Nipradilol depresses cardiac contractility and O2 consumption without decreasing coronary resistance in dogs.

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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 (Emax, 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

*PMID: 8096354 [PubMed - indexed for MEDLINE]
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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 (Emax, 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 aminopropanol 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 (Bokusu-Brown, Tokyo, Japan). The left atrium was electrically paced at 129 ± 21 (SD) beats/min.

Contractility. Emax (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 Emax from the rising phase of the R wave of the ECG, was determined. T_max

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was used as a measure of the speed of contraction. Emax and Tmax were computed on-line with a signal processor (7T18, 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 (Nichirui 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 (VO₂) was obtained as the product of total coronary flow and arteriovenous oxygen content difference. It was divided by heart rate to obtain VO₂ per beat in steady state. Right ventricular (RV) VO₂ 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 VO₂ (7, 8). LV PVA-independent VO₂ was calculated by subtracting RV PVA-independent VO₂ from the biventricular PVA-independent VO₂ 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 nifedipine 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 a wide range of VO₂ and PVA. Peak isovolumic pressure ranged between 0-150 mmHg. Although we used only isovolumic contractions, we assumed that the contraction mode did not affect the result, since the VO₂-PVA relation is virtually independent of the mode of contraction (9, 11, 13). Emax, VO₂ 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.

Nifedipine run. We fixed LV volume at an intermediate level (14.8-20.8 ml) where peak isovolumic pressure was within 80-115 mmHg. Emax was decreased in steps at about 4-15 min intervals to obtain four to eight sets of Emax, VO₂ and PVA at the preset volume, as shown in Fig. 2. Emax, VO₂, 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 nifedipine used in this study was 0.001%. The maximum dose of nifedipine 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 nifedipine 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 VO₂-PVA relation. The control VO₂ and PVA data were subjected to linear regression analysis to obtain a control regression equation (7, 8, 13): VO₂ = aPVA + b, where a is the slope of the regression line and b is the VO₂ intercept. Slope a indicates the oxygen cost of PVA (7-9). aPVA represents the PVA-independent VO₂ and b represents the PVA-independent VO₂ (7, 9, 11).

Oxygen cost of Emax. We calculated the oxygen cost of Emax when Emax decreased with nifedipine. PVA-independent VO₂ at each level of decreased Emax was calculated as LV VO₂ minus aPVA in the same way as before (12, 14). In this calculation, we assumed that slope a remained the same at all Emax levels. This assumption was based on the parallelism of the VO₂-PVA relation which had been established with various positive and negative isotropes such as catecholamines, calcium, a β-blocker propranolol, and a calcium antagonist verapamil (7-9, 12). Since the relation between these PVA-independent VO₂ values and the corresponding Emax values in nifedipine run in individual hearts was linear as described in the Results (Fig. 3), we obtained a regression line of PVA-independent VO₂ on Emax in each heart. The slope of this regression line determined the oxygen cost of Emax (12, 14). The y intercept (d) of this regression line was obtained as the PVA-independent VO₂ extrapolated to zero Emax (14).

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

Results

In every tested heart, VO₂ 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 VO₂-PVA data points in the control volume run and nifedipine run in a heart. The

<table>
<thead>
<tr>
<th>No. of hearts</th>
<th>Emax (mmHg/ml per 100 g)</th>
<th>VO₂-PVA correlation coefficient</th>
<th>Slope (a) (10⁻³ ml O₂ / (mmHg ml))</th>
<th>PVA-independent VO₂ (b) (ml O₂/beat per 100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>6.9 ± 2.5</td>
<td>0.957 ± 0.997</td>
<td>1.79 ± 0.41</td>
<td>0.0190 ± 0.006</td>
</tr>
</tbody>
</table>

Mean ± SD except for the range of correlation coefficient. For a and b, see Data Analysis section of Text.
control E\textsubscript{max} values, slope a and V\textsubscript{O\textsubscript{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\textsubscript{max} as its concentration was increased and moved the V\textsubscript{O\textsubscript{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 × 10\textsuperscript{-5} ml O\textsubscript{2}/(mmHg ml)) than that (1.22 × 10\textsuperscript{-5} ml O\textsubscript{2}/(mmHg ml)) of the control V\textsubscript{O\textsubscript{2}}-PVA relation in this heart.

PVA-independent V\textsubscript{O\textsubscript{2}} values were calculated for all decreased E\textsubscript{max} levels in the nipradilol run as explained above. Fig. 3 plots the PVA-independent V\textsubscript{O\textsubscript{2}} values thus obtained against corresponding E\textsubscript{max} values in the same heart as shown in Fig. 2. In this heart, PVA-independent V\textsubscript{O\textsubscript{2}} decreased linearly with decreases in E\textsubscript{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\textsubscript{O\textsubscript{2}} on E\textsubscript{max} (y = 0.00326x + 0.0154). The oxygen cost of decreasing E\textsubscript{max} is given by the slope c of this relation because of its linearity over the covered E\textsubscript{max} range. Oxygen cost of E\textsubscript{max} was 0.00326 (ml O\textsubscript{2}/(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\textsubscript{O\textsubscript{2}} were too small to obtain meaningful statistical results. Table 2 summarizes the results.

Table 3 lists E\textsubscript{max}, V\textsubscript{O\textsubscript{2}}, PVA and other data before nipradilol and at the maximal dose of nipradilol. The data

<table>
<thead>
<tr>
<th>No. of hearts</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range of E\textsubscript{max} (mmHg/ml per 100 g)</td>
<td>9.5 – 2.6</td>
</tr>
<tr>
<td>V\textsubscript{O\textsubscript{2}}-PVA correlation coefficient</td>
<td>0.981 – 0.993</td>
</tr>
<tr>
<td>Slope of the V\textsubscript{O\textsubscript{2}}-PVA relation (10\textsuperscript{-3} ml O\textsubscript{2}/(mmHg ml))</td>
<td>4.53 ± 1.59</td>
</tr>
<tr>
<td>PVA-independent V\textsubscript{O\textsubscript{2}}-E\textsubscript{max} correlation coefficient</td>
<td>0.951 – 0.982</td>
</tr>
<tr>
<td>Slope (c) (ml O\textsubscript{2}/(mmHg/ml) per 100 g)</td>
<td>0.00305 ± 0.00022</td>
</tr>
<tr>
<td>PVA-independent V\textsubscript{O\textsubscript{2}} at zero E\textsubscript{max} (ml O\textsubscript{2}/beat per 100 g)</td>
<td>0.0159 ± 0.0080</td>
</tr>
</tbody>
</table>

Range of E\textsubscript{max}, maximum range of E\textsubscript{max} covered in nipradilol run. Mean ± SD except for the ranges of E\textsubscript{max} and correlation coefficients. For c and d, see Data Analysis section of Text.
Table 3  Summary of the effects of nepadilol on cardiac mechanoenergetics

<table>
<thead>
<tr>
<th></th>
<th>No. of hearts</th>
<th>$E_{max}$ (mmHg/ml per 100g)</th>
<th>$T_{max}$ (msec)</th>
<th>PVA ($10^{-2}$ mmHg ml per 100g)</th>
<th>$V_{O_2}$ (ml O$_2$/beat per 100g)</th>
<th>CF (ml/min per 100g)</th>
<th>BP (mmHg)</th>
<th>CR (mmHg/(ml/min per 100g))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-nepadilol</td>
<td>4</td>
<td>6.9 ± 2.5</td>
<td>171 ± 19</td>
<td>714 ± 76</td>
<td>0.046 ± 0.012</td>
<td>173 ± 93</td>
<td>110 ± 6</td>
<td>1.27 ± 0.86</td>
</tr>
<tr>
<td>Maximum nepadilol</td>
<td>4</td>
<td>4.1 ± 1.7</td>
<td>179 ± 16</td>
<td>466 ± 204</td>
<td>0.034 ± 0.003</td>
<td>155 ± 78</td>
<td>101 ± 19</td>
<td>1.28 ± 0.76</td>
</tr>
<tr>
<td>% decrease</td>
<td>4</td>
<td>65 ± 24*</td>
<td>105 ± 12</td>
<td>64 ± 25*</td>
<td>77 ± 17*</td>
<td>89 ± 9</td>
<td>91 ± 13</td>
<td>105 ± 14</td>
</tr>
</tbody>
</table>

$E_{max}$ 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-nepadilol.

Fig. 4  Time trends of total coronary resistance under intracoronary infusion of graded doses of nepadilol 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 nepadilol is shown at infusion rate 0.

indicate that (i) $E_{max}$ decreased significantly (p < 0.05) to 65 ± 24% of the pre-nepadilol; (ii) PVA significantly (p < 0.05) decreased to 64 ± 25% of the pre-nepadilol; (iii) $V_{O_2}$ decreased significantly (p < 0.05) to 77 ± 17% of the pre-nepadilol. 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 nepadilol (Table 3 and Fig. 4).

Discussion

Nepadilol 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 ± 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 inotropic by propranolol was not due to decreases in coronary flow and $O_2$ supply. The present result that nepadilol 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 inotropic of nepadilol is not associated with decreases in coronary flow and $O_2$ supply, but is due to the β-adrenergic receptor blocking action of nepadilol on myocardium.

On the other hand, nepadilol 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 nepadilol potently relaxed the isolated canine large coronary artery. The vasodilating nature of nepadilol 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 nepadilol on the large coronary artery may possibly be an antianginal action similar to that of nitroglycerin. However, our present result has indicated that nepadilol only slightly decreased coronary perfusion pressure and flow without changing total coronary resistance throughout the nepadilol infusion. In anesthetized dogs myocardial $V_{O_2}$ was significantly decreased by nepadilol at 100 μg/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-

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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 VO₂. However, total coronary resistance was not increased by nipradilol infusion; no correlation between myocardial VO₂ and coronary resistance was found. Therefore, a decrease in coronary flow due to the coronary autoregulation associated with the diminished VO₂ may have been masked by the direct vasodilatory action of nipradilol. The contribution of vasocontractile action mediated via α-adrenoceptor after β₂-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 (Eₘₐₓ), 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.

Acknowledgments. The first author (D. D. Z.) greatly appreciates the Sasakawa Medical Scholarship. We greatly thank Prof. T. Tsuji, Chairman of the 1st Department of Medicine for generously allowing us to use his departmental 77-T 18 signal processor. We also thank Kowa Co. Ltd. for generously providing nipradilol. This study was partly supported by Grants-in-Aid (04237219, 04557041, 04454267) from the Ministry of Education, Science and Culture of Japan, Research Grants for Cardiovascular Diseases (3A-2, 4C-4) from the Ministry of Health and Welfare, and grants from Suzuki Memorial Foundation and Nakatani Electronic Measuring Technology Association of Japan.

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Received August 25, 1992; accepted September 28, 1992.