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Abstract

Nipradilol (3,4-dihydro-8-(2-hydroxy-3-isopropylamino) propoxy-3-nitroxy-2H-1-benzopyran) is a newly synthesized chemical agent designed to possess beta-adrenoceptor blocking and vasodilating actions. Nipradilol decreased left ventricular contractility index (E_{max}, slope of the ventricular end-systolic pressure-volume relation), systolic pressure-volume area (PVA, a measure of ventricular total mechanical energy) and oxygen consumption in cross-circulated excised dog hearts. However, nipradilol did not decrease total coronary resistance. These results indicate that nipradilol, like propranolol, depresses myocardial mechanoenergetics and that the vasodilating action of nipradilol could not be detected in the present study.

KEYWORDS: cardiac mechanics, cardiac energetics, coronary circulation, ventricle, β -blocker

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Nipradilol Depresses Cardiac Contractility and O₂ Consumption without Decreasing Coronary Resistance in Dogs

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Nipradilol (3, 4-dihydro-8-(2-hydroxy-3-isopropylamino) propoxy-3-nitroxy-2H-1-benzopyran) is a newly synthesized chemical agent designed to possess β -adrenoceptor blocking and vasodilating actions. Nipradilol decreased left ventricular contractility index (E_{max}, slope of the ventricular end-systolic pressure-volume relation), systolic pressure-volume area (PVA, a measure of ventricular total mechanical energy) and oxygen consumption in cross-circulated excised dog hearts. However, nipradilol did not decrease total coronary resistance. These results indicate that nipradilol, like propranolol, depresses myocardial mechanoenergetics and that the vasodilating action of nipradilol could not be detected in the present study.

Key words : cardiac mechanics, cardiac energetics, coronary circulation, ventricle, β -blocker

Nipradilol (3, 4-dihydro-8-(2-hydroxy-3-isopropylamino) propoxy-3-nitroxy-2H-1-benzopyran) is a newly synthesized vasodilating β -adrenoceptor blocker (1) (Fig. 1) that also possesses an α -blocking action. The aminopropranol side chain and nitroester group of this molecule are expected to exert β -adrenoceptor blocking and vasodilatory actions, respectively. Actually many investigators have reported that nipradilol exerts potent β -adrenoceptor and less potent α -adrenoceptor blocking actions and a nitroglycerin-like vasodilative action on the

coronary artery (1-6).

In the present study, the effects of nipradilol, continuously infused intracoronarily, on cardiac mechanics, energetics and coronary circulation were examined in cross-circulated excised dog hearts.

Materials and Methods

The materials and methods used in this study were essentially the same as previously described (7, 8). Two mongrel dogs were anesthetized with pentobarbital sodium (25 mg/kg, i.v.) after premedication with ketamine hydrochloride (50 mg per dog, i.m.) in each experiment. The cross-circulated heart was excised under coronary perfusion. A flabby rubber balloon with an unstretched volume of 50 ml was fitted into the left ventricle (LV). The balloon, primed with water, was connected to a custom-made volume servo pump (Bokusui-Brown, Tokyo, Japan). The left atrium was electrically paced at 129 ± 21 (SD) beats/min.

Contractility. E_{max} (slope of ventricular end-systolic pressure-volume relation) of the LV was assessed by the ratio of peak isovolumic LV pressure divided by LV volume above V₀ (7, 8). V₀ was determined as the volume at which peak isovolumic pressure was zero. T_{max}, defined as the time to E_{max} from the rising phase of the R wave of the ECG, was determined. T_{max}

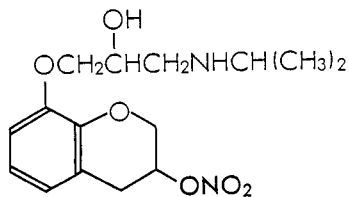


Fig. 1 Chemical structure of nipradilol (3,4-dihydro-8-(2-hydroxy-3-isopropylamino) propoxy-3-nitroxy-2H-1-benzopyran)

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was used as a measure of the speed of contraction. E_{max} and T_{max} were computed on-line with a signal processor (7T 18, NEC San-ei, Tokyo).

Pressure-volume area. PVA, an abbreviation of systolic ventricular pressure-volume (P-V) area (7-9), was obtained as the area in the LV P-V diagram which was bounded by the end-systolic P-V line, the end-diastolic P-V relation curve and the isovolumic P-V trajectory.

Oxygen consumption. Total coronary blood flow (CF) was measured with an electromagnetic blood flowmeter (Nihon Kohden, MFV-3200, Tokyo) in the coronary venous cross-circulation tube. Coronary arteriovenous oxygen content difference was continuously measured with a custom-made oximeter (PWA-200S, SHOE TECHNICA Inc, Chiba) (10). The oximeter was calibrated against an oxygen content analyzer (IL-382 CO-oximeter). Cardiac oxygen consumption (V_{O_2}) was obtained as the product of total coronary flow and arteriovenous oxygen content difference. It was divided by heart rate to obtain V_{O_2} per beat in steady state. Right ventricular (RV) V_{O_2} was minimized by collapsing the RV by continuous hydrostatic drainage of the coronary venous return. The collapsed RV was assumed to have virtually zero PVA and, hence, no PVA-dependent V_{O_2} (7, 8). LV PVA-independent V_{O_2} was calculated by subtracting RV PVA-independent V_{O_2} from the biventricular PVA-independent V_{O_2} in each contractile state as described previously (11, 12).

Coronary resistance. Systemic arterial blood pressure (BP) of the support dog, which corresponded to coronary perfusion pressure in the isolated heart, was measured in the left common carotid artery. BP was divided by CF to obtain total coronary resistance.

Experimental protocol. The experimental protocol consisted of two runs: control run and nipradilol run.

Control run. In a stable control contractile state, steady-state isovolumic contractions were produced at four to six different end-diastolic volumes to cover wide ranges of V_{O_2} and PVA. Peak isovolumic pressure ranged between 0 mmHg (at V_0) and 150 mmHg. Although we used only isovolumic contractions, we assumed that the contraction mode did not affect the result, since the V_{O_2} -PVA relation is virtually independent of the mode of contraction (9, 11, 13). E_{max} , V_{O_2} and PVA and other data were measured three times in steady state at each LV volume and these values were averaged to obtain a single set of mean data for each LV volume.

Nipradilol run. We fixed LV volume at an intermediate level (14.8-20.8 ml) where peak isovolumic pressure was within 80-115 mmHg. E_{max} was decreased in steps at about 4-15 min intervals to obtain four to eight sets of E_{max} , V_{O_2} and PVA at the preset volume, as shown in Fig. 2. E_{max} , V_{O_2} , PVA and other data were measured three times in steady state at each contractility level and these values were averaged to obtain one set of mean values for each contractility level. The concentration of nipradilol used in this study was 0.01%. The maximum dose of nipradilol was 0.027-0.067 mg/min into the coronary arterial tubing. We calculated these doses to correspond to blood concentrations of 0.17-1.26 mg/L of nipradilol under coronary flow of 53-153 ml/min. This

dosage is comparable to those used previously *in vivo* experiments in dogs (5).

Data Analysis

Control V_{O_2} -PVA relation. The control V_{O_2} and PVA data were subjected to linear regression analysis to obtain a control regression equation (7, 8, 13): $V_{O_2} = aPVA + b$, where **a** is the slope of the regression line and **b** is the V_{O_2} intercept. Slope **a** indicates the oxygen cost of PVA (7-9). **aPVA** represents the PVA-dependent V_{O_2} and **b** represents the PVA-independent V_{O_2} (7, 9, 11).

Oxygen cost of E_{max} . We calculated the oxygen cost of E_{max} when E_{max} decreased with nipradilol. PVA-independent V_{O_2} at each level of decreased E_{max} was calculated as LV V_{O_2} minus **aPVA** in the same way as before (12, 14). In this calculation, we assumed that slope **a** remained the same at all E_{max} levels. This assumption was based on the parallelism of the V_{O_2} -PVA relation which had been established with various positive and negative inotropic agents including catecholamines, calcium, a β -blocker propranolol, and a calcium antagonist verapamil (7-9, 12). Since the relation between these PVA-independent V_{O_2} values and the corresponding E_{max} values in nipradilol run in individual hearts was linear as described in the Results (Fig. 3), we obtained a regression line of PVA-independent V_{O_2} on E_{max} in each heart. The slope (**c**) of this regression line determined the oxygen cost of E_{max} (12, 14). The y intercept (**d**) of this regression line was obtained as the PVA-independent V_{O_2} extrapolated to zero E_{max} (14).

Statistics. Comparison of mean values of the control data with nipradilol data was performed by paired *t* test (Table 3). P values smaller than 0.05 were considered statistically significant. Data are presented as mean \pm SD.

Results

In every tested heart, V_{O_2} increased linearly with PVA with a correlation coefficient (*r*) close to unity (0.981) in the control run with a stable contractile state. Fig. 2 shows representative V_{O_2} -PVA data points in the control volume run and nipradilol run in a heart. The

Table 1 Summary of E_{max} and V_{O_2} -PVA relation in control run

No. of hearts	4
E_{max} (mmHg/ml per 100 g)	6.9 ± 2.5
V_{O_2} -PVA correlation coefficient	0.975 - 0.997
Slope (a) (10^{-5} ml O_2 / (mmHg ml))	1.79 ± 0.41
PVA-independent V_{O_2} (b) (ml O_2 /beat per 100 g)	0.0190 ± 0.006

Mean \pm SD except for the range of correlation coefficient. For **a** and **b**, see Data Analysis section of Text.

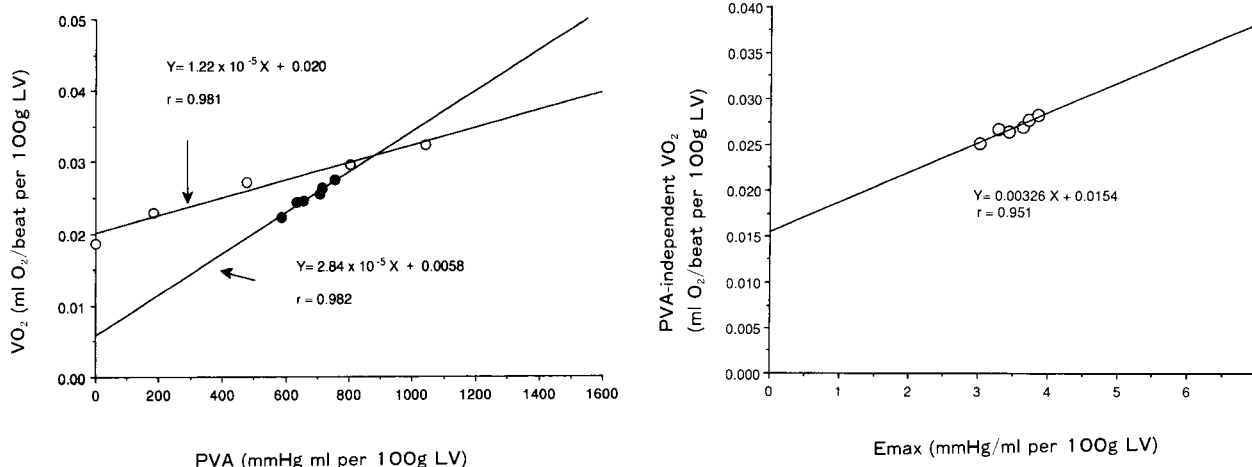


Fig. 2 (Left) Gradual downward deviation of the V_{O_2} (cardiac oxygen consumption per beat)-PVA (systolic ventricular pressure-volume area) data points (solid circles) with decreases in E_{max} (slope of the ventricular end-systolic pressure-volume relation) from 3.9 to 3.0 mmHg/ml per 100 g caused by intracoronary infusion of graded doses of nipradilol (0.027-0.067 mg/min). The slope of the V_{O_2} -PVA relation is $2.84 \times 10^{-5} \text{ ml O}_2/(\text{mmHg ml})$ with a correlation coefficient (r) of 0.982. Solid line connecting open circles indicates the control V_{O_2} -PVA relation before nipradilol. Slope (a) of the V_{O_2} -PVA relation is $1.22 \times 10^{-5} \text{ ml O}_2/(\text{mmHg ml})$ ($r = 0.981$). PVA-independent V_{O_2} (b) is $0.020 \text{ ml O}_2/\text{beat per } 100 \text{ g}$.

Fig. 3 (Right) Gradually decreased PVA-independent V_{O_2} with gradually decreased E_{max} by intracoronary infusion of nipradilol in the same heart as in Fig. 2. The relation had an r value of 0.951. Solid diagonal line is the linear regression line. The slope (c) of this line indicates the oxygen cost of E_{max} .

control E_{max} values, slope **a** and V_{O_2} intercept **b** as shown in Table 1 were similar to our previous results in the same type of dog heart preparation (7, 9, 12). Nipradilol gradually decreased E_{max} as its concentration was increased and moved the V_{O_2} -PVA data points (solid circles; $r = 0.982$) downward to the left from the pre-nipradilol data point. The slope of this relation was

obviously greater ($2.84 \times 10^{-5} \text{ ml O}_2/(\text{mmHg ml})$) than that ($1.22 \times 10^{-5} \text{ ml O}_2/(\text{mmHg ml})$) of the control V_{O_2} -PVA relation in this heart.

PVA-independent V_{O_2} values were calculated for all decreased E_{max} levels in the nipradilol run as explained above. Fig. 3 plots the PVA-independent V_{O_2} values thus obtained against corresponding E_{max} values in the same heart as shown in Fig. 2. In this heart, PVA-independent V_{O_2} decreased linearly with decreases in E_{max} with an r value close to unity (0.951). The nipradilol run in this heart yielded a linear regression line of PVA-independent V_{O_2} on E_{max} ($y = 0.00326x + 0.0154$). The oxygen cost of decreasing E_{max} is given by the slope **c** of this relation because of its linearity over the covered E_{max} range. Oxygen cost of E_{max} was $0.00326 \text{ (ml O}_2/\text{beat)/}(\text{mmHg/ml})$ per 100 g in this heart (Fig. 3). Similar results were obtained in two other hearts. However, in the other heart, changes in LV contractility and V_{O_2} were too small to obtain meaningful statistical results. Table 2 summarizes the results.

Table 2 Summary of varied E_{max} , V_{O_2} -PVA relation and PVA-independent V_{O_2} - E_{max} relation in nipradilol run

No. of hearts	3
Range of E_{max} (mmHg/ml per 100 g)	9.5 - 2.6
V_{O_2} -PVA correlation coefficient	0.981 - 0.993
Slope of the V_{O_2} -PVA relation ($10^{-5} \text{ ml O}_2/(\text{mmHg ml})$)	4.53 ± 1.59
PVA-independent V_{O_2} - E_{max} correlation coefficient	0.951 - 0.982
Slope (c) ((ml O ₂ /beat)/(mmHg/ml) per 100 g)	0.00305 ± 0.00022
PVA-independent V_{O_2} at zero E_{max} (d) (ml O ₂ /beat per 100 g)	0.0159 ± 0.0080

Range of E_{max} , maximum range of E_{max} covered in nipradilol run. Mean \pm SD except for the ranges of E_{max} and correlation coefficients. For **c** and **d**, see Data Analysis section of Text.

Table 3 lists E_{max} , V_{O_2} , PVA and other data before nipradilol and at the maximal dose of nipradilol. The data

Table 3 Summary of the effects of nipradilol on cardiac mechanoenergetics

	No. of hearts	E_{\max} (mmHg/ml per 100g)	T_{\max} (msec)	PVA (10^{-5} mmHg ml per 100g)	V_{O_2} (ml O_2 /beat per 100g)	CF (ml/min per 100g)	BP (mmHg)	CR (mmHg/(ml/min) per 100g)
Pre-nipradilol	4	6.9 ± 2.5	171 ± 19	714 ± 76	0.046 ± 0.012	173 ± 93	110 ± 6	1.27 ± 0.86
Maximum nipradilol	4	4.1 ± 1.7	179 ± 16	466 ± 204	0.034 ± 0.003	155 ± 78	101 ± 19	1.28 ± 0.76
% decrease	4	$65 \pm 24^*$	105 ± 12	$64 \pm 25^*$	$77 \pm 17^*$	89 ± 9	91 ± 13	105 ± 14

E_{\max} , slope of end-systolic pressure-volume relation. T_{\max} , time from onset of R wave of left ventricular epicardial electrocardiogram to E_{\max} . PVA, systolic pressure-volume area. V_{O_2} , O_2 consumption per beat. CF, coronary flow. BP, blood pressure of the support dog. CR, coronary resistance (= BP/CF). *, significantly different ($p < 0.05$) from pre-nipradilol.

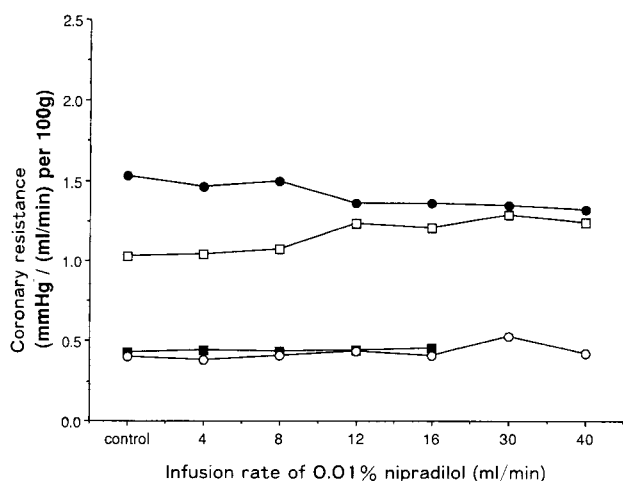


Fig. 4 Time trends of total coronary resistance under intracoronary infusion of graded doses of nipradilol in four hearts. Each line indicates data from each heart. Three of four preparations were further infused at 30 ml/min and 40 ml/min; coronary resistance was not changed during these infusions. An infusion rate of 16 ml/min corresponds to 0.027 mg/min. Control coronary resistance before infusion of nipradilol is shown at infusion rate 0.

indicate that (i) E_{\max} decreased significantly ($p < 0.05$) to $65 \pm 24\%$ of the pre-nipradilol; (ii) PVA significantly ($p < 0.05$) decreased to $64 \pm 25\%$ of the pre-nipradilol; (iii) V_{O_2} decreased significantly ($p < 0.05$) to $77 \pm 17\%$ of the pre-nipradilol. Coronary flow and perfusion pressure (which was equal to BP of the support dog) were only slightly reduced. Coronary resistance remained unchanged even at the maximal nipradilol (Table 3 and Fig. 4).

Discussion

Nipradilol depressed LV contractility in terms of

E_{\max} , mechanical energy in terms of PVA and V_{O_2} at a given LV end-diastolic volume like a β -adrenoceptor blocker propranolol (8). Suga *et al.* (8) have reported that propranolol (which retained coronary flow and O_2 supply) decreased E_{\max} to $51 \pm 11\%$ of control and lowered the V_{O_2} -PVA relation with a decreased PVA-independent V_{O_2} and without a change in slope. They concluded that negative inotropism by propranolol was not due to decreases in coronary flow and O_2 supply. The present result that nipradilol decreased E_{\max} without changes in coronary perfusion pressure and flow is in accordance with the previous report of propranolol (8). Therefore, we conclude that the negative inotropism of nipradilol is not associated with decreases in coronary flow and O_2 supply, but is due to the β -adrenergic receptor blocking action of nipradilol on myocardium.

On the other hand, nipradilol is expected to exert a vasodilating action due to the nitroester group of this molecule besides the negative inotropic β -adrenergic blocking action. Uchida *et al.* (1) reported that nipradilol potently relaxed the isolated canine large coronary artery. The vasodilating nature of nipradilol appeared to resemble that of nitroglycerin which has already been reported to act preferentially on the large coronary artery (15). Therefore, Uchida *et al.* (1) suggested that the potent relaxant action of nipradilol on the large coronary artery may possibly be an antianginal action similar to that of nitroglycerin. However, our present result has indicated that nipradilol only slightly decreased coronary perfusion pressure and flow without changing total coronary resistance throughout the nipradilol infusion. In anesthetized dogs myocardial V_{O_2} was significantly decreased by nipradilol at $100 \mu\text{g}/\text{kg}$ i.v. (5). Coronary blood flow was increased transiently and then decreased in association with diminished myocardial V_{O_2} (5, 6). Total coronary resistance decreased transiently and then increased gradu-

ally, whereas the resistance of the large coronary artery decreased consistently (6). The transient decrease in total coronary resistance and the dilation of the large coronary artery are likely to be due to the nitroglycerin-like vasodilator action of nipradilol.

In the present study, nipradilol actually decreased myocardial V_{O₂}. However, total coronary resistance was not increased by nipradilol infusion; no correlation between myocardial V_{O₂} and coronary resistance was found. Therefore, a decrease in coronary flow due to the coronary autoregulation associated with the diminished V_{O₂} may have been masked by the direct vasodilatory action of nipradilol. The contribution of vasoconstrictile action mediated via α -adrenoceptor after β_2 -blockade by nipradilol can be excluded, since nipradilol also has an α -blocking action (1-4). Alternatively, the β -adrenoceptor blocking action of nipradilol may decrease myocardial production of the vasodilator substances (16). The dilating action of nipradilol on the large coronary artery may not have been detected in this study, where the dilation may have been too small to decrease total coronary resistance.

In conclusion, nipradilol decreased myocardial contractility (E_{max}), systolic pressure-volume area (PVA) and oxygen consumption per beat in cross-circulated excised dog hearts. Nipradilol did not decrease total coronary resistance in these hearts.

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