Impaired Ability to Secrete Atrial Natriuretic Peptide in Response to Isoproterenol Infusion in Patients With Dilated Cardiomyopathy

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Abstract

Objectives. The myocardium has 2 functions *in vivo*, that of pump and endocrine organ. Therefore, simultaneous examinations of cardiac systolic reserve and endocrine reserve are important in evaluating the activities of the myocardial cells. This study investigated the relationship between cardiac systolic reserve and secretion of atrial natriuretic peptide (ANP) in response to isoproterenol infusion in patients with dilated cardiomyopathy.

Methods. Isoproterenol was infused intravenously in 6 healthy individuals (control group) and 32 patients with dilated cardiomyopathy. The left ventricular systolic responses and plasma ANP concentrations were measured.

Results. Patients with dilated cardiomyopathy were classified into 2 groups: patients with a good response (change in fractional shortening $>$ 7%, 17 patients) and those with a poor response (change in $\leq$ 7%, 15 patients). There was no significant difference in end-diastolic dimension, fractional shortening, heart rate, or systolic blood pressure between the 2 groups of patients with dilated cardiomyopathy at rest. The resting plasma ANP concentration in the poor-response group (88.8 ± 59.0 pg/m*l*) was significantly higher than that in the other 2 groups (good: 47.0 ± 35.9 pg/m*l*, $p < 0.05$, control: 9.8 ± 4.1 pg/m*l*, $p < 0.01$, respectively). The percentage change in ANP after isoproterenol infusion in the poor-response group (-7.1 ± 16.7%) was significantly less than that in the other 2 groups (good: 12.6 ± 27.3%, $p < 0.05$, control: 31.5 ± 24.6%, $p < 0.01$, respectively).

Conclusions. The resting plasma ANP concentration can be used to evaluate the cardiac systolic reserve in patients with dilated cardiomyopathy. Decreased myocardial systolic reserve is also associated with impaired ability to secrete ANP.

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Key Words

■ **Beta-adrenergic receptor agonists (isoproterenol)** ■ **Natriuretic peptide, atrial**
■ **Cardiomyopathies, dilated** ■ **Stress echocardiography**

INTRODUCTION

Plasma atrial natriuretic peptide (ANP) concentrations are increased in patients with congestive heart failure[1−5]. The atria and ventricles can synthesize substantial amounts of ANP in patients with dilated cardiomyopathy[6−8]. The infusion of synthetic ANP significantly decreases the pulmonary capillary wedge pressure and increases the stroke volume index in patients with congestive heart fail-

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ure[9]. Therefore, increased plasma levels of ANP may help to improve hemodynamic deterioration in chronic heart failure. ANP measurements may be useful to evaluate the severity of symptoms and cardiac dysfunction in patients with chronic heart failure. Evaluation of the left ventricular responses to adrenergic stimulation is also useful in predicting the course of dilated cardiomyopathy[10−13]. The myocardium has 2 functions *in vivo*, as a pump and an endocrine organ. Therefore, simultaneous examinations of cardiac systolic reserve and endocrine reserve are important in evaluating the activities of the myocardial cells. However, there is no consensus about the relationship between changes in cardiac systolic function and changes in ANP secretion with adrenergic stimulation in patients with dilated cardiomyopathy.

We studied the relationship between cardiac systolic reserve and ANP secretion by determining the changes in left ventricular systolic responses to isoproterenol and the ability to secrete ANP in response to isoproterenol infusion in patients with dilated cardiomyopathy.

SUBJECTS AND METHODS

Patients

Six healthy individuals (control group) and 32 patients with dilated cardiomyopathy admitted to Tsukuba University Hospital or followed in the outpatient clinic were studied. Patients were aged from 32 to 78 years (mean age: 57 ± 12 years) and included 20 men and 12 women. The diagnosis of dilated cardiomyopathy was based on findings obtained at echocardiography or cardiac catheterization using the following criteria: left ventricular dilation [left ventricular end-diastolic dimension ≥ 55 mm or ≥ 36 mm/m² (body surface area < 1.35 m²)]; impaired systolic function defined as an M-mode fractional shortening < 25%; and absence of coronary artery disease, severe valvular heart disease, severe systemic hypertension, cor pulmonale, chronic systemic disease involving the heart muscle, and increased alcohol intake. Coronary angiography was performed in 25 of 32 patients, and no significant coronary lesions were detected. The remaining 7 patients had no clinical history to suggest ischemic heart disease. Clinical characteristics of the patients are summarized in **Table 1**. Five patients were in New York Heart Association functional class Ⅰ, 20 in class Ⅱ, and 7 in class Ⅲ. Among the 32 patients, 24 were in sinus rhythm and 8 had atrial fibrillation. Concerning concurrent agents, diuretics were prescribed for 23 patients, angiotensin-converting enzyme inhibitors for 16, digitalis for 9, and calcium channel blockers for 2. The patients did not receive β-blockers before the isoproterenol stress test. The study was explained to each patient and informed consent was obtained.

Table 1 Clinical characteristics of control and dilated cardiomyopathy groups

	Control group (*n*=6)	DCM group (*n*=32)	*p* value
Age (yr)	38±12	57±12	<0.01
Sex (males/females)	4/2	20/12	NS
Atrial fibrillation	0/6	8/24	NS
Dd (mm)	47±9	63±6	<0.01
Ds (mm)	31±8	55±6	<0.01
FS (%)	36±7	14±5	<0.01

Continuous values are mean±SD.
DCM=dilated cardiomyopathy; Dd=end-diastolic dimension; Ds=end-systolic dimension; FS=fractional shortening.

Echocardiographic studies

All 6 healthy individuals and 32 patients underwent real-time two-dimensional and M-mode echocardiographic examination. M-mode and cross-sectional echocardiograms were obtained with a Toshiba SSH-160A, SSA-380A or SSA-390A ultrasonoscope (Toshiba Co.) equipped with a 2.5- or 3.75-MHz transducer and a Toshiba line scan recorder, LSR-100A. The paper speed was 50 mm/sec. Left ventricular echocardiograms were obtained at the level of the chordae tendineae just below the tips of the mitral leaflets using two-dimensional echocardiographic guidance. Electrocardiograms and phonocardiograms were recorded simultaneously with the echocardiograms. Fractional shortening was calculated as [left ventricular end-diastolic dimension (mm) − left ventricular end-systolic dimension (mm)]/left ventricular end-diastolic dimension (mm) × 100 (%).

Isoproterenol stress echocardiography

The isoproterenol test was performed in the afternoon in all 6 healthy individuals and 32 patients using a previously described technique[10, 14−16]. Briefly, the patient lay in the supine position in a darkened room and isoproterenol was infused intravenously for 5 min through an antecubital vein at doses of 0.01 and 0.02 μg/kg/min using a calibrated infusion pump. During isoproterenol infusion, electrocardiogram monitoring was performed continuously. Blood pressure was also measured with a mercury column sphygmomanometer at rest and during isoproterenol infusion every one minute. M-mode echocardiography was performed before and immediately after isoproterenol infusion using a line scan recorder at 50 mm/sec. The change in the fractional shortening with isoproterenol infusion was determined as fractional shortening immediately after isoproterenol infusion at a doses of 0.02 μg/kg/min(%) − fractional shortening at rest(%).

Plasma atrial natriuretic peptide concentration

Venous blood samples were obtained from the antecubital vein via an indwelling butterfly needle after the patients had rested in the supine position for 20 min and again at the end of the protocol to measure plasma ANP concentrations. Plasma ANP concentrations were determined by immunoradiometric assay. The minimal detectable level of ANP was 5 pg/m*l*.

Statistical analysis

Data were presented as mean ± standard deviation. Significant differences were determined with the paired or unpaired *t*-test as appropriate. Differences in frequencies were analyzed with the Fisher's exact probability test or the chi-square statistic test. Statistical calculations were performed using Statview software. A p value of < 0.05 was considered statistically significant.

RESULTS

Isoproterenol stress echocardiography

In the control group, the change in fractional shortening with isoproterenol ranged from 14% to 20%(mean: 17 ± 2%). In patients with dilated cardiomyopathy, the change in fractional shortening with isoproterenol infusion ranged from −3% to 15%(mean: 7 ± 4%). In this study, the criterion for a good response to isoproterenol was defined as a > 7% increase in fractional shortening(the mean value in patients with dilated cardiomyopathy). The patients with dilated cardiomyopathy were divided into 2 groups: patients with a good response(change in fractional shortening > 7%; good-response group)and those with a poor response(change in fractional shortening ≤ 7%; poor-response group). Fifteen of the 32 patients with dilated cardiomyopathy had a poor response and 17 had a good response(**Table 2**). There was no significant difference in the left ventricular resting end-diastolic dimension, the left ventricular resting end-systolic dimension, resting fractional shortening, New York Heart Association functional class, the number of outpatients or inpatients, and incidence of atrial fibrillation between the 2 groups of patients with dilated cardiomyopathy(**Table 2**). Diuretics were prescribed to 13 of 17 patients in the good-response group and to 10 of 15 patients in the poor-response group. Angiotensin-converting enzyme inhibitors were used in 9 of 17 patients in the good-response group and in 7 of 15 patients in the poor-response group. Digitalis was prescribed for 6 good-response patients and 3 poor-response patients. Calcium channel blockers were prescribed for 2 good-response patients. There were no differences in medication between the 2 groups of patients with dilated cardiomyopathy(**Table 2**). In addition, there was no difference in heart rate or systolic blood pressure either at rest or immediately after isoproterenol infusion between the 3 groups (**Table 3**). In response to isoproterenol infusion, the heart rate increased significantly($p < 0.01$),

Table 2 Patient characteristics

	Good-response group(n=17)	Poor-response group(n=15)	p value
Age(yr)	55±13	59±10	NS
Sex(males/females)	13/4	7/8	NS
NYHA class(I/II/III)	3/12/2	2/8/5	NS
In-/outpatients	12/5	12/3	NS
Atrial fibrillation	5	3	NS
Dd(mm)	63±7	64±5	NS
Ds(mm)	54±8	55±4	NS
FS(%)	14±5	13±5	NS
ΔFS(%)	10±2	4±3	<0.01
Diuretics	13	10	NS
ACE inhibitors	9	7	NS
Digitalis	6	3	NS
Ca channel blockers	2	0	NS

Continuous values are mean±SD.
NYHA=New York Heart Association; ΔFS=change in fractional shortening with isoproterenol infusion; ACE=angiotensin-converting enzyme; Ca=calcium. Other abbreviations as in Table 1.

Table 3 Heart rate and systolic blood pressure at rest and immediately after isoproterenol infusion in 3 groups

	Control group		Good-response group		Poor-response group	
	Before	After ISP	Before	After ISP	Before	After ISP
Heart rate (beats/min)	67±9	104±17*	71±12	107±25*	70±16	110±36*
SBP (mmHg)	117±10	128±19	117±19	125±38	109±21	108±24

*$p<0.01$ vs before ISP.
ISP = isoproterenol; SBP = systolic blood pressure.

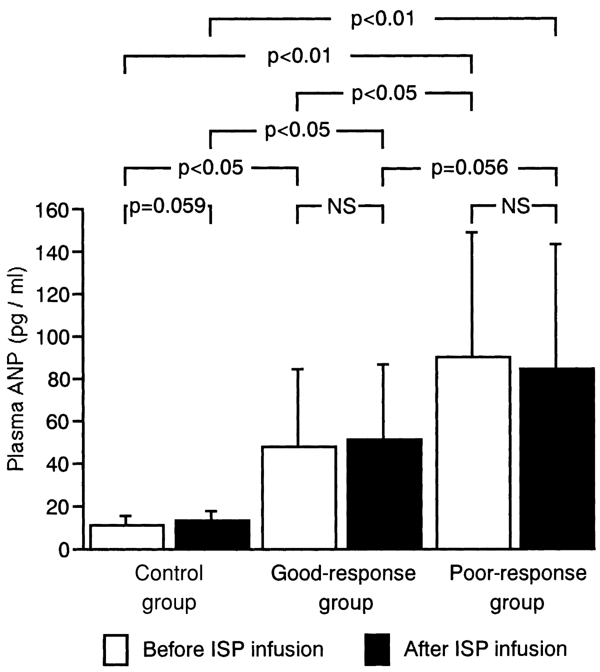

Fig. 1 Plasma atrial natriuretic peptide concentrations both at rest and immediately after isoproterenol infusion
ANP = atrial natriuretic peptide. Other abbreviation as in Table 3.

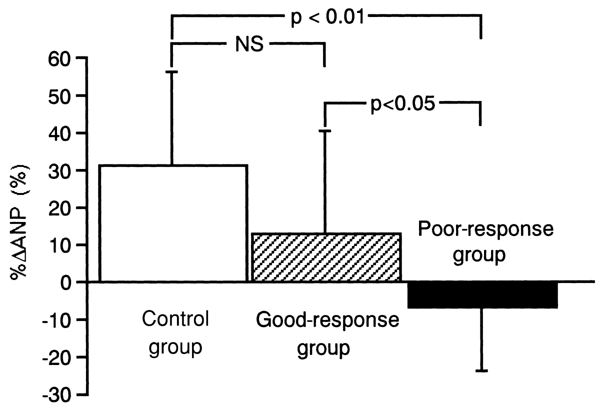

Fig. 2 Percentage change in atrial natriuretic peptide after isoproterenol infusion (%ΔANP)
Abbreviation as in Fig. 1.

although the systolic blood pressure did not change in all 3 groups (**Table 3**).

Plasma atrial natriuretic peptide concentrations and changes in response to isoproterenol

Our data indicate that cardiac systolic reserve as assessed by isoproterenol stress echocardiography is related to resting plasma ANP concentrations and percentage change in ANP after isoproterenol infusion [{(Plasma ANP immediately after isoproterenol infusion − plasma ANP before isoproterenol infusion)/plasma ANP before isoproterenol infusion} × 100(%)].

Fig. 1 summarizes the plasma ANP concentrations before and immediately after isoproterenol infusion in the poor-response, good-response, and control groups. At rest, the plasma concentration of ANP in the poor-response group (88.8 ± 59.0 pg/m*l*) was significantly higher than in both good-response (47.0 ± 35.9 pg/m*l*, $p < 0.05$) and control (9.8 ± 4.1 pg/m*l*, $p < 0.01$) groups. Immediately after isoproterenol infusion, the plasma concentration of ANP in the poor-response group (83.5 ± 58.4 pg/m*l*) was significantly ($p < 0.01$) higher than in the control group (12.4 ± 4.6 pg/m*l*) and tended to be higher than in the good-response group (49.9 ± 35.8 pg/ m*l*, $p = 0.056$; **Fig. 1**). Plasma concentration of ANP in the good-response group was significantly ($p < 0.05$) higher than in the control group before and after isoproterenol infusion. The plasma ANP concentration after isoproterenol infusion tended to be higher than that before the infusion in the control group ($p = 0.059$; **Fig. 1**).

The percentage change in ANP after isoproterenol infusion in the poor-response group (−7.1 ± 16.7%) was lower than in the control group (31.5 ± 24.6%, $p < 0.01$) and in the good-response group (12.6 ± 27.3%, $p < 0.05$; **Fig. 2**). The change in ANP secretion with isoproterenol infusion was not associated with aging in the control group (data not shown).

DISCUSSION

Our results indicate that cardiac systolic reserve is inversely related to resting plasma ANP concentration in patients with dilated cardiomyopathy. Resting plasma ANP concentration in patients with dilated cardiomyopathy is correlated inversely with the percentage increase in the cardiac index in response to adrenergic stimulation[17], but heart rate, systolic blood pressure, left ventricular end-diastolic volume, and incidence of atrial fibrillation were not determined[17]. In contrast, our study found that these factors did not differ between the poor-response group and the good-response group. Infusion of ANP improves left ventricular function in patients with congestive heart failure[9]. We thought that increases in ANP secretion reduce preload and afterload in patients with a poor response, and, as a result, the left ventricular end-diastolic dimension and fractional shortening at rest would be similar in the 2 groups.

Our results also demonstrate the relationship between the cardiac systolic reserve and the ability to increase the rate of ANP secretion. Patients with a poor response to isoproterenol infusion also failed to augment ANP secretion. These results indicate that not only cardiac systolic reserve but also ability to secrete ANP was impaired in patients with a poor response. We thought that in patients with a poor response, a high level of ANP contributed to the regulation of fluid volume and blood pressure at rest, whereas the increase in the rate of ANP secretion under strenous conditions was impaired and the supply of ANP could not meet the demand for ANP under stress.

Previous studies have shown that plasma ANP concentration in patients with heart disease is generally related to the magnitude of increases in right atrial pressure or pulmonary artery wedge pressure. Cardioacceleration with increased atrial pressure has been shown to further elevate plasma ANP concentration. In our study, the heart rate increased significantly in the 3 groups in response to isoproterenol infusion. However, there was no difference in heart rate either at rest or immediately after isoproterenol infusion between the 3 groups. We did not measure the right atrial pressure and pulmonary artery wedge pressure in this noninvasive study. However, the change in fractional shortening with isoproterenol in the poor-response group was smaller than in both good-response and control groups. We thought that the improvement in cardiac hemodynamics with isoproterenol in the poor-response group was less than in both the good-response and control groups.

Some studies have demonstrated that isoproterenol induces the release of ANP[18−20]. In experimental models, isoproterenol induces the release of ANP by directly stimulating β-adrenoreceptors. However, in rats with congestive heart failure which received chronic infusion of isoproterenol, isoproterenol failed to increase the plasma ANP concentration[18]. These results suggest that down-regulation of β-adrenoreceptors diminished the myocardial systolic reserve and ANP secretion. In our study, isoproterenol increased the rate of ANP secretion in the healthy individuals, but failed to increase the rate of ANP secretion in the poor-response group. We think that fibrotic changes and either degeneration or down-regulation of β-adrenoreceptors in the patients with a poor response were responsible for the decreased cardiac systolic reserve and the blunted changes in the plasma ANP concentration during isoproterenol infusion. The healthy individuals were significantly younger than the patients with dilated cardiomyopathy. The inotropic response of catecholamines in the aged myocardium diminishes in healthy individuals[21]. Plasma ANP concentration is not associated with aging in healthy individuals[22]. Therefore, the age differences between healthy individuals and the patients with dilated cardiomyopathy might influence the differences in response to isoproterenol, but the differences in age did not greatly affect the correlation between cardiac systolic reserve and resting plasma ANP concentration in the 3 groups. In our study, the change in ANP secretion with isoproterenol infusion was not associated with aging in healthy individuals (data not shown). So the differences in age did not extremely influence the correlation between cardiac systolic reserve and the changes in ANP secretion with isoproterenol infusion in the 3 groups.

Study limitations

We did not measure the pulmonary artery wedge pressure, right atrial pressure, and left ventricular end-diastolic pressure in this noninvasive study.

The possibility remains that these indices are higher in patients with a poor response than in patients with a good response.

CONCLUSIONS

Our results indicate that resting plasma ANP concentration can be used to evaluate cardiac systolic reserve in patients with dilated cardiomyopathy. Decreased myocardial systolic reserve is also associated with reduced increase in the rate of ANP secretion in response to isoproterenol.

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要　約

拡張型心筋症のイソプロテレノール静注に対する心房性ナトリウム利尿ペプチド分泌予備能の検討

西　功　飯田　啓治　河野　了　増見　智子　山口　巖

目　的: 心臓はポンプおよび内分泌器官の役割を持っている．それゆえ，ポンプ器官としての予備能(心収縮予備能)と内分泌器官としての予備能[心房性Na利尿ペプチド(ANP)分泌予備能]を同時に知ることは，心筋細胞の活性度を評価するうえで重要と考えられる．本研究では，拡張型心筋症患者にイソプロテレノール負荷心エコー図法を行い，薬物負荷による心収縮予備能と血漿ANP濃度の動態との関連を検討した．

方　法: 拡張型心筋症患者32例と正常対照者6例を対象にイソプロテレノールを静注した．安静時と負荷直後にそれぞれ心エコー図を記録し，血漿ANP濃度を測定した．

結　果: イソプロテレノール負荷前後の左室内径短縮率(FS)の変化分(ΔFS: 負荷直後FS－安静時FS)により，負荷反応良好群(ΔFS＞7%: 17例)と負荷反応低下群(ΔFS≦7%: 15例)に分類した．反応良好群と反応低下群の間において安静時の左室拡張末期径，FS，心拍数，収縮期血圧には有意差はなかった．安静時血漿ANP濃度は，反応低下群(88.8±59.0 pg/m*l*)で反応良好群(47.0±35.9 pg/m*l*, p＜0.05)，対照群(9.8±4.1 pg/m*l*, p＜0.01)よりいずれも有意に高値であった．また，反応低下群(－7.1±16.7%)の[(後ANP濃度－前ANP濃度)/前ANP濃度×100(%)]の式により求められた血漿ANP濃度の変化率では，反応良好群(12.6±27.3%, p＜0.05)および対照群(31.5±24.6%, p＜0.01)と比較して有意に小であった．

結　論: 拡張型心筋症において安静時血漿ANP濃度は，心収縮予備能を評価するのに有用と考えられた．心収縮予備能の減少はANP分泌予備能の低下と関連していた．

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