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Effects of nipradilol on myocardial ischaemia produced by coronary stenosis in dogs

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1 Effects of nipradilol which is a new β-adrenoceptor blocking agent endowed with nitroglycerin-like vasodilator actions, its denitrated derivative (denitro nipradilol) and propranolol on abnormalities of regional myocardial shortening produced by partial occlusion of the left circumflex coronary artery (LCX) were studied in anaesthetized open-chest dogs.

2 In the presence of LCX stenosis, nipradilol (0.1 mg kg^{-1}, i.v.) produced marked decreases in heart rate and LV*dP/dt* without a significant increase in left ventricular end-diastolic pressure (LVEDP). It improved impaired myocardial segment shortening and restored normal cardiac lactate metabolism.

3 Denitro nipradilol (0.2 mg kg^{-1} i.v.) and propranolol (0.2 mg kg^{-1} i.v.) both caused similar haemodynamic changes to nipradilol but also produced a significant increase in LVEDP. However, improvement by these two agents of regional dysfunction in the ischaemic myocardium was comparable to those seen with nipradilol.

4 All three agents markedly inhibited isoprenaline-induced tachycardia, but vehicle did not.

5 Atrial pacing abolished the beneficial effect of nipradilol on myocardial shortening in the ischaemic region without affecting other haemodynamic parameters.

6 These results indicate that nipradilol alleviates acute myocardial ischaemia produced by coronary stenosis with similar efficacy to denitro nipradilol and propranolol suggesting, that a major part of the beneficial effect of nipradilol may be attributable to its β-adrenoceptor blocking action.

Introduction

Although the effectiveness of β-adrenoceptor antagonists, particularly propranolol, on myocardial ischaemia has been well established, all the actions of propranolol are not always beneficial. Propranolol decreases both myocardial contractility and heart rate while it simultaneously causes an increase in left ventricular end-diastolic volume which tends to increase myocardial oxygen consumption and to compromise endocardial perfusion. Furthermore, unopposed α-adrenergic vasoconstriction (Robertson *et al.*, 1982; Vatner & Hintze, 1983) causes an increase in coronary resistance which may produce myocardial ischaemia in certain circumstances. On the other hand, organic nitrates, another group of antianginal drugs, decrease left ventricular end-diastolic volume mainly through systemic venodilatation and also cause potent coronary vasodilatation. However, the use of nitrates is sometimes associated with reflex tachycardia and positive inotropic effects. Thus, it seems reasonable that concurrent use of β-adrenoceptor antagonists and nitrates may provide increased efficacy over single drug use (Frishman, 1985).

Nipradilol (K-351), 3,4-dihydro-8-(2-hydroxy-3-isopropylamino)propoxy-3-nitroxy-2H-1-benzopyran, is a recently synthesized agent which has a propranolol-like structure and contains a nitrate moiety. It has been demonstrated that nipradilol has not only a β-adrenoceptor blocking action (Uchida *et al.*, 1983; Sakanashi *et al.*, 1984; Nagatomo *et al.*, 1984) but also a nitroglycerin-like vasodilator action (Uchida *et al.*, 1983; Kou & Suzuki, 1983). Furthermore, Uchida (1982) and Sakanashi *et al.* (1985) reported that after the administration of nipradilol, left ventricular end-diastolic pressure did not significantly increase, despite marked decreases in heart rate and left ventricular *dP/dt* in the anaesthetized dog. These pharmacological properties suggest that this agent might be more effective in the treatment of angina pectoris than a classical β-adrenoceptor antagonist such as propranolol. However, the effects

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of nipradilol in an experimental model of myocardial ischaemia have not been investigated.

This study was conducted to evaluate whether or not nipradilol would alleviate abnormalities in regional myocardial function and lactate metabolism produced by a flow-limiting coronary stenosis in dogs. Additionally, to estimate the role of the vasodilator properties of nipradilol in the mechanism of its action, the effects of a denitrated derivative of nipradilol (Yoshimura *et al.*, 1985) (which has been found to be devoid of nitroglycerin-like vasodilator actions but to possess a β-adrenoceptor blocking action; Kou & Suzuki, 1983) and of propranolol, on myocardial dysfunction and haemodynamic variables during coronary stenosis, were compared with those of nipradilol in the same model.

Methods

Thirty seven mongrel dogs of either sex weighing 11 to 20 kg were anaesthetized with sodium pentobarbitone (25 mg kg^{-1} i.v.) and were ventilated by a Harvard respirator (model 607). A catheter-tip manometer (Millar, PC-350) was introduced through the right femoral artery into the left ventricle to measure the left ventricular pressure. A polyethylene catheter filled with heparinized saline (0.9% w/v NaCl solution) was inserted through the left carotid artery into the aortic root and connected to a Statham pressure transducer (P23ID) to measure the aortic pressure. A left thoracotomy was performed through the fifth intercostal space. The pericardium was opened, and the heart was suspended in a pericardial cradle. The left circumflex coronary artery (LCX) was dissected free near its origin, and a snare-type occluder was placed around it. An appropriately sized electromagnetic flow probe (Statham, SP7515) was placed proximal to the occluder and connected to an electromagnetic flowmeter (Statham, SP2204) for the measurement of coronary blood flow. There was no branch between the probe and occluder. In 12 dogs, a polyethylene catheter, inserted through the left fermoral artery into the aorta, and a 6.5 F NIH catheter advanced from the left jugular vein into the coronary sinus, were used for withdrawal of arterial and coronary sinus blood samples, respectively. The plasma lactate concentration was measured by enzymatic analysis (Lactate, UV. Test, Boehringer Mannheim). Percentage lactate extraction in the myocardium was calculated by the following equation: % lactate extraction = (the difference between lactate levels of arterial and coronary sinus blood/ the lactate level of arterial blood) × 100.

Regional myocardial function was measured with ultrasonic dimension gauges (Theroux *et al.*, 1974). Two pairs of 5 MHz ultrasonic crystals (2 mm in diameter) were positioned in the left ventricular wall approximately 10 mm apart in a circumferential plane close to the endocardium. One pair of crystals was placed in the wall within the distribution of the LCX, and another pair was placed in the anterior wall in the left anterior descending coronary artery (LAD)-perfused area. The leads of each crystal were connected to an ultrasonic amplifier (MECC, UDM-5B) which transformed the acoustic impulse transmitted between the two crystals into an electronic signal proportional to the distance between the paired crystals. The signals were monitored on an oscilloscope (Hitachi, V-202F) throughout experiments. End-diastolic segment length (EDL) was determined just before the onset of isovolumic contraction, as determined from left ventricular dP/dt. End-systolic segment length (ESL) was measured 20 ms before peak negative dP/dt (Theroux *et al.*, 1977). Percentage segment shortening (%SS), an index of regional myocardial function, was calculated from the following equation: %SS = (EDL − ESL)/ EDL × 100.

Mean coronary blood flow was obtained by using an electronic resistance-capacitance filter with a 2 s time constant. Left ventricular dP/dt (LV$dP/dt$) was derived by differentiating the left ventricular pressure signal using an electronic differentiator (Nihon Kohden, ED-601G). Heart rate was continuously counted with a cardiotachometer (Nihon Kohden, AT-600G) triggered by the pressure pulse. Data were continuously recorded on an 8-channel pen recorder (Nihon Kohden, WT-685G) and simultaneously on a magnetic tape (Sony, A47).

Experimental protocol

Experiments were started at least 30 min after the instruments had been set up. Control haemodynamics and regional myocardial shortening were measured. The LCX was then gradually constricted with the occluder, and a stenosis of the LCX was made sufficient to reduce resting coronary blood flow and to decrease percentage segment shortening in the LCX area to around 2–3%. This situation is one in which active shortening in the LCX-perfused myocardium disappears almost completely, indicating that there is insufficient blood supply to this area. When hypofunction within the LCX area could not be obtained, the data were discarded. A minimum of 5 min after establishing an appropriate degree of hypofunction in the LCX-perfused area was allowed to confirm the stability of haemodynamics and regional myocardial function, and then nipradilol (0.1 mg kg^{-1}, $n = 10$), its vehicle (0.5 ml kg^{-1}, $n = 15$), a denitrated derivative of nipradilol (0.2 mg kg^{-1}, $n = 6$) or propranolol (0.2 mg kg^{-1}, $n = 6$) was administered intravenously. The average time between the beginning of coronary stenosis and drug administration was 31.6 ± 1.4 min ($n = 37$), and there was no significant difference in the

time amongst the different treatment groups. Doses of nipradilol, denitro nipradilol and propranolol employed in this study were selected to produce a similar depression of contractility and heart rate by taking into account, first, the results in preliminary experiments using the same model as in the present study and, second, the previous study (Uchida *et al.*, 1983) in which dose-response curves for negative chronotropic activities of nipradilol and denitro nipradilol were demonstrated in anaesthetized dogs. Coronary constriction was released 30 min after drug administration. In 4 dogs of the nipradilol group and 7 dogs of the vehicle group, atrial pacing was performed for 10 min before the release of coronary stenosis in order to increase heart rate.

To prevent blood coagulation, 200 u kg^{-1} of heparin was administered intravenously before coronary stenosis. Efficacy of β-blockade after administration of nipradilol, denitro nipradilol, propranolol or vehicle was tested by comparing the response to (−)-isoprenaline (100 ng kg^{-1} i.v.) 10–15 min before stenosing, with that 10–15 min after the release of a stenosis.

Drugs

Nipradilol (Kowa) was dissolved in 0.5 ml of 0.01 N HCl and then diluted with physiological saline (0.9% NaCl) to a final concentration of 0.2 mg ml^{-1}. Denitro nipradilol (Kowa), (±)-propranolol hydrochloride (ICI) and (−)-isoprenaline hydrochloride (Nikken Kagaku) were dissolved in physiological saline.

Data analysis

Time sequence data were analyzed by analysis of variance and paired data were analysed by paired *t* test. The level of statistical significance was $P < 0.05$. All results were expressed as the mean ± standard error.

Results

Effects of nipradilol, denitro nipradilol and propranolol on haemodynamic variables and regional myocardial function during coronary stenosis

As seen in Figures 1 and 2, partial occlusion of the LCX decreased resting LCX flow to 26–43% of the control value associated with increases in left ventricular end-diastolic pressure (LVEDP) and decreases in LV*dP/dt*. More marked increases in ESL than EDL following coronary stenosis occurred in the LCX segment, indicating pronounced impairment of ischaemic segment shortening (Figure 2 and Table 1). The measured parameters were relatively constant for at least 20 min after the coronary stenosis and were not significantly affected by the administration of vehicle, although a small change in LV*dP/dt* was observed 30 min after the vehicle administration (Figure 2).

Administration of nipradilol immediately produced mild but sustained hypotension and a transient decrease in mean coronary blood flow (Figures 1 and 2). Heart rate and LV*dP/dt* markedly decreased by 21 ± 2% ($P < 0.01$) and 23 ± 3% ($P < 0.01$) of the respective preadministration values (139 ± 7 beats min^{-1}; 1823 ± 99 mmHg s^{-1}), while LVEDP was not significantly changed after nipradilol (Figure 2). Haemodynamic changes caused by denitro nipradilol or propranolol, were similar to those induced by nipradilol except for LVEDP (Figure 2). After administration of denitro nipradilol and propranolol, heart rate significantly decreased by 22 ± 3% and 18 ± 4%, and LV*dP/dt* decreased by 24 ± 3% and 24 ± 5% of the respective predrug value. Transient, small decreases in mean aortic pressure were observed after denitro nipradilol or propranolol (Figure 2). Both agents did not appreciably alter LCX except flow for an early, small reduction associated with hypotension as noted in the case of propranolol. LVEDP was significantly and sustainedly increased by these two agents (Figure 2).

Impaired systolic shortening of the myocardium distal to the coronary stenosis (LCX area) tended to increase after the administration of each of three agents as seen in Figure 2, while that in the LAD area tended to decrease. Changes in percentage segment shortening are summarized in Table 1. Nipradilol, denitro nipradilol and propranolol all improved segment myocardial function in the ischaemic area (3.2% to 10.2%, 1.5% to 7.8% and 3.3% to 8.4%, respectively), whereas vehicle did not (Table 1). The data obtained 15 or 30 min after drug administration were significantly larger than the corresponding value after the vehicle.

All three agents significantly reduced responses to isoprenaline 100 ng kg^{-1} i.v., while the vehicle did not. Nipradilol, denitro nipradilol and propranolol inhibited ($P < 0.01$) isoprenaline-induced tachycardia by 79 ± 2%, 63 ± 9% and 61 ± 11% of the respective control response (71 ± 6, 52 ± 5 and 55 ± 6 beats min^{-1}).

Effect of nipradilol on cardiac lactate metabolism

In 5 of 10 dogs, the effect of nipradilol on lactate metabolism in the heart was estimated (Figure 3). Constriction of the LCX caused a significant increase in the lactate level of coronary sinus blood while that of arterial blood remained unchanged. As shown in Figure 3, the coronary sinus lactate concentration significantly decreased after administration of nipradilol without a change in the arterial concentra-

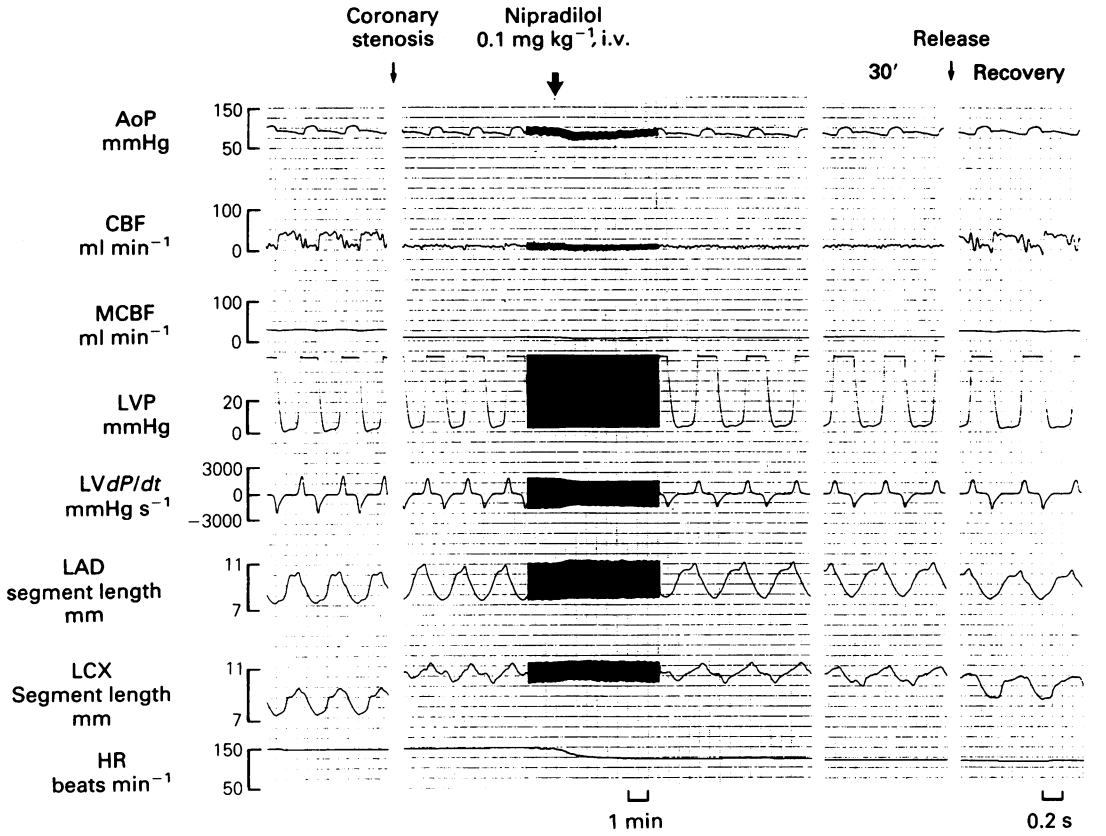

Figure 1 Representative tracings of effects of nipradilol (0.1 mg kg^{-1}, i.v.) on haemodynamic variables and myocardial segment shortening in the presence of stenosis of the left circumflex coronary artery (LCX). AoP = aortic pressure. CBF = blood flow of the LCX. MCBF = mean blood flow of the LCX. LVP = left ventricular pressure. LV*dP/dt* = left ventricular *dP/dt*. LAD = left anterior descending coronary artery-perfused area. LCX = LCX-perfused area. HR = heart rate.

tion, indicating that the net production of lactate in the heart was reduced. The change in lactate extraction (Figure 3) corresponded temporally with that in percentage segment shortening in the ischaemic myocardium (Table 1). On the other hand, lactate extraction of the control group was not changed by vehicle administration (Figure 3), although coronary stenosis caused comparable changes in the lactate metabolism to those seen with the nipradilol group.

Effect of atrial pacing on improved regional function after nipradilol

To estimate the role of bradycardia induced by nipradilol in its beneficial effects on myocardial ischaemia, atrial pacing (which increased the resting heart rate of 110 ± 7 beats min^{-1} (24 ± 4%) i.e. near to the rate before drug administration) was performed 30 min after the administration of nipradilol for 10 min in 4 dogs. Although haemodynamic parameters were not significantly changed by pacing, regional myocardial function in the ischaemic segment deteriorated from 7.5 ± 2.6% obtained just before pacing to 4.2 ± 2.4% ($P < 0.05$). In 7 vehicle-injected dogs, atrial pacing increased the resting heart rate of 145 ± 8 beats min^{-1} by 22 ± 1%, which was performed on the same time-course as in the four nipradilol-treated dogs, and also reduced ischaemic segment shortening from 4.0 ± 1.5% to − 1.1 ± 1.5% ($P < 0.01$).

Discussion

Since administration of the nipradilol vehicle did not cause any significant changes in any measured haemodynamic variable or in regional contractility

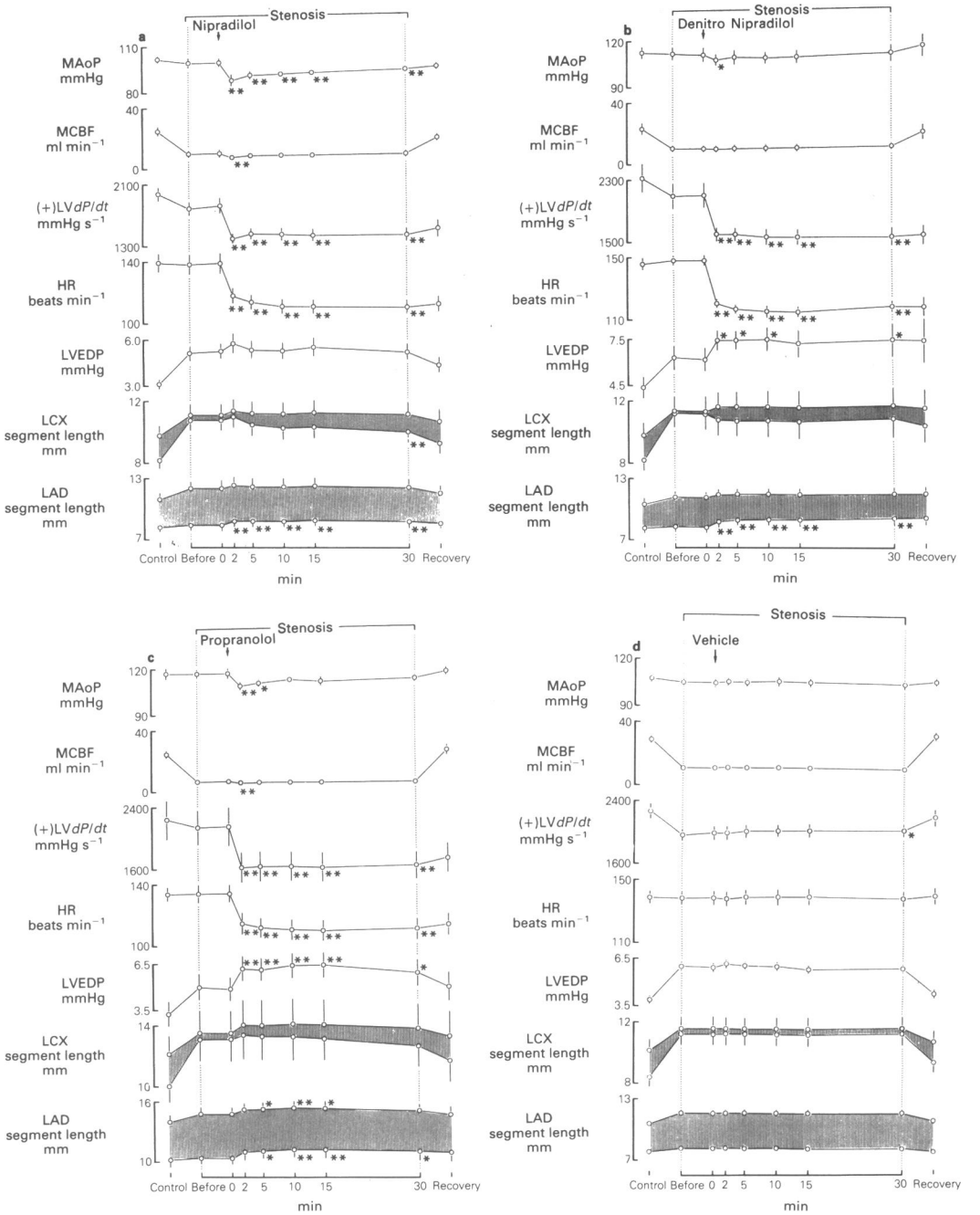

Figure 2 Effects of nipradilol (0.1 mg kg^{-1} i.v., $n = 10$; a), its denitrated derivative (0.2 mg kg^{-1} i.v., $n = 6$; b), propranolol (0.2 mg kg^{-1} i.v., $n = 6$; c) and vehicle ($n = 15$; d) on haemodynamic variables and myocardial segment shortening in ischaemic (LCX) and non-ischaemic (LAD) region. MAoP = mean aortic pressure. (+)LV$dP/dt$ = positive left ventricular dP/dt. LVEDP = left ventricular end-diastolic pressure. See the legend to Figure 1 for other abbreviations. Data obtained during coronary stenosis were analysed by two-way analysis of variance and asterisks indicate significant differences from the respective predrug value (*$P < 0.05$; **$P < 0.01$). Data represent mean with vertical lines showing s.e.

Table 1 Effects of vehicle ($n = 15$), nipradilol (0.1 mg kg^{-1}, $n = 10$), denitro nipradilol (0.2 mg kg^{-1}, $n = 6$) and propranolol (0.2 mg kg^{-1}, $n = 6$) on percentage segment shortening in ischaemic (LCX-perfused) and non-ischaemic (LAD-perfused) myocardium

		Stenosis			
			After administration		
	No stenosis	*Before*	*15 min*	*30 min*	*Recovery*
Ischaemic area					
Vehicle	17.5 ± 1.3	2.7 ± 0.8	2.9 ± 1.0	2.8 ± 1.0	12.6 ± 1.3
Nipradilol	16.2 ± 1.3	3.2 ± 0.7	8.4 ± 1.1**[b]	10.2 ± 1.4**[b]	13.0 ± 1.1
Denitro nipradilol	16.3 ± 1.3	1.5 ± 0.9	8.4 ± 2.3**[a]	7.8 ± 2.1**[a]	10.0 ± 1.6
Propranolol	17.4 ± 1.4	3.3 ± 0.7	6.5 ± 0.6**	8.4 ± 1.1**[a]	12.4 ± 0.7
Non-ischaemic area					
Vehicle	25.4 ± 2.1	29.5 ± 2.1	29.9 ± 2.2	29.8 ± 2.1	27.9 ± 2.0
Nipradilol	24.9 ± 1.7	29.6 ± 2.2	26.6 ± 2.1**	26.6 ± 2.2**	24.8 ± 2.2
Denitro nipradilol	22.5 ± 2.4	26.4 ± 2.2	21.9 ± 2.2**	21.0 ± 2.5**	20.2 ± 2.1
Propranolol	27.4 ± 2.1	30.1 ± 2.1	27.2 ± 3.0*	27.1 ± 3.2*	25.9 ± 3.0

*$P < 0.05$, **$P < 0.01$ when data during coronary stenosis were compared with those obtained just before drug administration.

[a] $P < 0.05$, [b] $P < 0.01$ when compared with the corresponding data of vehicle group. Data are expressed as mean ± s.e.

during coronary stenosis, the preparation used in the present study was stable. Thus, changes of these variables observed during the corresponding period after drug administration were due to pharmacological effects.

We found that nipradilol improved the impared regional contractility in the ischaemic myocardium and this was accompanied by amelioration of abnormal cardiac lactate metabolism. These data clearly indicate that nipradilol alleviates myocardial ischaemia induced by a coronary stenosis. Improvement of systolic function in post-stenotic myocardium was observed also after administration of a denitro derivative of nipradilol or propranolol, which lack the vasodilator property of nipradilol. These findings are in agreement with the previous studies that a β-adrenoceptor blocking agent(s) given during coronary stenosis exerted beneficial effects on the ischaemic myocardium in anaesthetized (Buck *et al.*, 1979; Abiko & Sakai, 1980; Thuillez *et al.*, 1983) and conscious dogs (Tomoike *et al.*, 1978). Doses of all three agents employed in this study produced significant negative inotropic and chronotropic actions. It is likely that the mechanism of action of denitro nipradilol involved an improvement of regional myocardial function distal to a stenosis. It is also likely that propranolol acted in a similar way, since the time course and the extent of changes in haemodynamic variables and regional myocardial contractility after denitro nipradilol closely resembled those after propranolol, and were associated with comparable inhibitions of isoprenaline-induced changes in heart rate (Figure 2).

Denitro nipradilol and propranolol significantly increased LVEDP, associated with decreases in heart rate and myocardial contractility but nipradilol had no effect on LVEDP. This haemodynamic characteristic of nipradilol, distinct from those of the other two agents may have resulted from systemic venodilation due to the nitrate moiety in its structure (Kou & Suzuki, 1983). Myocardial oxygen consumption is proportional to the left ventricular diastolic volume, in addition to heart rate and contractility. Endocardial perfusion in the ischaemic area, which has been demonstrated to correlate with regional myocardial function (Vatner, 1980; Gross *et al.*, 1984), is likely to be compromised by an increase in LVEDP (Kjekshus, 1973). Thus, theoretically, lessening the preload should lead to reduced ischaemic damage in the heart. If an increase in preload to the heart, caused by denitro nipradilol or propranolol, had an important influence on myocardial ischaemia, nipradilol should possess an advantage over the former agents. However, all three drugs equally increased percentage segment shortening distal to a coronary stenosis (Table 1). Therefore, these findings suggest that the main mechanism of action of nipradilol was attributable to the decrease in heart rate and contractility through blockade of β-adrenoceptors in the heart. Although a venodilator action of nipradilol probably served to prevent an increase in LVEDP despite its negative chronotropic and inotropic actions, this effect seems to play only a minor role in lessening myocardial ischaemia.

Recently, Geffin *et al.* (1986) showed that dyskinesis in the ischaemic region of canine heart diminished as ventricular filling increased, suggesting that an increase in LVEDP might passively enhance percentage systolic shortening in the ischaemic myocardium

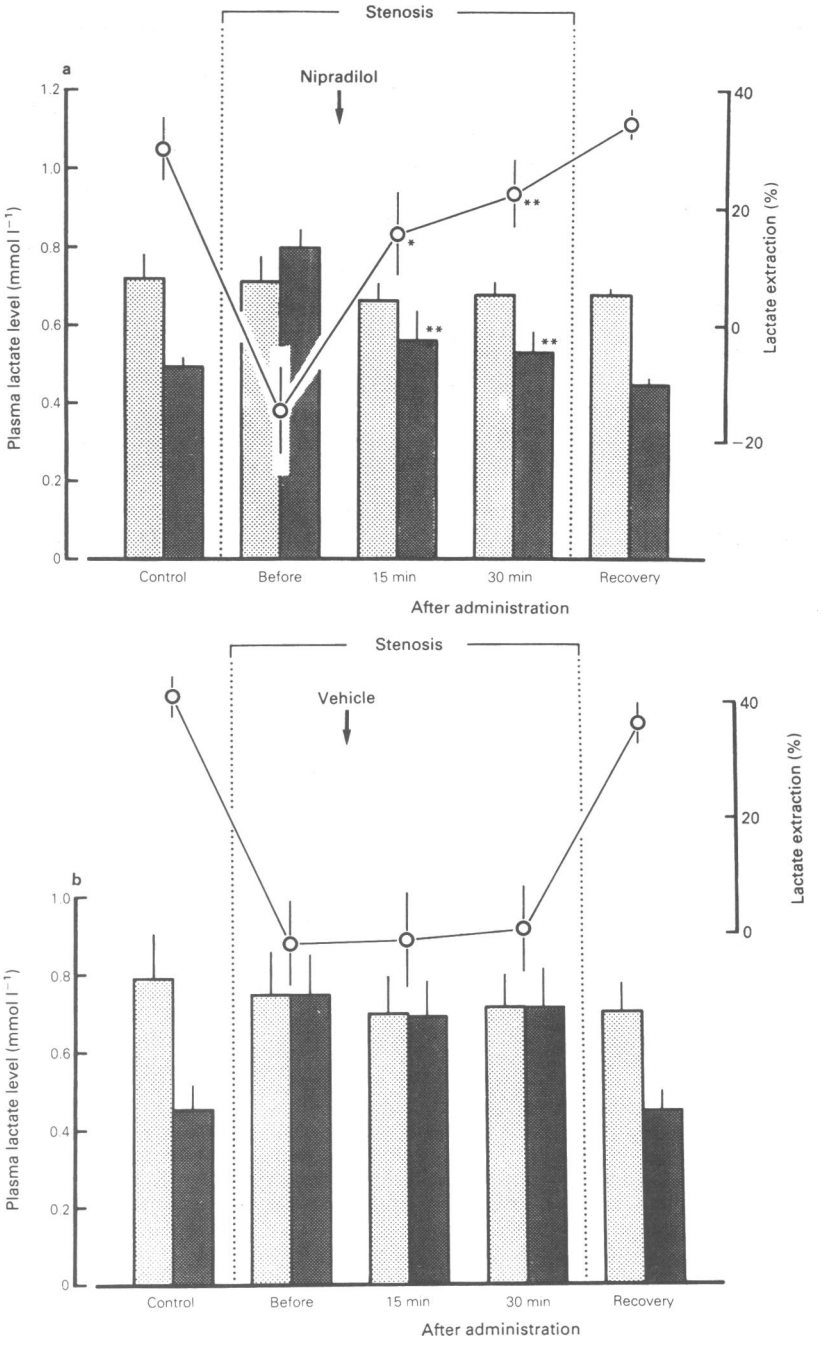

Figure 3 Effects of nipradilol (0.1 mg kg^{-1} i.v., $n = 5$; a) and the vehicle ($n = 7$; b) on lactate levels (mmol l^{-1}) in arterial (stippled columns) and coronary sinus (solid columns) blood and percentage lactate extraction in the heart (○). Percentage lactate extraction was calculated from the following equation: %lactate extraction = (the difference between lactate levels of arterial and coronary sinus blood/the level of arterial blood) × 100. Note that a negative value of percentage lactate extraction means net production of lactate in the heart. *$P < 0.05$; **$P < 0.01$, when compared with the respective predrug value by two-way analysis of variance. Data represent mean with s.e. indicated by vertical lines.

without actual improvement of the regional contractility. From this point of view, a critical comparison of the beneficial effects of nipradilol, denitro nipradilol and propranolol on myocardial ischaemia may require further clarification.

Improvement by nipradilol of ischaemic segment function was almost abolished after atrial pacing, with little change in the other haemodynamic variables. These results may be consistent with the view that slowing of heart rate is of importance in the mechanisms related to the restoration of regional function in the ischaemic area distal to a coronary stenosis (Schamhardt *et al.*, 1981; Gross *et al.*, 1984; Berdeaux *et al.*, 1984).

Nipradilol has been reported to possess an α-adrenoceptor blocking action (Uchida *et al.*, 1983; Asada *et al.*, 1982; Nanjo & Kitamura, 1984) as well as a non-selective β-adrenoceptor blocking action (Uchida *et al.*, 1983; Sakanashi *et al.*, 1984; Nagatomo *et al.*, 1984), although the α-blocking action of nipradilol has been shown to be approximately 50 times less potent than the β-blocking action (Uchida *et al.*, 1983). A membrane stabilizing action of this agent has been also demonstrated in canine cardiac tissues (Nakaya *et al.*, 1984). These effects may, in part, contribute to the beneficial influences of nipradilol.

In conclusion, nipradilol can alleviate acute myocardial ischaemia produced by coronary stenosis, as shown by improvement of regional myocardial function and lactate metabolism. The major part of the beneficial effects seems to result from depression of myocardial contractility and, in particular, a decrease in heart rate.

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