Effect of a New Beta-Blocker, Nipradilol, on Cardiac Function and Neurohumoral Factors in Idiopathic Dilated Cardiomyopathy

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This study investigated the therapeutic efficacy of a new beta-blocker, nipradilol, a non-selective agent with vasodilating activity, for the treatment of idiopathic dilated cardiomyopathy (DCM). The New York Heart Association functional class improved in the nipradilol group ($n=9$, $p<0.01$), but not in the control group who received conventional therapy ($n=9$). The observation period was 19 ± 7 months in the nipradilol group, and 20 ± 9 months in the control group. Before therapy there was no difference in heart rate between the 2 groups (76 ± 12 vs 79 ± 15 beats/min). The end-diastolic and end-systolic left ventricular dimensions decreased in the nipradilol group ($p<0.05$), but not in the control group. Radionuclide ventriculography revealed that the left ventricular ejection fraction increased in the nipradilol group (27 ± 8 to $41\pm18\%$, $p<0.05$), but not in the control group (27 ± 11 to $27\pm8\%$). Plasma norepinephrine tended to be lowered, although not significantly, whereas plasma atrial natriuretic peptide significantly decreased after the therapy ($p<0.01$) in the treatment group. Lymphocyte beta-adrenoceptors were up-regulated in the nipradilol group ($p<0.05$). None of these parameters changed during the observation period in the control group. Thus, nipradilol improved symptoms and cardiac function with a favorable effect on neurohumoral factors in patients with DCM.

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LONG-TERM use of inotropic agents, including sympathomimetic amines or phosphodiesterase inhibitors, adversely affects survival in patients with heart failure by accelerating myocardial damage or serious arrhythmia^{1–4}. Myocardial beta-adrenoceptors are down-regulated⁵ and myocardial catecholamines are depleted⁶ in terminal heart failure. In addition, there is

accumulating evidence suggesting that neurohumoral activation reduces life expectancy in patients with heart failure^{7–9}. Beta-blocker is a new therapeutic alternative, especially in patients with idiopathic dilated cardiomyopathy (DCM)^{10–19}. Metoprolol, a beta-1-selective agent, has been used almost exclusively^{10–15,17,19}. A recent large-scale double-blind placebo-controlled trial on metoprolol demonstrated that beta-blocker therapy decreased the risk of cardiac transplantation in patients with DCM²⁰. However, it is unclear whether beta-1-selectivity is essential for the therapeutic efficacy of beta-

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TABLE I PATIENT CHARACTERISTICS

Age	Gender	NYHA	Duration	Rhythm	Biopsy	Beta-blocker	dig	Diuretics	ACE-I
65	M	II	48	NSR	—	nipradilol	+	+	+
39	F	III	5	NSR	+	nipradilol	—	—	—
55	M	IV	60	AF	+	nipradilol	+	+	+
43	M	II	1	NSR	+	nipradilol	+	+	—
35	M	II	3	NSR	+	nipradilol	—	+	—
64	M	II	48	AF	—	nipradilol	+	—	—
66	F	II	120	NSR	—	nipradilol	+	+	—
60	M	II	108	NSR	—	nipradilol	+	+	—
63	M	III	10	NSR	+	nipradilol	+	+	+
45	M	II	123	NSR	—	—	+	+	+
53	M	II	36	AF	+	—	+	+	+
55	M	II	12	AF	+	—	+	+	+
62	M	II	144	NSR	+	—	+	+	—
62	M	II	60	AF	+	—	+	+	—
52	M	II	3	NSR	+	—	+	+	+
38	M	II	12	AF	+	—	+	+	—
57	M	III	84	NSR	—	—	—	+	+
45	M	II	72	NSR	+	—	—	+	—

Duration, months after diagnosis; NSR, normal sinus rhythm; AF, atrial fibrillation; dig, digitalis glycosides; ACE-I, ACE inhibitors.

blockade therapy for DCM. Nipradilol is a unique non-selective beta-blocker with vasodilating activity²¹ The present study investigated the therapeutic efficacy of nipradilol in beta-blocker therapy for DCM.

MATERIALS AND METHODS

Study Population

Eighteen patients with DCM, who fulfilled the criteria of the WHO/ISFC task force²² were examined. Entry criteria included New York Heart Association (NYHA) functional class II to IV and left ventricular ejection fraction less than 45% on left ventriculography or radionuclide ventriculography. Exclusion criteria were extreme bradycardia, hypotension or general contraindications to beta-blocker, such as obstructive pulmonary disease. Patients with a history of alcohol abuse or active myocarditis were also excluded. All patients underwent coronary arteriography to exclude those with ischemic heart disease who showed significant stenosis in the major branch of the coronary arteries. A right ventricular endomyocardial biopsy, performed in 12 patients, showed no significant cell infiltration or granuloma. Nine patients were treated with nipradilol. The

remaining 9 patients, who fulfilled the criteria and were potential candidates for beta-blocker therapy, underwent conventional therapy and served as a control group. Care was taken to avoid difference in disease severity and duration. Informed consent was obtained from all of the patients who received beta-blocker therapy.

Titration and Follow-up

In all cases, beta-blocker treatment was initiated on admission. Nipradilol was started at a dose of 1.5 mg, and titrated weekly and then monthly up to 9 mg. Patients were discharged from the hospital at a dose of 3.0 mg nipradilol. NYHA functional class, heart rate and blood pressure were checked at monthly out-patient visits. Chest X-ray and 12-lead electrocardiogram were checked before and 2 weeks and 6 months after therapy. Ventricular dimensions were monitored by ultrasonic echocardiography using a Hewlett Packard ultrasonic system or a Toshiba SONOLAYER-S. The left ventricular ejection fraction was measured in 15 patients before and 6 months and then annually after treatment using radionuclide ventriculography. Arrhythmias were checked in all patients by ambulatory 24 h electrocardiogram

TABLE II BASELINE CARDIOVASCULAR PARAMETERS

	Nipradilol	Control
Heart rate (beats/min)	76±12	79±15
Pulmonary capillary wedge pressure (mmHg)	9±8	11±8
Cardiac output (l/min per m ²)	2.41±0.62	2.69±0.64
End-diastolic volume (ml/m ²)	144±32	129±48
Ejection fraction (%)	26±10	29±10

using the Marquette system. A cardiac event was defined as a cardiac death or hospitalization due to aggravated heart failure.

Neurohumoral Factors

Plasma catecholamines²³, renin²⁴, aldosterone, arginine-vasopressin and alpha-atrial natriuretic peptide²⁵ and lymphocyte beta-adrenoceptors were determined before and 6 months after introduction of the therapy. Samples were drawn in the supine position after a 15 min bed rest. Lymphocyte beta-adrenoceptors were determined using ¹²⁵I-iodocyanopindolol (Amersham, Japan) radioligand binding assay as described previously²⁶.

Statistical Analysis

Data were expressed as means±standard deviation. Differences between the 2 groups were determined by a non-paired t-test. Changes within each group were assessed by a paired t-test. The least squares method was used for the Scatchard analysis of beta-adrenoceptors using the Statview-II program on a Macintosh computer²⁷. Statistical significance was set at $p < 0.05$.

RESULTS

Table I shows the baseline characteristics of the patients. The mean age was 54 ± 12 year in the nipradilol group and 52 ± 8 year in the control group. There was no difference in age or gender between the 2 groups. The NYHA functional class was similar: 2.4 ± 0.7 in the nipradilol group and 2.1 ± 0.3 in the control group. The duration of the disease was also similar: 45 ± 45 months in

Fig 1. The NYHA functional class before (pre) and after (post) therapy: ** $p < 0.01$ pre vs post.

Fig 2. The left ventricular end-diastolic (left panel) and end-systolic (right panel) dimensions before (pre) and after (post) therapy: * $p < 0.05$ pre vs post.

the nipradilol group and 61 ± 50 months in the control group. Two patients in the nipradilol group and 4 patients in the control group had persistent atrial fibrillation, but none of the patients had a history of recent atrial fibrillation or tachycardia. There was no difference in concomitant medications, including digitalis glycosides (78% vs 78%), diuretics (78% vs 100%), and ACE inhibitors (33% vs 55%). One patient in the control group received denopamine. Table II shows hemodynamic variables, volume and ejection fraction, calculated from contrast left ventriculography. All of these variables were comparable between the 2 groups. The mean observation period was 19 ± 7 months in the nipradilol group and 20 ± 9 months in

TABLE III VENTRICULAR ECTOPIC ACTIVITIES

	Beta-blocker		Control	
	pre	post	pre	post
total	5571±10097	1883±3217	4699±7147	3155±7237
VT	11±24	2±4	5±7	70±168
max run	4±3	2±1	4±2	8±11

Values are expressed as beats/day. VT, frequency of 3 or more consecutive runs; max run, number of max runs.

Fig 3. The left ventricular ejection fraction measured by radionuclide ventriculography: * $p < 0.05$ pre vs post.

Fig 4. Maximal binding sites of lymphocyte beta-adrenoceptors: * $p < 0.05$ pre vs post.

the control group.

The final dose of beta-blockers was 5.8 ± 2.6 mg in the nipradilol group. Heart rate decreased from 76 ± 12 to 65 ± 5 beats/min in the nipradilol group ($p < 0.01$). Systolic blood pressure decreased from 122 ± 17 to 101 ± 18 mmHg soon after introduction of the beta-blocker ($p < 0.01$). There was no change in either the heart rate or the systolic blood pressure in the control group. Cardiothoracic ratio on chest roentgenography decreased from $55.9 \pm 6.6\%$ to $51.9 \pm 5.6\%$ in the nipradilol group ($p < 0.01$). There was no significant change in the control group (from $56.8 \pm 7.3\%$ to $59.7 \pm 6.7\%$).

Fig 1 shows the change in the NYHA functional class. The NYHA functional class improved from 2.4 ± 0.7 to 1.6 ± 1.0 in the nipradilol group. There was no change in the control group (from 2.1 ± 0.3 to 2.6 ± 1.1). Fig 2 shows the left ventricular dimension measured by an ultrasonic echocardiography. The end-diastolic dimension decreased from 6.5 ± 0.7 to 5.9 ± 0.7 cm in the

nipradilol group. The end-systolic dimension also decreased from 5.6 ± 0.8 to 4.7 ± 0.8 cm. In the control group, there was no change in either the end-diastolic or end-systolic dimension (from 6.7 ± 0.7 to 6.7 ± 1.0 cm and from 5.9 ± 0.8 to 5.8 ± 1.1 cm, respectively). Neither left atrial size nor degree of mitral regurgitation changed in the beta-blocker group. In the control group, left atrial size increased from 4.1 ± 0.7 to 5.1 ± 0.8 cm ($p < 0.05$), although the degree of mitral regurgitation was similar. Table III shows ventricular ectopic activities in 24 h of electrocardiographic monitoring. There was no change in total ectopic activities, non-sustained ventricular tachycardia or max run in either group. Fig 3 shows changes in the left ventricular ejection fraction, measured by radionuclide ventriculography. The left ventricular ejection fraction increased in the nipradilol group (from $27 \pm 8\%$ to $41 \pm 18\%$), but not in the control group (from $27 \pm 11\%$ to $27 \pm 8\%$).

Fig 4 shows the changes in lymphocyte

Fig 5. Plasma norepinephrine and alpha-atrial natriuretic peptide (ANP): ** $p < 0.01$ pre vs post.

beta-adrenoceptors. In the beta-blocker group, maximal binding sites increased from 6.7 ± 1.8 to 9.8 ± 1.4 fmol/mg protein after introduction of beta-blocker therapy. The dissociation constant did not change significantly. In the control group, no change was detected during the observation period. Fig 5 shows the changes in plasma norepinephrine and alpha-atrial natriuretic peptide. The plasma norepinephrine level tended to be lowered (0.53 ± 0.44 to 0.36 ± 0.22 ng/ml), although not significantly. Plasma alpha-atrial natriuretic peptide decreased significantly after therapy (152 ± 99 to 45 ± 42 pg/ml). There was no change in either plasma norepinephrine (0.62 ± 0.57 to 0.67 ± 0.37 ng/ml) or alpha-atrial natriuretic peptide in the control group (157 ± 175 to 150 ± 164 pg/ml). There was also no change in the plasma epinephrine, renin, aldosterone or arginine-vasopressin level in either group during the observation period.

During the observation period, 2 cases showed deteriorating heart failure in the nipradilol group. One of these showed a favorable response from NYHA class IV to III soon after introduction of therapy, but then deteriorated to class IV. Beta-blocker therapy was discontinued after 6 months in this patient. The other patient continued to receive beta-blocker therapy. In the control group, 6 patients showed deterioration and 1 patient died of heart failure. Cardiac events were less common in the nipradilol group (22%) than in the control group (78%, $p < 0.05$).

DISCUSSION

This study demonstrated that nipradilol, a non-selective beta-blocker, improved symptoms and cardiac function in patients with DCM. Lymphocyte beta-adrenoceptors were up-regulated and plasma alpha-atrial natriuretic peptide decreased in the nipradilol group, but not in the control group. Cardiac events were less common in the nipradilol group than in the control group.

Significance of Non-selective Beta-blocker

The beta-1-selective blocker metoprolol is a traditional standard in beta-blocker therapy for DCM.^{10-15,17,19} Few studies have included non-selective beta-blockers. Recently, several investigators have reported that the non-selective beta-blocker bucindolol is effective in the treatment of heart failure.^{16,18,28-30} Gilbert et al²⁸ showed that bucindolol improved symptoms, decreased pulmonary artery wedge pressure and increased left ventricular ejection fraction, cardiac index, and left ventricular stroke work index, but not treadmill exercise duration or maximal oxygen consumption in a double-blind, randomized study for DCM. Woodley et al³⁰ noted that bucindolol increased left ventricular ejection fraction, cardiac index and stroke work index, and decreased pulmonary artery wedge pressure in patients with DCM, but not in those with ischemic cardiomyopathy, although a reduction of end-diastolic dimension was observed in both groups. Therefore, beta-1-selectivity is not essential for producing the therapeutic efficacy of beta-blockers in heart failure.

Role of the Vasodilating Activity of Nipradilol

Nipradilol contains a nitrate residue in its structure, which results in a vasodilating activity.²¹ Vasodilating activity, resulting in a reduction of afterload, is an advantage in beta-blocker therapy. This property may prevent the excessive decline in cardiac output induced by the beta-blocker in the early period. Recent reports, using bucindolol^{16,18,28-30} and carvedilol³¹ have suggested that beta-blockers with vasodilating activity produce a favorable outcome. It is clear that a vasodilating agent, such as an angiotensin-converting enzyme inhibitor or hydralazine

plus isosorbide dinitrate, improves long-term survival in patients with heart failure^{8,9}. It is possible that the effect of beta-blockers with vasodilating activity is greater than that of metoprolol in the treatment of heart failure, although the efficacy of beta-blockade in ischemic heart failure has not yet been determined^{18,19,30}.

Effects on Neurohumoral Factors

The present study showed that lymphocyte beta-adrenoceptors were up-regulated and that plasma alpha-atrial natriuretic peptide decreased after the introduction of a beta-blocker. The plasma norepinephrine level also tended to be lowered, although not significantly. Few studies have addressed changes in neurohumoral factors after the introduction of beta-blockers in patients with heart failure. Using bucindolol in patients with DCM, Gilbert et al²⁸ demonstrated that the central venous norepinephrine level decreased after beta-blocker therapy. Woodley et al³⁰ also detected a significant decrease in the central venous norepinephrine level after bucindolol administration in patients with DCM, but not in those with ischemic cardiomyopathy. Andersson et al³² showed that the arterial-coronary sinus norepinephrine difference during exercise decreased during long-term metoprolol administration in patients with heart failure due to DCM. In contrast, Eichhorn et al²⁹ did not observe any changes in the plasma norepinephrine level after the introduction of a beta-blocker in patients with DCM. The discrepancy between these results cannot be explained clearly, but differences in sampling sites, conditions and timing may be responsible. We did not find a statistically significant decrease in the plasma norepinephrine level, but a study with a larger number of patients may reveal such a decrease.

Beta-2-receptor is predominant in membrane preparations of lymphocytes³³. In our study, significant up-regulation was noted in the nipradilol group, which may reflect beta-2-blocking activity. The significance of the up-regulation of beta-adrenoceptors on the therapeutic outcome is still uncertain. Wagstein et al¹⁴ showed that myocardial beta-adrenoceptors were up-regulated during metoprolol administration in biopsy samples from the right ventricle. Heilbrunn et al¹⁵

demonstrated that the up-regulation of myocardial beta-adrenoceptors was associated with an improved response to dobutamine. They concluded that the up-regulation of beta-adrenoceptors was related to the therapeutic efficacy. In another study, both metoprolol and carvedilol were useful in the treatment of patients with DCM, despite the fact that myocardial beta-adrenoceptors were up-regulated in patients who received metoprolol, but not in those who received carvedilol³¹. It is still uncertain whether up-regulation per se is the primary cause of therapeutic efficacy, although it is clear that it is one of the factors related to a favorable outcome.

It is difficult to interpret the effects of beta-blockers on neurohumoral factors. Previous investigators^{28,30,32} have speculated that the decrease in the plasma norepinephrine level may be the consequence of an improvement in cardiac function and hemodynamics. The decrease in alpha-atrial natriuretic peptide and up-regulation of lymphocyte beta-receptors observed in the present study may also be the result of the beneficial effects of beta-blocker on contractile function, resulting in a reduction of atrial pressure. Nipradilol is a non-selective beta-blocker which possesses beta-2-blocking activity. It is possible that the up-regulation of beta-adrenoceptors in lymphocytes was derived from the anti-beta-2-receptor activity of the agent. Non-selective beta-blockers possibly affect the presynaptic beta-2-receptor, inhibiting neurotransmitter release from the nerve terminals³⁴ and resulting in a reduction of the plasma norepinephrine level. Atrial natriuretic peptides interfere with sympathetic nerve activity through a direct or indirect pathway, such as the sensitization of baroreceptor function³⁵ although it is still possible that the improvement of cardiac function, which results in a decrease in atrial pressure, is responsible for the decrease in plasma alpha-atrial natriuretic peptide.

Limitations of This Study

The present study was an uncontrolled trial. We cannot exclude the possibility that the 2 groups were not sufficiently similar in severity and natural course. A large-scale randomized study is needed to resolve this issue. It is also unclear whether lymphocyte

beta-adrenoceptors reflect myocardial beta-adrenoceptors,^{36,37} which were not examined in this study. There is no direct evidence supporting the up-regulation of myocardial beta-adrenoceptors. Hemodynamic abnormalities in the study population were minimal. Since hemodynamic data were not necessarily obtained just before the introduction of beta-blocker therapy, these data do not reflect those when beta-blocker therapy was begun.

Summary

Nipradilol, a new non-selective beta-blocking agent with vasodilating activity, improved symptoms and cardiac function in patients with DCM. Lymphocyte beta-adrenoceptors were up-regulated and plasma alpha-atrial natriuretic peptide decreased after treatment. Thus, nipradilol is a potent drug that achieves therapeutic efficacy as beta-blocker therapy for DCM.

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