Use of Thallium-201 Myocardial Scintigraphy for the Prediction of the Response to β -Blocker Therapy in Patients With Dilated Cardiomyopathy

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This study was performed to evaluate whether thallium-201 myocardial scintigraphy (Tl-201) and iodine-123-metaiodobenzylguanidine (MIBG) myocardial scintigraphy could predict the usefulness of β -blocker therapy in patients with dilated cardiomyopathy (DCM). Tl-201 and MIBG were performed in 47 patients before β -blocker therapy. Patients were classified into group A, if their cardiac function improved, and group B, whose function remained unchanged. Two types of extent score (ES) by Tl-201 were proposed to quantitate myocardial damage, mean $\pm$ 2SD (ES-2) and mean $\pm$ 3SD (ES-3). The ES difference between ES-2 and ES-3 was calculated, and according to ES and ES difference, DCM cases were classified into 3 groups: mild-defect type (mild-type), moderate-defect type (moderate-type) and severe-defect type (severe-type). The heart-to-mediastinum (H/M) MIBG uptake ratio was evaluated, and the percent washout ratio of myocardial MIBG was obtained from these data. Group A comprised 18 mild-type, 14 moderate-type and 1 severe-type cases, and group B comprised 5 mild-type, 4 moderate-type and 5 severe-type cases. A significant relation was observed between the defect type on Tl-201 and the response to β -blocker therapy ($p=0.0090$). Both H/M MIBG uptake ratios and washout ratio were not significantly different in the 2 groups. Tl-201 may be useful for predicting the response to β -blocker therapy in patients with DCM. (Circ J 2002; 66: 1139–1143)

Key Words: β -blocker; Dilated cardiomyopathy; MIBG; Scintigraphy; Thallium

In 1975, Waagstein et al reported for the first time that patients with severe heart failure showed clinical improvement after the administration of β -blocker,¹ and since then the beneficial effect of β -blocker therapy in patients with chronic congestive heart failure has been confirmed in many studies.^{2–7} However, some patients with chronic heart failure show little response to β -blocker therapy and therefore predicting whether patients with heart failure will respond favorably to the therapy is important.

A few recent studies have reported that iodine-123-metaiodobenzylguanidine (MIBG) myocardial scintigraphy may be useful for predicting the outcome of β -blocker treatment for heart failure.^{8–10} Other reports document the usefulness of thallium-201 (Tl-201) myocardial scintigraphy for predicting prognosis for patients with dilated cardiomyopathy (DCM).^{11,12} In the present study, we examined if Tl-201 scintigraphy or MIBG scintigraphy can predict a good response to β -blocker therapy in patients with DCM.

Methods

Study Population

Patients were considered eligible for the study if they had symptomatic heart failure for more than 3 months and they had a left ventricular fractional shortening less than 25%. In addition, study patients had to be clinically stable under the standard therapy of digoxin, diuretics, and angiotensin-converting enzyme inhibitor. The study population consisted of 47 patients (mean age, 54 ± 14 years; 38 men, 9 women). All patients were diagnosed as having DCM according to the criteria of the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies.¹³ Patients were excluded if they had obstructive lung disease, asthma or symptomatic peripheral vascular disease. All patients participated in the present study after giving informed consent.

Echocardiographic Study

In all patients, M-mode and 2-dimensional echocardiographic studies were performed with an Aloka SSD 870 or SSD 9000 imaging system (Tokyo, Japan) with 2.5- or 3.5-MHz transducers. The M-mode echocardiogram was recorded on a strip-chart recorder at a paper speed of 50 mm/s or 100 mm/s. From the M-mode echocardiographic study, the following conventional variables were measured according to the criteria of the American Society of Echocardiography¹⁴: left ventricular dimension at end-diastole (LVDd) and end-systole (LVDs). Left ventricular volume was calculated with Teichholtz's formula, and the ejection fraction (EF) was determined. At the time of the echocar-

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Fig 1. Bull's-eye maps (Left column) and extent maps (Middle column, ES-2; Right column, ES-3) show the defined mild-type, moderate-type and severe-type (Upper row, mild-type; Middle row, moderate-type; Lower row, severe-type). Extent score (ES) difference is 5.7% for mild-type, 20.8% for moderate-type and 13.7% for severe-type.

diographic study, arterial blood pressure was determined in duplicate via cuff sphygmomanometer.

Thallium-201 Myocardial Scintigraphy and the Determination of Extent Score

Tl-201 scintigraphy at rest was performed in all patients with DCM, using a method described previously.¹⁵ Briefly, subjects were examined in the morning after an overnight fast. Imaging at rest was begun 10 min after administration of 111 MBq of thallium-201, and the imaging was repeated 5 h later. The single photon emission computed tomography (SPECT) system (GCA 9300; Toshiba, Tokyo, Japan; and Scintipac 2400; Shimadzu, Kyoto, Japan) consisted of a triple-head, digital gamma camera equipped with high-resolution, low-energy, parallel-hole collimators. A scintillation camera was rotated for 90 s for each of 36 projections over 360° circular orbits. Energy discrimination was provided by a 15% window centered on the 72 keV photopeak of thallium-201. A series of each 3.5-mm-thick slices was reconstructed with filtered backprojection by a ramp filter. Attenuation correction was made by uniform correction of the Chang method to multiply the original reconstructed image by the correction matrix;¹⁶ scatter correction was also made.

The computerized thallium-201 tomographic method proposed by Garcia et al¹⁷ was used to quantify the size of myocardial perfusion defects. A polar map was formulated by comparing the normalized maximal count value at each point with the normal value at the corresponding point. To depict 2 kinds of extent polar map, we selected 2 kinds of lower normal limits, mean–2SD and mean–3SD. The extent score (ES) was defined as the number of points that fell below the lower normal limits and was expressed as a percentage of the total left ventricular points on the extent polar map.¹⁸ We named these 2 kinds of extent score ES-2 and ES-3, respectively. In order to quantitate the size of mild to moderate myocardial perfusion defects, the ES

Table 1 Clinical Characteristics of the 2 Groups

	Group A (n=33)	Group B (n=14)
Mean Age (years)	53±15	55±11
Sex (M/F)	25:8	13:1
NYHA functional class (n)		
I	2	3
II	24	8
III	7	3
Concomitant medications n (%)		
Furosemide	31 (94%)	12 (86%)
Spironolactone	23 (70%)	6 (43%)
Digoxin	17 (52%)	9 (64%)
ACEI or AII type 1 receptor antagonist	32 (88%)	13 (93%)
Atrial fibrillation (n)	7 (21%)	4 (29%)
ANP	47±49	75±98
BNP	103±103	188±202

NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitor; AII, angiotensin II; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

difference between ES-2 and ES-3 was calculated in each case. Patients were classified according to the degree of ES-2 and ES difference: mild-defect type (mild-type) was defined as one with ES-2 <26% (the basis of the median value of ES-2), moderate-defect type (moderate-type) was defined as one with ES-2 ≥26% and ES difference ≥14% (the basis of the median value of ES difference) and severe-defect type (severe-type) was defined as one with ES-2 ≥26% and ES difference <14% (Fig 1).

Iodine-123-Metaiodobenzylguanidine Myocardial Scintigraphy

MIBG scintigraphy was performed in 41 of the 47 patients. On the day of imaging, patients were instructed not to have breakfast and to continue fasting until the end of the last imaging session. Iodine-123-metaiodobenzylguanidine (111 MBq) was intravenously administered, and myocardial SPECT images were obtained at 15 min (early image) and 5 h (delayed image) after administration. The SPECT system was the same as that used for Tl-201 scintigraphy. Energy discrimination was provided by a 15% window centered on the 160 keV photopeak of iodine-123. A series of each 3.5-mm-thick slices was reconstructed under the same conditions described for Tl-201 scintigraphy. The polar map for MIBG scintigraphy was determined in the same way as for Tl-201 scintigraphy.

For quantitative analysis of the myocardial iodine-123-metaiodobenzylguanidine accumulation, anterior planar projection images were acquired in the SPECT studies. A region of interest (ROI) was selected to encompass the whole heart, and a square ROI, usually 10×10 pixels in size, was selected to include the mediastinum on both the early and delayed images. The counts per pixel were measured for each ROI, and the heart-to-mediastinum (H/M) iodine-123-metaiodobenzylguanidine activity ratio was calculated. The activity of iodine-123-metaiodobenzylguanidine was corrected by time interval and background, and the myocardial washout rate of iodine-123-metaiodobenzylguanidine was determined as the percentage of change in activity from early image to delayed image. The normal range of the myocardial washout rate in our institute was 3–23%.

Table 2 Hemodynamics and Cardiac Functional of the 2 Groups During the 6 Months Follow-up

	HR (beats/min)	SBP (mmHg)	LVDd (mm)	LVDs (mm)	EF (%)
Group A (n=33)					
Before	71±13	116±13	65±7	54±8	35±10
After	64±7	119±13	59±7	45±8	47±10
p value	0.0004	0.2122	<0.0001	<0.0001	<0.0001
Group B (n=14)					
Before	72±12	113±12	63±7	50±9	42±12 [#]
After	66±9	115±13	62±6	49±8	43±11
p value	0.0310	0.3262	0.0538	0.0637	0.3084

Values are the mean±standard deviation, [#]p<0.05 compared with group A. HR, heart rate; SBP, systolic blood pressure; LVDd, left ventricular dimension at end-diastole; LVDs, left ventricular dimension at end-systole; EF, ejection fraction.

Measurement of Plasma Concentrations of Atrial and Brain Natriuretic Peptide

Plasma atrial and brain natriuretic peptide (ANP and BNP) concentrations were determined as reported previously.¹⁹ A blood sample was taken from the antecubital vein in the morning after 30 min of supine rest. Blood was immediately transferred into chilled glass tubes containing disodium EDTA (1 mg/ml) and aprotinin (500 U/ml) and centrifuged at 3,000 rpm for 10 min at 4°C. The plasma was frozen and stored at -80°C until radioimmunoassay (RIA) was performed for measurement of the plasma concentrations of ANP (Shiono RIA assay kit, Shionogi Co, Ltd, Osaka, Japan) and BNP (S-1215, Shionogi Co, Ltd). At our institution, the normal values are <43.0 pg/ml for plasma ANP and <17.0 pg/ml for plasma BNP.

-Blocker Therapy

Twenty-two patients were treated with metoprolol, 10 patients were treated with carvedilol and 15 patients were treated with bevantolol. Patients received titrated doses of -blockers beginning with a low value of 2.5 or 5 mg and increasing gradually to the maximal dose determined by one of three end points, which were either a decrease in systolic blood pressure to less than 90 mmHg, a decrease in heart rate (HR) at rest to less than 50 beats/min, or clinical deterioration. Mean maintenance doses were 39±15 mg (from 15 mg to 70 mg) for metoprolol, 13±3 mg (from 10 mg to 20 mg) for carvedilol and 55±25 mg (from 20 mg to 120 mg) for bevantolol. Under the same standard therapy, all patients were treated with -blocker for 6 months.

Echocardiographic studies were performed before and 6 months after treatment. Patients were classified into group A (n=33), if their LVDd decreased by 5 mm or more or the EF improved by 5% or more with -blocker therapy, and group B (n=14), for those whose LVDd change was less than 5 mm and EF change was less than 5%.²⁰

Statistical Analysis

Data are presented as mean±S.D. Baseline characteristics, except for ANP and BNP, were analyzed with an unpaired t test or chi-square test (for nonparametrically distributed values). Between group differences in ANP and BNP were tested by Wilcoxon signed rank test. The relationship between the defect type and response to -blocker therapy was analyzed by chi-square test. Multivariate logistic regression analysis was performed to determine independent predictors of response to -blocker therapy. All calculations were performed on a personal computer with the statistical package StatView (Abacus, Concepts, Inc, Berkeley, CA, USA 1994). A value of p<0.05 was consid-

Table 3 TI-201 and MIBG Scintigraphic Findings of the 2 Groups

	Group A (n=33)	Group B (n=14)	p value
ES-2 (%)	26±16	33±19	0.1897
ES-3 (%)	11±11	21±18	0.0282
ES difference (%)	15±7	12±6	0.2902
Early H/M	1.78±0.22	1.82±0.33	0.6464
Delayed H/M	1.76±0.29	1.81±0.42	0.6321
Washout rate (%)	28±10	27±11	0.8141

Values are the mean±standard deviation. ES, extent score; H/M, heart-to-mediastinum ratio.

ered significant.

Results

Clinical Characteristics and Natriuretic Peptides of the 2 Groups at Baseline

When clinical characteristics and natriuretic peptides were evaluated at the start of the study, no significant between-group differences were found in age, sex, New York Heart Association (NYHA) functional class, concomitant medications and number of atrial fibrillations (Table 1). There were also no significant differences in mean dose of concomitant medications of the 2 groups. And finally, ANP and BNP values did not differ significantly between the 2 groups.

Hemodynamics, Cardiac Function, and TI-201 Scintigraphic and MIBG Scintigraphic Findings in the 2 Groups

Table 2 shows the hemodynamics and cardiac function in the 2 groups. Although there were no significant differences in HR, systolic blood pressure, LVDd and LVDs between the 2 groups at the start of the study, EF was significantly greater in group B than in group A. Table 3 shows TI-201 and MIBG scintigraphic findings in the 2 groups at the start of the study. Although ES-2 and ES difference were not significantly different between the 2 groups, ES-3 was greater in group B than in group A. Early H/M, delayed H/M and washout rate were not significantly different between the 2 groups.

Relation Between the Defect Type on TI-201 Scintigraphy and Response to -Blocker

The relation between the defect type on TI-201 scintigraphy and response to -blocker therapy was examined for the 2 groups at the start of the study. Group A comprised 18 mild-type, 14 moderate-type and 1 severe-type cases,

Table 4 Independent Predictors of Response to β -Blocker Therapy

	Odds ratio	95% confidence interval	p value
Age	1.010	0.964–1.059	0.6669
ANP	1.006	0.996–1.016	0.2463
BNP	1.020	0.999–1.009	0.1020
LVDd	0.959	0.871–1.055	0.3884
LVDs	0.942	0.868–1.022	0.1527
EF	1.065	0.999–1.136	0.0546
ES-2	1.025	0.988–1.064	0.1897
ES-3	1.051	1.002–1.102	0.0417
ES difference	0.948	0.861–1.045	0.2852
Mild-type	0.278	0.103–0.748	0.0113
Moderate-type	1.029	0.232–4.559	0.9704
Severe-type	18.000	1.691–191.565	0.0166
Early H/M	0.961	0.119–32.234	0.6374
Delayed H/M	1.704	0.204–14.251	0.6228
Washout ratio	0.991	0.924–1.063	0.8084

HR, heart rate; SBP, systolic blood pressure; LVDd, left ventricular dimension at end-diastole; LVDs, left ventricular dimension at end-systole; EF, ejection fraction; ES, extent score; H/M, heart-to-mediastinum ratio.

and group B comprised 5 mild-type, 4 moderate-type and 5 severe-type cases. A significant relation was observed between the defect type on TI-201 scintigraphy and response to β -blocker therapy (chi-square=9.430, $p=0.0090$).

Logistic Analysis and Probability of Response

Results of multivariate logistic regression analysis to determine independent predictors of response to β -blocker therapy are shown in Table 4. Of all the dependent variables, ES-3, mild-type and severe-type remained statistically significant as independent predictors. Among 41 patients with mild-type or moderate-type, 32 patients responded to β -blocker therapy. With the value of mild-type or moderate-type, the defect type showed a sensitivity of 78%, specificity of 83% and accuracy of 79%.

Discussion

In the present study, the defect score and pattern on TI-201 scintigraphy in patients with DCM were associated with a response to β -blocker therapy. In contrast, the parameters established with MIBG scintigraphy showed no significant relation to the response to β -blocker therapy.

We previously reported that left ventricular end-systolic wall stress is a potent prognostic variable in patients with DCM²¹ and in that study, left ventricular end-systolic wall stress and ES of TI-201 scintigraphy were significantly positively correlated.²¹ Doi et al¹¹ and Shiotani et al¹² reported that the severity of TI-201 perfusion defects in patients with DCM is associated with a poor prognosis. Bukley et al²² indicated that constant perfusion defects seen on thallium scans in patients with DCM might represent areas of myocardial fibrosis and scarring. Li et al²³ also reported a significant relation between perfusion defect on TI-201 and myocardial fibrosis.

Yamada et al²⁴ demonstrated that patients with mild fibrinogenesis on myocardial biopsy responded to β -blocker therapy, but those with severe fibrinogenesis did not. They also demonstrated that β -blocker therapy would be expected to be more effective in patients in whom the dominant type of fibrosis was interfascicular rather than intercellular. Nishi et al²⁵ reported that isoproterenol stress echocardiography predicted the response to β -blocker therapy in patients with

DCM and they speculated that the severely reduced response to isoproterenol might be because of myocardial damage caused by fibrosis or irreversible degeneration. In our study, the defect score and pattern of TI-201 were associated with the response to β -blocker therapy. We think that the area of difference between ES-2 and ES-3 may express the area of mild to moderate myocardial damage. We also think that DCM patients with mild-type or moderate-type are responsive to β -blocker therapy and TI-201 may detect reversible damage of the myocardium. We suggest that DCM patients with the mild to moderate type should be treated with β -blocker.

Some investigators^{26,27} reported that a favorable response occurs in patients with a higher heart rate and more advanced left ventricular dysfunction. However, Eichhorn et al²⁸ and Yamazaki et al¹⁰ reported that EF before the administration of β -blocker did not predict the response to therapy. In our data, patients with a lower EF showed a good response to β -blocker. Left ventricular variables for predicting the effect of β -blocker therapy remain controversial in patients with DCM and the exact mechanisms for this remained to be determined. Despite the lack of significant difference in the values of ANP and BNP, these values were less in group A than in group B, which may be related to the response to β -blocker therapy.

MIBG scintigraphy is considered a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with heart failure.^{29,30} Recently some studies noted a potential role for MIBG scintigraphy in predicting therapeutic response to β -blocker in patients with heart failure. Suwa et al⁸ reported that the H/M ratio on the delayed image is a good predictor of response to β -blocker therapy with a threshold of 1.7 (sensitivity=91%, specificity=92%). Choi et al³¹ reported that the washout rate showed a significant inverse correlation with the increase of ejection fraction in patients treated with β -blocker. Fukuoka et al⁹ and Yamazaki et al¹⁰, however, observed no difference between responders and non-responders to β -blocker therapy in terms of washout rate and delayed H/M ratio before β -blocker therapy. In the present study, there was no significant difference between responders and non-responders to β -blocker therapy in washout rate and delayed H/M ratio at the start of the therapy, and MIBG scintigraphy could not predict the response to β -blocker therapy in patients with DCM. Approximately half of the patients studied by Suwa et al⁸ were in NYHA functional class IV, but most patients in our study were in NYHA II–III and this difference in NYHA functional class may result in the different results for MIBG in predicting the response to β -blocker therapy.

Study Limitations

None of the patients was in NYHA functional class IV at the start of this study, thus it is unclear whether the effect of β -blocker therapy can be predicted by the defect score and pattern of TI in DCM patients in that functional class. Second, the ES has been established previously, but the definition of defect type is an original idea. However, we think that this method could be distinguish between mild to moderate myocardial perfusion defects and severe myocardial perfusion defects. Third, this study could not investigate the relation between defect type noted on TI-201 scintigraphy and myocardial pathologic findings. It is not necessarily correct that DCM patients with mild to moderate defect type always have less myocardial fibrosis or less

myocardial degeneration. The implication of the present data, however, suggests that the more severe the defect score on Tl-201 scintigraphy, the more extensive the myocardial damage. Further study is required in a larger number of DCM patients with severe heart failure to resolve these questions.

Conclusions

Tl-201 is useful to predict whether patients with DCM will respond to β -blocker therapy and those DCM patients with a mild to moderate defect-type on Tl-201 should be positively treated with β -blocker.

References

1. Waagstein F, Hjalmarson Å, Varnaukas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J* 1975; **37**: 1022–1036.
2. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993; **342**: 1441–1446.
3. Krum H, Sackner-Bernstein JD, Goldsmith RL, Kukin ML, Schwartz B, Penn J, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation* 1995; **92**: 1499–1506.
4. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996; **334**: 1349–1355.
5. CIBIS II investigators and committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): A randomised trial. *Lancet* 1999; **353**: 9–13.
6. Sturm B, Pacher R, Strametz-Juranek J, Berger R, Frey B, Stanek B. Effect of beta 1 blockade with atenolol on progression of heart failure in patients pretreated with high-dose enalapril. *Eur J Heart Fail* 2000; **2**: 407–412.
7. Hara Y, Hamada M, Shigematsu Y, Suzuki M, Kodama K, Kuwahara T, et al. Effect of beta-blocker on left ventricular function and natriuretic peptides in patients with chronic heart failure treated with angiotensin-converting enzyme inhibitor. *Jpn Circ J* 2000; **64**: 365–369.
8. Suwa M, Otake Y, Moriguchi A, Ito T, Hirota Y, Kawamura K, et al. Iodine-123 metaiodobenzylguanidine myocardial scintigraphy for prediction of response to β -blocker therapy in patients with dilated cardiomyopathy. *Am Heart J* 1997; **133**: 353–358.
9. Fukuoka S, Hayashida K, Hirose Y, Shimotsu Y, Ishida Y, Kakuchi H, et al. Use of iodine-123 metaiodobenzylguanidine myocardial imaging to predict the effectiveness of β -blocker therapy in patients with dilated cardiomyopathy. *Eur J Nucl Med* 1997; **24**: 523–529.
10. Yamazaki J, Muto H, Kabano T, Yamashina S, Nanjo S, Inoue A. Evaluation of β -blocker therapy in patients with dilated cardiomyopathy—Clinical meaning of iodine-123 metaiodobenzylguanidine myocardial single-photon emission computed tomography. *Am Heart J* 2001; **141**: 645–652.
11. Doi YL, Chikamori T, Takata J, Yonezawa Y, Poloniecki JD, Ozawa T, et al. Prognostic value of thallium-201 perfusion defects in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1991; **67**: 188–193.
12. Shiotani H, Yamabe H, Fukuzaki H. The clinical and prognostic significance of dipyridamole Tl-201 emission computed tomography in patients with dilated cardiomyopathy. *Jpn Circ J* 1987; **51**: 1016–1021.
13. Report of the 1995 World Health Organization/International Society and Federation of Cardiology task force on the definition and classification of cardiomyopathies. *Circulation* 1996; **93**: 841–842.
14. Sahn DJ, DeMaria A, Kisslo J, Weyman A. The Committee on M-mode Standardization of The American Society of Echocardiography: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 1978; **58**: 1072–1083.
15. Abe M, Hamada M, Matsuo H, Shigematsu Y, Sumimoto T, Hiwada K. Myocardial scintigraphic characteristics in patients with primary aldosteronism. *Hypertension* 1994; **23**(Suppl 1): 1-164–1-167.
16. Chang LT. A method for attenuation correction in radionuclide computed tomography. *IEEE Trans Nucl Sci* 1978; **NS-25**: 638–643.
17. Garcia EV, Van Train K, Maddahi J, Prigent F, Friedman J, Areeda J, et al. Quantification of rotational thallium-201 myocardial tomography. *J Nucl Med* 1985; **26**: 17–26.
18. Gupta NC, Esterbrooks DJ, Hilleman DE, Mohiuddin SM. Comparison of adenosine and exercise thallium-201 single-photon emission computed tomography (SPECT) myocardial perfusion imaging. *J Am Coll Cardiol* 1992; **19**: 248–257.
19. Hamada M, Shigematsu Y, Kawakami H, Minamino N, Kangawa K, Matsuo H, et al. Increased plasma levels of adrenomedullin in patients with hypertrophic cardiomyopathy: Its relation to endothelin-1, natriuretic peptides and noradrenaline. *Clin Sci* 1998; **94**: 21–28.
20. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hersherberger RE, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996; **94**: 2807–2816.
21. Hara Y, Hamada M, Hiwada K. Left ventricular end-systolic wall stress is a potent prognosis variable in patients with dilated cardiomyopathy. *Jpn Circ J* 1999; **63**: 196–200.
22. Bulkley BH, Hutchins GM, Bailey I, Strauss HW, Pitt B. Thallium 201 imaging and gated cardiac blood pool scans in patients with ischemic and idiopathic congestive cardiomyopathy: A clinical and pathologic study. *Circulation* 1977; **55**: 753–760.
23. Li L, Nohara R, Okuda K, Hosokawa R, Hata T, Tanaka M, et al. Comparative study of ²⁰¹Tl-scintigraphic image and myocardial pathologic findings in patients with dilated cardiomyopathy. *Ann Nucl Med* 1996; **10**: 307–314.
24. Yamada T, Fukunami M, Ohmori M, Iwakura K, Kumagami K, Kondoh N, et al. Which subgroup of patients with dilated cardiomyopathy would benefit from long-term beta-blocker therapy? A histologic viewpoint. *J Am Coll Cardiol* 1993; **21**: 628–633.
25. Nishi I, Iida K, Kawano S, Masumi T, Yamaguchi I. Using isoproterenol stress echocardiography to predict the response to carvedilol in patients with dilated cardiomyopathy. *Jpn Circ J* 2001; **65**: 514–518.
26. Engelmeier RS, O'Connell JB, Walsh R, Rad N, Scanlon PJ, Gunnar RM. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: A double-blind, randomized, placebo-controlled trial. *Circulation* 1985; **72**: 536–546.
27. Anderson JL. Treatment of cardiac myopathies with beta blockers. What do we know, where do we go from here? *Postgrad Med* 1988; **29**: 104–112.
28. Eichhorn EJ, Heesch CM, Risser RC, Marcoux L, Hatfield B. Predictors of systolic and diastolic improvement in patients with dilated cardiomyopathy treated with metoprolol. *J Am Coll Cardiol* 1995; **25**: 154–162.
29. Henderson EB, Kahn JK, Corbett JR, Jansen DE, Pippin JJ, Kulkarni P, et al. Abnormal I-123 metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive cardiomyopathy. *Circulation* 1988; **78**: 1192–1199.
30. Schofer J, Spielmann R, Schuchert A, Weber K, Schlüter M. Iodine-123 metaiodobenzylguanidine scintigraphy: A noninvasive method to demonstrate myocardial adrenergic nervous system disintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1988; **12**: 1252–1258.
31. Choi JY, Lee K, Hong KP, Kim B, Seo JD, Lee WR, et al. Iodine-123 MIBG imaging before treatment of heart failure with carvedilol to predict improvement of left ventricular function and exercise capacity. *J Nucl Cardiol* 2001; **8**: 4–9.