Normal area	0	−2 ± 0.2 A–B NS	2.0 ± 0.2 A–C NS	4.0 ± 1.1 B–D NS	0 C–E NS	2.0 ± 1.1 D–F NS

$n = 10$.
† Abbreviations and symbols as in Table 1.

LAD, especially in the sub-epicardium and the endo/epi ratio was increased to 1.08. In the presence of a critical stenosis, the ischaemia produced by subsequent LAD occlusion became more severe; MBF in the ischaemic area decreased further, mainly in the subepicardium. We assume that during control occlusions of the LAD, the subendocardial circulation has already maximally decreased and a further augmentation is unlikely. At the same time the subepicardium is less affected by the occlusion, in such a case a critical constriction of LCX exhausts the epicardial reserve of the ischaemic area.

In this model of severe ischaemia using LAD occlusion in the presence of LCX constriction, dil-

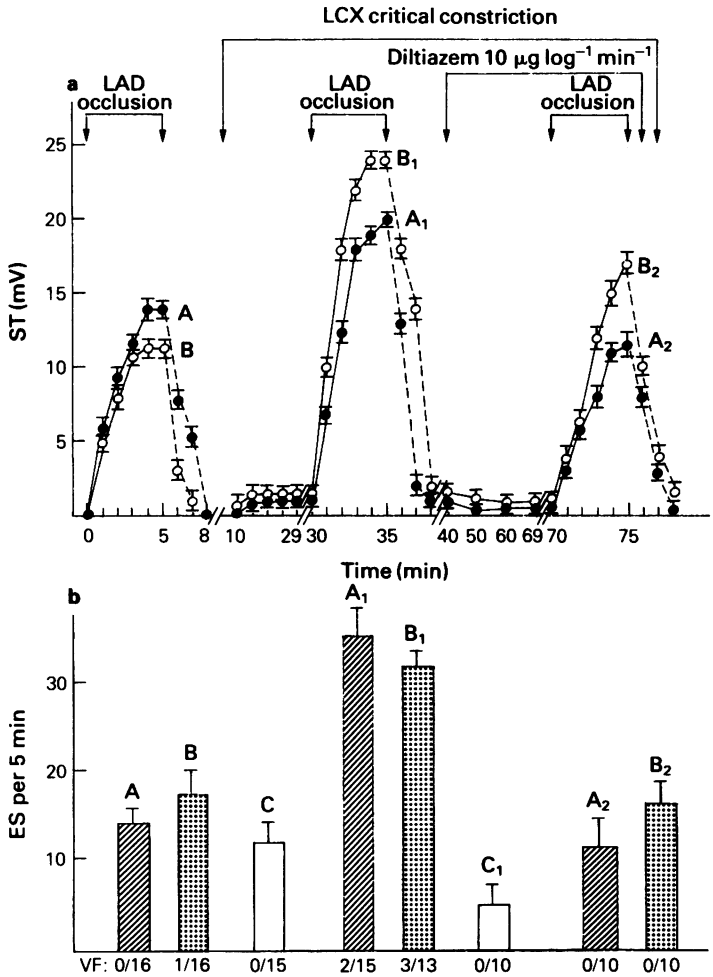

Figure 2 (a) Changes in the ST-segment elevation of the epicardial (O) and endocardial (●) ECG leads of the ischaemic area. Abscissa scale: time (min). Ordinate scale: ST-segment elevation (mV). Values are: mean with s.e.mean shown by vertical lines. A, B; A_1B_1 and A_2B_2 mean maximal values of ST-segment elevation used for comparison and calculation of statistical significance. Level of significance as in Figure 1. Differences were as follows: A–B**; A_1–B_1***; A_2–B_2***; A–A_1***; B–B_1***; B_1–B_2***; A_1–A_2***. (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, finally after diltiazem treatment. Ordinate scale = ES per 5 min. Time scale and intervention as indicated in (a). Hatched columns number of ESs during LAD occlusion (A, A_1, A_2) stippled column number of ESs during reperfusion (B, B_1, B_2) open columns number of ESs during critical LCX constriction (C, C_1, C_2). Values are mean with s.e.mean shown by vertical lines. Level of significance as in Figure 1. Differences were as follows: A–A_1***; B–B_1***; C–C_1***; A_1–A_2***; B–B_2***. VF below horizontal line = number of animals developing ventricular fibrillation following different interventions (as indicated by the columns).

tiazem increased the MBF both in areas served by LCX and LAD. This enhanced blood supply moderated the diminution of MBF following LAD occlusion both in the LCX and in the LAD regions but was not able to alter the flow distribution as compared with the situation in the absence of diltiazem. The arbitrary endo/epi ratio thus remained at 1.15.

Electrophysiological parameters and extrasystolic activity

Table 3 shows the changes at the unipolar and multipolar electrode sites recorded from both areas served by LAD and LCX. Inhomogeneity of electrical 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 and at the same time there was ST-segment elevation of 11 mV (epicardium) and 14 mV (endocardium). In the presence of a critical stenosis of the LCX, the inhomogeneity of electrical activation was more marked both in the areas supplied by the LAD and LCX. Additional occlusion of the LAD increased ventricular inhomogeneity and ST-segment elevation in the ischaemic area, especially in the epicardium. Diltiazem significantly reduced this inhomogeneity as well as the ST-segment elevation (Table 3).

Figure 2 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 VF. In the presence of an intact coronary circulation, LAD occlusion caused moderate myocardial ischaemia with no or only slight extrasystolic activity but a significant increase in the ST-segment elevation. In the presence of a stenosed LCX, LAD occlusion led to more marked myocardial ischaemia and an enhanced elevation of the ST-segment. The incidence and severity of arrhythmias increased significantly; in one third of the animals (5/15) ventricular fibrillation occurred either during the occlusion (2/15) or after its release (3/13).

Diltiazem markedly reduced ST-segment elevation, especially in the endocardium and reduced the number of extrasystoles. No ventricular fibrillation occurred after LAD occlusion or during reperfusion.

Discussion

This study describes the effects of diltiazem in a new 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. This model may approximate the real clinical situation, where multivessel coronary artery disease is common. This fact has not been taken account of in previous experimental infarction models. We have found that the harmful consequences of myocardial ischaemia due to LAD occlusion were aggravated by simultaneous constriction of the LCX. In the area served by the LCX, the compensatory increase in bloood flow was absent; in the area supplied 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 occlusion.

This study was performed, in order to assess the effects of diltiazem on haemodynamics, myocardial blood flow and on the incidence of arrhythmias in an experimental model in which more than one coronary artery was involved.

Diltiazem treatment mitigated the detrimental ischaemic changes mentioned before. The explanation for this beneficial effect is probably complex (Weishaar *et al.*, 1979; Sasayama *et al.*, 1981; Patterson *et al.*, 1983). Several investigators have observed (Fleckenstein, 1977; Franklin *et al.*, 1980; Millard, 1980) that diltiazem has a peripheral vasodilator action and thus reduces left ventricular afterload (Stone *et al.*, 1980; Bush *et al.*, 1981). Furthermore it has slight negative inotropic (Millard 1980; Nagao *et al.*, 1980; Warltier *et al.*, 1981) and chronotropic (Bourassa *et al.*, 1980; Stone *et al.*, 1980; Warltier *et al.*, 1981) effects, which also contribute to a decrease in myocardial oxygen consumption. Diltiazem could improve cardiac pumping function in terms of an increase in cardiac output (due to reduced afterload) despite a negative inotropic action (Futamura *et al.*, 1982). One of the main effects of calcium antagonists is the relaxation of the vascular smooth muscle (Fleckenstein, 1977). This explains their benefit in angina pectoris (Bourassa *et al.*, 1980; Bertrand *et al.*, 1982) and particularly in Prinzmetal's variant angina (Schroeder *et al.*, 1980; Tartaglione *et al.*, 1981). Calcium antagonists would thus be expected to increase coronary blood flow by means of direct coronary vasodilatation (Nakajima *et al.*, 1976; Franklin *et al.*, 1980; Nakamura *et al.*, 1980; Millard, 1980; Futamura *et al.*, 1982; Millard *et al.*, 1982).

In our experiments diltiazem significantly increased LCX inflow despite the critical constriction. Following LAD occlusion this enhanced flow (which previously played a compensatory role) was absent. In spite of the stenosis (Futamura *et al.*, 1982) diltiazem increased blood flow to the whole left ventricle including the ischaemic myocardium and despite reduction in perfusion pressure. This diltiazem-induced increase in blood flow within the ischaemic zone occurred mainly in the subendocardium and resulted in a further increase in the endo/epi flow ratio. ST-segment elevation was, as a consequence, considerably reduced both in the epicardium and endocardium.

There is good agreement concerning the improvement of collateral circulation in the ischaemic area by diltiazem (Franklin *et al.*, 1980; Nakamura *et al.*, 1980; Millard *et al.*, 1980; Warltier *et al.*, 1981; Millard, 1982; Futamura *et al.*, 1982), but views are more controversial as to the mechanism of action of this enhanced blood flow. Some authors (Millard, 1980; Nakamura *et al.*, 1980; Franklin *et al.*, 1980) found that diltiazem augmented perfusion in the ischaemic zone by improving collateral circulation, while others (Franklin *et al.*, 1980; Warltier *et al.*, 1981; Zyvoloski *et al.*, 1982) suggested that diltiazem enhanced blood supply in both normal and the ischaemic areas.

Our finding that the beneficial effect of diltiazem on blood flow was more marked in the subendocardium of the ischaemic zone is supported by a number of other investigators (Franklin *et al.*, 1980; Millard, 1980; Warltier *et al.*, 1981; Bache & Dymek, 1982; Futamura *et al.*, 1982; Zyvoloski *et al.*, 1982); others have found that diltiazem increased blood flow to the subepicardium of the ischaemic area (Nakamura *et al.*, 1980; Jolly *et al.*, 1981; Hof, 1983).

Ischaemia produced by LAD occlusion was very severe in the presence of a critical stenosis. In many experiments acute coronary occlusion performed before or after the drug administration has shown that the effect of diltiazem may depend on the degree of stenosis (Futamura *et al.*, 1982). We observed a beneficial effect of diltiazem during severe myocardial ischaemia and that this effect was related to the preferential increase in blood flow to the subendocardium (Marshall & Parratt, 1974). The mechanism involved in this redistribution of flow within the ischaemic zone is unknown; it may be related to the decrease in LVEDP (Futamura *et al.*, 1982). LAD occlusion in the presence of a critical stenosis caused a particularly marked increase in LVEDP and diltiazem decreased this significantly. This would protect against the decrease of subendocardial blood flow (Futamura *et al.*, 1982).

On the basis of the beneficial haemodynamic and electrophysiological effects of diltiazem we expected a preventive action against ventricular arrhythmias and fatal ventricular fibrillation due to severe myocardial ischaemia. This expectation was realised since diltiazem markedly decreased the inhomogeneity of electrical activation and ST-segment elevation. During LAD occlusion in the presence of a critical stenosis, diltiazem significantly reduced the number of extrasystoles and ventricular fibrillation did not occur either during the occlusion or its release. Diltiazem thus decreased ventricular arrhythmias to the level observed during control LAD occlusion in the absence of a critical stenosis.

There are some reports indicating, that diltiazem reduces ischaemia-induced conduction delay (Bush *et al.*, 1981; Nakaya *et al.*, 1981; Peter *et al.*, 1982). This effect is assumed to play a protective role against ventricular fibrillation in dogs subjected to coronary occlusion. In contrast, Patterson *et al.* (1983) and Sheehan & Epstein (1982) have found that the development of ventricular fibrillation was not prevented by diltiazem either during myocardial ischaemia (Patterson *et al.*, 1983) or during subsequent reperfusion (Sheehan & Epstein, 1982). Sheehan & Epstein (1982) found that ventricular fibrillation rarely occurred on reperfusion in dogs with a high collateral blood flow or when the region perfused by the occluded artery is small. In our experiments ischaemia was very severe since the ischaemic zone was surrounded by an area in which the perfusion was restricted by a critical constriction. Under such circumstances the incidence and severity of arrhythmias increased and ventricular fibrillation commonly occurred. Diltiazem, by its vasodilator effect increased blood flow within this restricted area and directed flow to the ischaemic zone by improvement of the collateral circulation (Franklin *et al.*, 1980; Millard, 1980; Nagao *et al.*, 1980).

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