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Effect of Nipradilol on Myocardial Energy Metabolism in the Dog Ischaemic Heart

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Abstract—The effect of nipradilol, a newly developed β-adrenoceptor blocking agent with a vasodilatory action, on myocardial energy metabolism has been examined in the dog ischaemic heart, and compared with that of propranolol. Ischaemia was induced by ligating the left anterior descending coronary artery. Either saline, nipradilol (0·3 mg kg^{-1}), or propranolol (1 mg kg^{-1}) was injected intravenously 5 min before coronary ligation. After 3 or 30 min of coronary ligation, the ischaemic region of the myocardium was removed, and the endocardial portion used to determine the levels of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), creatine phosphate (CrP) and lactate. Ischaemia decreased the levels of ATP and CrP, and increased the levels of ADP, AMP and lactate. Immediately after the injection of nipradilol, rapid falls in blood pressure and heart rate were observed. Pretreatment with nipradilol lessened the decreases in the levels of ATP and CrP and the increases in the levels of AMP and lactate, caused by 3 min of ischaemia, to the same extent as propranolol. However, after 30 min of ishchaemia, nipradilol had no effect on myocardial metabolism unlike propranolol. These results indicate that nipradilol can reduce ischaemic influences on myocardial metabolism as well as propranolol, but only in the early stages of ischaemia.

β-Adrenoceptor blocking agents reduce the severity of ischaemic injury in the myocardium because they decrease myocardial oxygen consumption. Propranolol, a typical representative of this group, decreases both myocardial contractility and heart rate, while at the same time tending to inhibit the vasodilatory effect due to β-adrenergic action (Robertson et al 1982; Vatner & Hintze 1983). This inhibitory action on vasodilation causes an increase in coronary resistance which may worsen myocardial ischaemia. On the other hand, organic nitrates, another group of anti-anginal drugs, also decrease oxygen consumption of the ischaemic myocardium through systemic vasodilation. 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 blocking agents and nitrates may provide increased efficacy over single drug use (Frishman 1985; Kaski et al 1985).

Nipradilol, 3,4-dihydro-8-(2-hydroxy-3-isopropylamino)-propoxy-3-nitroxy-2H-l-benzopyran, is a recently synthesized agent which has a propranolol-like structure and contains a nitrate moiety (Uchida et al 1987). It shows both β-adrenoceptor blocking activity and a nitroglycerin-like vasodilatory activity (Uchida et al 1983). Noguchi & Sakanashi (1987) reported that nipradilol alleviates acute myocardial ischaemia produced by partial occlusion of the left circumflex in the anaesthetized dog. Higuchi & Asakawa (1987) using an extra-corporeal circuit method, reported that nipradilol improves the ischaemic derangement of both transmural energy metabolism and haemodynamics in dogs, and Haneda et al (1989) observed a protective effect of nipradilol on the ischaemic myocardium in the rat isolated perfused heart.

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We have attempted to evaluate anti-anginal and anti-ischaemic effects of a drug using anaerobic metabolism in the ischaemic myocardium, as an indicator. Under these conditions, ischaemia changes myocardial metabolism from aerobic to anaerobic, and a drug that reduces ischaemic injury can switch the metabolism back to the aerobic mode. The present study was undertaken to examine the effects of nipradilol on ischaemic myocardial metabolism and to compare them with the effects of propranolol.

Materials and Methods

Healthy mongrel dogs of either sex, 6·2 to 14 kg, were anaesthetized with sodium pentobarbitone, (30 mg kg^{-1} i.v.), and endotracheally intubated and ventilated with a respirator. A left thoracotomy was performed between the fourth and fifth ribs to expose the left ventricular wall. After the heart was suspended in a pericardial cradle, the main trunk of the left anterior descending coronary artery (LAD) was dissected free from the adjacent tissues just proximal to the first diagonal branch, and was loosely encircled with a 2-0 silk thread ligature. Ischaemia was initiated by ligating the LAD. Ischaemia of the myocardium was assessed by visible cyanosis and by the elevation of ST segment of the electrocardiogram measured by a wire electrode attached to the surface of the left ventricular wall. Heart rate was monitored from the electrocardiogram reference lead on the limb. Arterial blood pressure was measured via a cannula introduced into the left carotid artery. Coronary blood flow was measured with an electromagnetic flow probe positioned proximal to the ligature. All parameters were recorded on a polygraph (model 146, San-Ei Instrument, Tokyo, Japan).

After 30–60 min of control observations, the dogs were divided into three groups, i.e. saline-, nipradilol- and propranolol-treated animals. Two series of experiments were performed in each group, with and without ligation. In the

non-ligation experiments, 0·9% NaCl (saline) or drug solution was injected intravenously into the left femoral vein at a volume of 0·5 mL kg^{-1}. Propranolol (±propranolol HCl) was dissolved in saline, and nipradilol (Kowa Co., Tokyo, Japan) was dissolved in saline to which HCl was added at a final concentration of 0.0067%. The final concentrations were 0·6 mg mL^{-1} for nipradilol and 2 mg mL^{-1} for propranolol, giving equiactive doses of nipradilol and propranolol of 0·3 mg kg^{-1} and 1 mg kg^{-1}, respectively (Uchida et al 1983). In the ligation experiments, saline or drug solution was also injected 5 min before LAD ligation. When the ischaemia had been produced for 3 min (3 min-ischaemia) or 30 min (30 min-ischaemia) a full thickness sample of the myocardium was taken from the centre of the ischaemic area. An equivalent sample was taken from the non-ligation experiments (without ischaemia). The samples were immediately pressed and frozen with clamps previously chilled in liquid nitrogen in such a way that the endocardial portion of the myocardium could be taken separately for analysis of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), creatine phosphate (CrP) and lactate in neutralized perchloric acid extract according to the standard enzymatic procedure (Bergmeyer 1974).

Data were evaluated using analysis of variance; a P value of 0·05 or less was considered significant.

Results and Discussion

The results of the experiments are shown in Fig. 1 and Tables 1 and 2. We have previously reported that propranolol inhibits myocardial metabolic changes by coronary ligation (Ichihara & Abiko 1977), and attenuates myocardial acidosis caused by ischaemia (Ichihara & Abiko 1982). We have also reported that nitroglycerin is effective in reducing ischaemic metabolic changes in the dog heart (Ichihara & Abiko 1975a; Shibano & Abiko 1983). These findings suggest that both propranolol and nitroglycerin protect the myocardium against ischaemic injury.

In the present study, nipradilol injection decreased systolic and diastolic blood pressure, heart rate and coronary flow. Similar results were obtained following the injection of propranolol, except that the blood pressure did not change (Fig. 1). Therefore, it is likely that the rapid decrease in systolic and diastolic pressure after nipradilol is due to the action of the nitro group in its chemical structure. The reason why the coronary flow after nipradilol decreased more markedly than that after propranol could be that decreases in blood pressure and heart rate in nipradilol-treated heart are more severe than those in the propranolol-treated heart.

Coronary artery ligation decreased the levels of ATP and CrP, and increased the levels of ADP, AMP and lactate (Tables 1, 2). These results indicate that the myocardium became deficient in energy and that myocardial metabolism was accelerated anaerobically in order to produce energy for the contraction. After a short period of ischaemia (3 min), animals pretreated with nipradilol showed a smaller decrease in ATP levels and a smaller increase in AMP levels ($P < 0·01$), compared with saline-treated controls. Nipradilol maintained the total adenine nucleotide store in the ischaemic myocardium at the level of that in the non-ischaemic myocardium (Table 1). Nipradilol also inhibited the decrease in CrP level and the increase in lactate level significantly ($P < 0·05$ and $P < 0·01$, respectively) (Table 2). These results suggest that nipradilol reduces the energy deficiency in the ischaemic myocardium, by switching metabolism back from

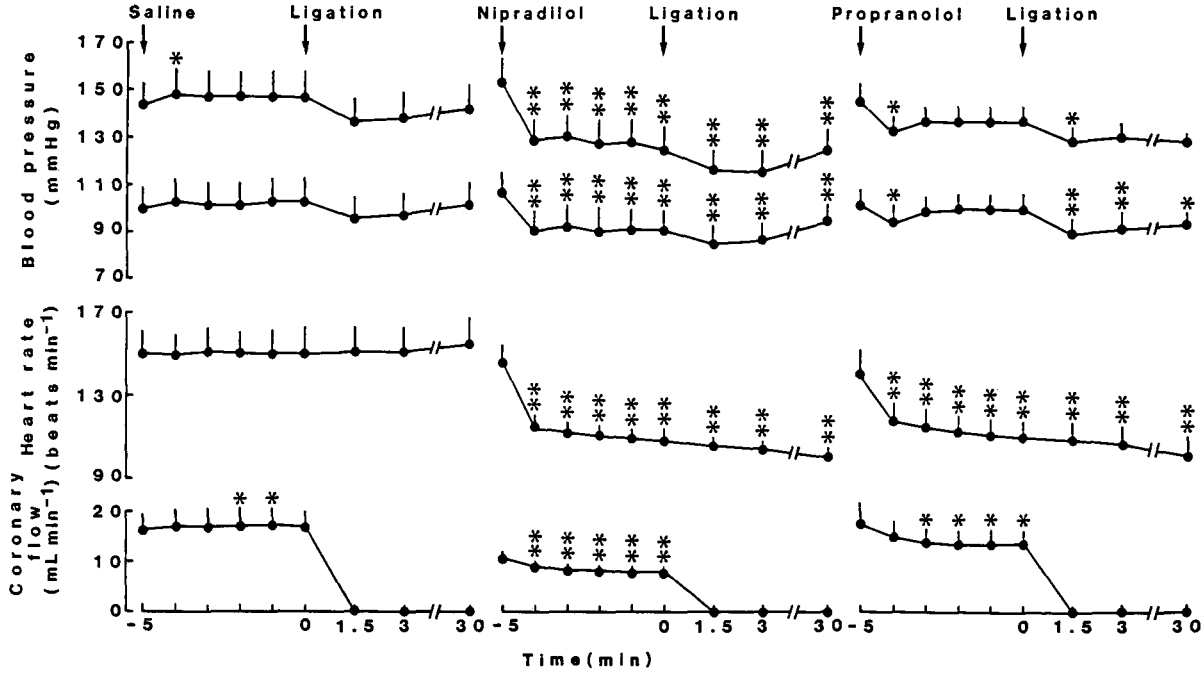

FIG. 1. Haemodynamic changes in the dogs with left anterior descending coronary artery ligated for 30 min. Either saline or drug (nipradilol 0·3 mg kg^{-1} or propranolol 1 mg kg^{-1}) was injected intravenously 5 min before the ligation. Data are means ± s.e.m. of 7–10 observations in each group. $*P < 0·05$, $**P < 0·01$, compared with the value 5 min before ligation in each group (paired data analysis).

Table 1. Effects of nipradilol and propranolol on changes in the levels of adenine nucleotides during ischaemia.

	n	ATP	ADP	AMP	Total adenine nucleotides
Non-ischaemia					
Saline	12	4·80 ± 0·10	1·01 ± 0·06	0·11 ± 0·02	5·92 ± 0·11
Nipradilol	10	4·89 ± 0·15	1·01 ± 0·04	0·10 ± 0·01	5·99 ± 0·16
Propranolol	5	5·08 ± 0·10	1·04 ± 0·06	0·18 ± 0·01††	6·29 ± 0·14
3 min-ischaemia					
Saline	8	3·77 ± 0·14**	1·33 ± 0·07*	0·20 ± 0·02**	5·31 ± 0·20*
Nipradilol	10	4·48 ± 0·16††	1·21 ± 0·06*	0·12 ± 0·01††	5·80 ± 0·16
Propranolol	7	4·53 ± 0·14**·††	1·12 ± 0·07	0·19 ± 0·02	5·84 ± 0·18
30 min-ischaemia					
Saline	10	2·68 ± 0·28**	0·83 ± 0·05*	0·17 ± 0·03	3·68 ± 0·27**
Nipradilol	8	2·43 ± 0·36**	0·94 ± 0·03	0·13 ± 0·02	3·50 ± 0·36
Propranolol	7	3·08 ± 0·46**	0·98 ± 0·04†	0·21 ± 0·02	4·27 ± 0·47**

Saline, nipradilol (0·3 mg kg^{-1}) or propranolol (1 mg kg^{-1}) was injected 5 min before coronary artery ligation.

Values are means (μmol g^{-1} wet weight) ± s.e.m.

* $P < 0·05$; ** $P < 0·01$, compared with "Non-ischaemia" in each group.

† $P < 0·05$; †† $P < 0·01$, compared with the respective groups in "Saline".

Table 2. Effects of nipradilol and propranolol on changes in the levels of CrP and lactate during ischaemia.

	n	CrP	Lactate
Non-ischaemia			
Saline	12	4·62 ± 0·37	1·83 ± 0·27
Nipradilol	10	6·85 ± 0·17††	1·52 ± 0·37
Propranolol	5	5·66 ± 0·46	0·91 ± 0·18†
3 min-ischaemia			
Saline	8	1·48 ± 0·23**	10·64 ± 0·98**
Nipradilol	10	3·37 ± 0·62**·†	5·54 ± 0·93**·††
Propranolol	7	3·48 ± 0·69*·†	5·46 ± 1·19**·††
30 min-ischaemia			
Saline	10	2·70 ± 0·39**	15·54 ± 2·87**
Nipradilol	8	1·50 ± 0·30**·†	21·72 ± 1·80**
Propranolol	7	2·81 ± 0·82*	8·15 ± 1·91**·†

Saline, nipradilol (0·3 mg kg^{-1}) or propranolol (1 mg kg^{-1}) was injected 5 min before coronary artery ligation.

Values are means (μmol g^{-1} wet weight) ± s.e.m.

* $P < 0·05$; ** $P < 0·01$, compared with "Non-ischaemia" in each group.

† $P < 0·01$; †† $P < 0·01$, compared with the respective groups in "Saline".

anaerobic to aerobic during the first 3 min of ischaemia. It is suggested that nipradilol inhibits the degradation and outflow of adenine nucleotides in the myocardium and keeps the energy state aerobic even after 4 min of ischaemia.

After the 30 min ischaemia, animals pretreated with nipradilol showed no attenuation of the ATP and CrP levels decreased by ischaemia, and lactate levels increased (Tables 1, 2). Thus, almost all the metabolic parameters of the nipradilol-treated heart suggested that nipradilol did not protect the myocardium after 30 min of ischaemia. This may be because blood pressure and heart rate remained low; coronary perfusion of the ischaemic area of the nipradilol-treated heart would be considerably less than that of the saline-treated heart.

The effect of pretreatment with propranolol was similar to that of nipradilol after 3 min of coronary ligation (Tables 1, 2). Propranolol protects the ischaemic myocardium largely because of its β-adrenoceptor blocking action (Ichihara & Abiko 1987). Propranolol and nipradilol decreased heart rate by about 25% (Fig. 1), suggesting that the β-adrenocep-

tor blocking action of nipradilol at 0·3 mg kg^{-1} is equivalent to that of propranolol at 1 mg kg^{-1}. This is in agreement with the findings of Uchida et al (1983) and Fujii et al (1986) who reported that the β-adrenoceptor blocking action of nipradilol is about two to three times as effective as that of propranolol. Furthermore, we (Hino et al 1989; Haneda et al 1989) have shown that nipradilol and propranolol can have similar effects on the ischaemic myocardium e.g. by improving recovery of mechanical function after reperfusion. However, after 30 min of ischaemia, nipradilol had even less effect on ATP, CrP and lactate changes than propranolol, probably as a result of the drug's sustained vasodilatory action which is considered useful for angina pectoris, because the critical ischaemic changes occur within a few minutes after the onset of ischaemia (Ichihara & Abiko 1975b).

In conclusion, nipradilol can protect the heart against the early stages of ischaemic change in the same way as propranolol.

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