Acta Medica et Biologica
Vol. 48, No.2, 69-74, 2000

Preserved Lusitropic Reserve of the Left Ventricles in Spite of Impaired Inotropic Reserve in Patients with Chronic Heart Failure

Makoto KODAMA*, Haruo HANAWA*, Kiminori KATO*, Yuichi NAKAMURA*, Yuji OKURA*, Satoru HIRONO*, Masahiro ITO*, Koichi FUSE*, [1]Hiroyuki HOSONO, [2]Makihiko SAEKI, [3]Minoru TAKAHASHI, [4]Sen KOYAMA, [5]Takashi TSUDA, [6]Kenichi WATANABE and Yoshifusa AIZAWA*

*First Department of Internal Medicine, Niigata University School of Medicine, Niigata, [1]Kariwagun Hospital, Kashiwazaki, [2]Nagaoka Chuo Hospital and [3]Tachikawa General Hospital, Nagaoka, [4]Tsubame Rosai Hospital, Tsubame, [5]Kido Hospital; and [6]Clinical Pharmacology, Niigata College of Pharmacy, Niigata, Japan

Received July 6 1999; accepted March 22 2000

Summary. **Inotropic and lusitropic reserves of failing hearts were investigated using a stepwise intravenous dobutamine loading test in patients with chronic heart failure. The forty-one patients enrolled in this study were classified into 4 groups according to the left ventricular end-systolic volume indices (LVESVI). The left ventricular size of Group 1 was within the normal range (LVESVI=37.0±3.5 ml/m^2), and this group served as the control. LVESVI of Group 2 was mildly dilated (53.9±6.4 ml/m^2), that of Group 3 was moderately dilated (77.3±4.7 ml/m^2), and Group 4 was severely dilated (120.0±34.9 ml/m^2). Left ventricular contractility and relaxation properties were estimated by left ventricular maximum positive dP/dt and minimum negative dP/dt. At the basal condition, both positive dP/dt and the absolute value of negative dP/dt were low in patients with chronic heart failure in accordance with LVESVI. Acceleration of positive dP/dt by dobutamine infusion was more attenuated in Group 4 than that of Group 1. However, responses of negative dP/dt were identical among the 4 groups. Thus, there was a dissociation between inotropic and lusitropic reserves of human failing hearts for β-adrenergic stimulation. These findings imply that a lusitropic reserve is preserved in the failing left ventricles in spite of an impairment to the inotropic reserve.**

Key words—chronic heart failure, β-adrenoceptor, dobutamine, inotropic reserve, lusitropic reserve.

Correspondence: Makoto Kodama, M.D., First Department of Internal Medicine, Niigata University School of Medicine, Asahimachi 1-757, Niigata 951-8510, Japan.

INTRODUCTION

Chronic heart failure due to left ventricular systolic dysfunction is usually accompanied by diastolic dysfunction of the left ventricle[1]. Abnormal relaxation properties are reported to be the initial and the most sensitive signs of failing hearts[2]. Failing hearts exhibit not only decreased contractility at the basal condition but also the impairment of inotropic reserves under various conditions, such as exercise, β-adrenergic stimulation, and tachycardia[3,4]. On the other hand, reserves of left ventricular relaxation properties, or lusitropic reserves, under the above mentioned conditions have not been fully examined in failing hearts[5,6].

β-adrenergic stimulation increases myocardial contractility through enhancing intracellular Ca^{++} cycling in both normal and failing hearts. The β-adrenoceptor signal pathway has not only enhancing effects on myocardial contractility but also stimulatory effects on myocardial relaxation[7-10]. The lusitropic effects of β-adrenoceptor stimulation act through the phosphorylation of phospholamban by protein kinase A. This process leads to an increase of Ca^{++} uptake by the sarcoplasmic reticulum. Because a β-adrenoceptor signal transduction system is impaired in the failing myocardium, lusitropic effects of β-adrenoceptor stimulation may be also attenuated to the same degree as the decrease of an inotropic reserve[11-13].

In this study, we examined inotropic and lusitropic

reserves of the left ventricles for β-adrenergic stimulation in patients with chronic heart failure.

MATERIALS AND METHODS

Patients

Forty-one patients with chronic heart failure or with a history of congestive heart failure were included in this study, but not those with coronary artery diseases or prominent valvular heart diseases. Congestive heart failure was controlled using diuretics, digitalis, and angiotensin converting enzyme inhibitors. Cardiac catheterization was performed after written informed consent was obtained from each patient.

Hemodynamic measurements

All patients initially underwent routine left and right diagnostic catheterization using a femoral approach. Diagnostic examination contained pressure studies, coronary arteriography and left ventriculography. After the diagnostic procedures, a 7F micromanometer-tipped catheter (Millar Industries, Houston, Tex.) was placed in the left ventricle. A 7F thermodilution floating catheter was placed in the pulmonary artery. A 5F pacing catheter was advanced to the right atrium in patients with sinus rhythm and to the right ventricle in patients with atrial fibrillation. Left ventricular pressure and the first derivatives of left ventricular pressure were recorded on a strip chart recorder during this study. Cardiac output was also examined serially. All parameters were obtained under the constant pacing rate of 110/min.

Groups

Patients were divided into four groups according to the left ventricular end-systolic volume indices (LVESVI) by left ventriculography. The normal range of LVESVI is 24 ± 10 ml/m^2 [14]. LVESVI of Group 1 were within the normal range (under 44 ml/m^2), and this group served as the control, which had minimal left ventricular dysfunction. Underlying diseases of Group 1 comprised arrhythmia, diabetes mellitus, alcohol abuse or renal failure. LVESVI of Group 2 ranged from 45 ml/m^2 to 64 ml/m^2. Those of Group 3 ranged from 65 ml/m^2 to 84 ml/m^2, and LVESVI of Group 4 were over 85 ml/m^2. Patient characteristics are presented in Table 1.

Intravenous dobutamine

Intravenous dobutamine was infused with an upward titration of the infusion rate at 5 minute intervals. Stepwise dobutamine loading was initiated at a dose of 2 μg/kg/min, and then the dose was increased to 4 μg/kg/min and 8 μg/kg/min. Three minutes after dobutamine infusion was initiated, a constant pacing of 110/min was started and hemodynamic parameters were measured at 5 min after dobutamine loading.

Statistics

All data were presented as mean$\pm$1SD. Both the one-way ANOVA and Duncan's test were used to calculate statistical differences among the four groups. Differences were considered significant at $p<0.05$.

Table 1. Patient characteristics

	Group 1	Group 2	Group 3	Group 4
Number	7	7	8	19
Male/female	4/3	4/3	3/5	17/2
Age	43.4±14.6	54.4±10.3	53.9±14.3	50.0±12.0
Dilated cardiomyopathy	0	2	7	15
Miscellaneous diseases	7	5	1	4
LVEDVI	76.2±16.2	104.0±15.8	118.0±14.2	166.0±38.0
LVESVI	37.0±3.5	53.9±6.4	77.3±4.7	120.0±34.9
LVEF	50.0±6.8	47.6±7.6	34.1±7.9	28.1±7.9

LVEDVI, left ventricular end-diatolic volume index; LVESVI, left ventricular endsystolic volume index; LVEF, left ventricular ejection fraction.

RESULTS

Contractility

Left ventricular contractility was estimated by use of the maximum positive dP/dt of left ventricular pressure[15]. At the baseline, the maximum positive dP/dt of Group 1 was 1210±187 mmHg/sec, that of Group 2 was 1310±203 mmHg/sec, Group 3 was 1040±132 mmHg/sec, and Group 4 was 865±241 mmHg/sec (Table 2). Positive dP/dt of Group 4 was significantly lower than those of Groups 1 and 2 at baseline values. Baseline values of positive dP/dt were inversely proportional to the left ventricular endsystolic volume indices. Values of the maximum positive dP/dt increased during stepwise dobutamine loading in all four groups. The increase rate of positive dP/dt of Group 4 was significantly lower than that of Group 1 at 4 μg/kg/min and at 8 μg/kg/min of dobutamine (Fig. 1). The increase rates of positive dP/dt by dobutamine loading were also inversely proportional to the left ventricular end-systolic volume indices.

Relaxation properties

The minimum negative dP/dt of left ventricular pressure served as the parameter of the left ventricular relaxation properties in this study. At the baseline, the minimum negative dP/dt of Group 1 was −1370±96 mmHg/sec, that of Group 2 was −1250±185 mmHg/sec, Group 3 was −1020±62 mmHg, and Group 4 was −809±180 mmHg/sec (Table 2). The absolute value of negative dP/dt of Group 4 was significantly lower than those of the groups 1 and 2 at the baseline. The absolute values of negative dP/dt in patients with chronic heart failure were inversely proportional to the left ventricular end-systolic volume indices, as were shown in positive dP/dt. Absolute values of negative dP/dt were increased in accordance with the doses of dobutamine in all four groups. The increase rates of absolute negative dP/dt did not differ among the four groups during dobutamine loading (Fig. 2).

Cardiac index

At the baseline, the cardiac index of Group 1 was

Table 2. Hemodynamic changes under stepwise dobutamine loading

	Baseline	Difference	Dobutamine 2μg/kg/min	Difference	Dobutamine 4μg/kg/min	Difference	Dobutamine 8μg/kg/min	Difference
Peak LV pressure								
Group 1	103±13.1		115±14.3		125±21.6		133±17.8	
Group 2	112±26.1		129±44.1		128±43.2		121±26.9	
Group 3	111±17.1		112±12.0		126±40.7		115±15.6	
Group 4	104±22.1		112±27.2		118±29.7		130±32.6	
+dP/dt (mmHg/sec)								
Group 1	1210±187	4	1560±258	4	1950±269	4	2630±523	4
Group 2	1310±203	3,4	1610±437	4	1930±818	4	2240±893	
Group 3	1040±132	2	1200±270		1440±271		1650±322	
Group 4	865±241	1,2	1060±371	1,2	1220±518	1,2	1570±813	1
−dP/dt (mmHg/sec)								
Group 1	−1370±96	3,4	−1560±235	3,4	−1770±242	3,4	−1940±314	3,4
Group 2	−1250±185	3,4	−1500±332	3,4	−1530±405	4	−1650±269	
Group 3	−1020±62	1,2,4	−1130±107	1,2	−1270±73	1	−1400±94	1
Group 4	−809±180	1,2,3	−958±259	1,2	−1130±344	1,2	−1290±339	1
Cardiac index (L/min/m²)								
Group 1	4.1±1.3	2,3,4	4.7±1.3	2,3,4	5.1±1.5	2,3,4	5.9±1.6	2,3,4
Group 2	3.1±0.8	1	3.6±1.2	1	4.0±1.0	1	4.5±1.1	1
Group 3	2.8±0.6	1	3.2±0.4	1	3.5±0.5	1	4.0±0.5	1
Group 4	2.5±0.6	1	2.8±0.7	1	3.2±0.7	1	3.6±0.9	1

The columns showing differences reveal that there are statistically significant differences between the indicated groups.

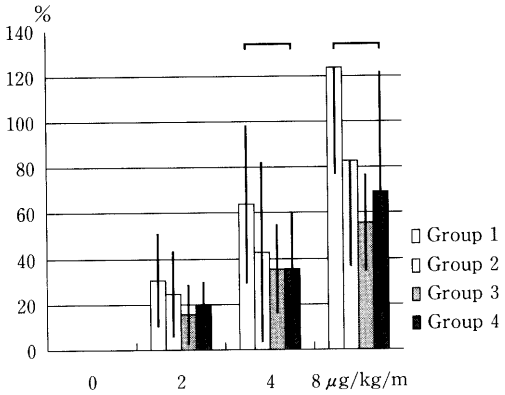

Fig. 1. The rate of increase of the positive dP/dt under dobutamine loading in the four groups. Upper transverse bars indicate that the differences in the rate of increase of positive dP/dt between the two indicated groups are statistically significant.

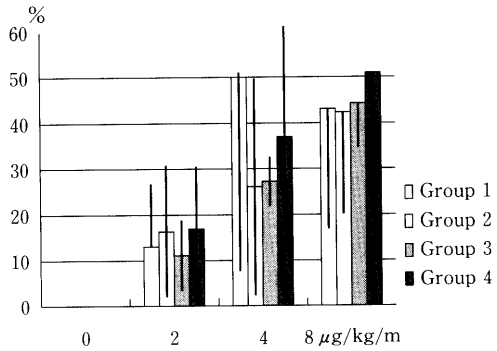

Fig. 2. The rate of increase of the absolute negative dP/dt in the four groups.

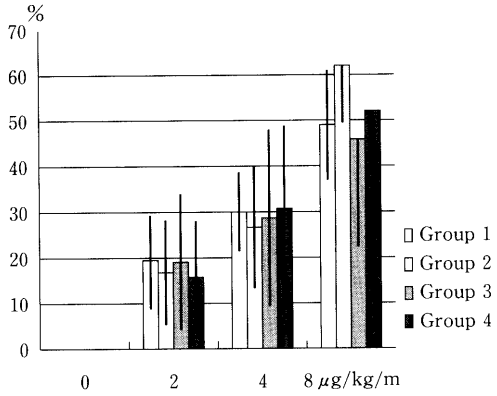

Fig. 3. The rate of increase of the cardiac index.

4.1±1.3 L/min/m^2, that of Group 2 was 3.1±0.8 L/min/m^2, Group 3 was 2.8±0.6 L/min/m^2, and Group 4 was 2.5±0.6 L/min/m^2. The cardiac index of Group 1 was significantly higher than those of the other groups. The cardiac indices of the four groups increased during dobutamine loading (Table 2). The increased rates of the cardiac indices by dobutamine did not differ among the four groups (Fig. 3).

DISCUSSION

In this study, left ventricular contractility and relaxation properties were impaired in patients with chronic heart failure at the baseline in accordance with the left ventricular volume. The left ventricular inotropic reserve was also impaired in patients with chronic heart failure in accordance with the left ventricular volume. On the other hand, the left ventricular lusitropic reserve, which was estimated by the responses of negative dP/dt for stepwise dobutamine loading, was preserved in patients with severe left ventricular dysfunction as well as patients with minimally impaired left ventricular function. Accordingly, patients with chronic heart failure exhibited discrepant inotropic and lusitropic reserves for β-adrenergic stimulation.

β-adrenoceptor stimulation on cardiomyocytes increases intracellular cyclic AML via activation of GTP-binding proteins and adenylate cyclase (Fig. 4). The increase in cytosolic cyclic AMP leads to the activation of cyclic AMP-dependent protein kinase, which acts to amplify contractility and relaxation through the phospholylation of voltage-dependent Ca^{++} channels and phospholambans. That is, both inotropic and lusitropic responses under β-adrenoceptor stimulation use the same signal transduction pathway up to the intracellular second messengers, cyclic AMP and protein kinase A, in the myocardium. If abnormal sites of signal transduction exist on the upstream of intracellular second messengers in the failing myocardium, both the inotropic and lusitropic reserves should be impaired similarly. Therefore, the discrepancy between the inotropic reserve and lusitropic reserve in patients with chronic heart failure suggests that major abnormal sites of β-adrenergic signal transduction pathway in the failing myocardium may exist on the downstream of protein kinase A. One possible explanation for this discrepancy is that phospholamban of the sarcoplasmic reticulum may compensate by being down regulated in patients with chronic heart failure in

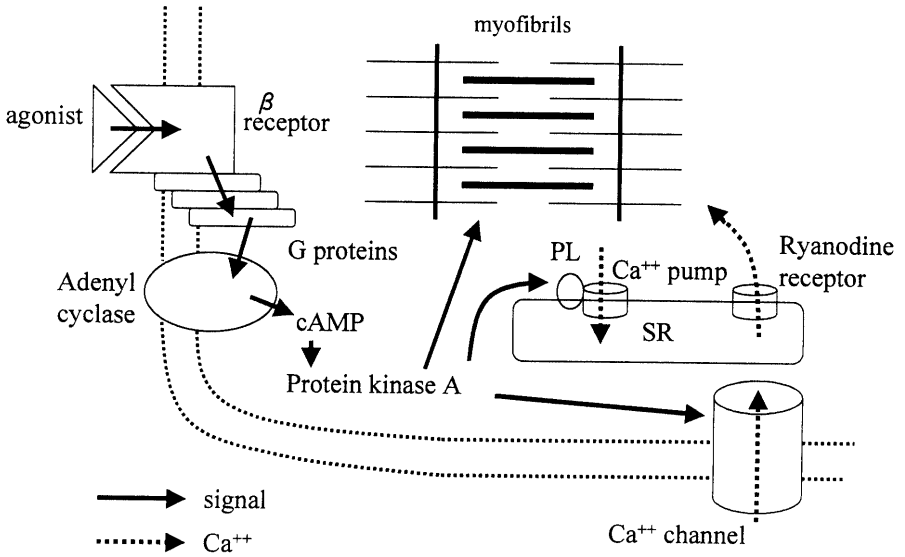

Fig. 4. Schema of the β-adrenoceptor and subcellular signal transduction system of cardiomyocytes. β-adrenoceptor stimulation by agonist increases intracellular cyclic AML through the activation of G-proteins and adenylate cyclase. The increase in cytosolic cyclic AMP leads to the activation of cyclic AMP-dependent protein kinase, protein kinase A, which acts to amplify contractility and relaxation by phospholylation of voltage-dependent Ca^{++} channels and phospholamban. PL, phospholamban; SR, sarcoplasmic reticulum.

accordance with the severity of ventricular dysfunction[16-18]. Consequently, the lusitropic reserve of the failing myocardium may be preserved.

This study has some limitations. We could not employ normal controls in this study. Group 1, which served as the disease control, was composed of patients with minimally impaired left ventricular function. Only one report has previously demonstrated that the lusitropic reserve of the left ventricle of patients with severe chronic heart failure was preserved in spite of the impairment of the inotropic reserve, compared with normal controls[6]. Our study demonstrated that the lusitropic reserves of patients with minimal, mild, moderate and severe left ventricular systolic dysfunction were equally preserved. We used the minimum negative dP/dt as the parameter for relaxation properties of the left ventricle. It is well known that a time constant of ventricular pressure decay is a more specific indicator of ventricular relaxation properties which is independent of an afterload[19-21]. The use of the minimum negative dP/dt was our instrumental limitation.

In this study, the left ventricular lusitropic reserve was preserved in patients with various degrees of left ventricular systolic dysfunction. Analysis of the mechanisms of the failing myocardium is important in order to develop a specific, individualized therapy for chronic heart failure. Assessment of left ventricular function under stepwise dobutamine loading is valuable to clarify the site of cellular dysfunction in failing hearts.

Acknowledgments. This study was supported in part by a grant for scientific research from the Ministry of Education, Science and Culture of Japan (10670636).

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