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Assessment of Myocardial Metaiodobenzylguanidine Uptake and Its Relation to Left Ventricular Systolic and Diastolic Functional Parameters in Dilated Cardiomyopathy

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Abstract

The purpose of this study was to assess the relation between myocardial metaiodobenzylguanidine (MIBG) uptake and left ventricular systolic and diastolic functional parameters, both of which are known as predictors of prognosis in patients with dilated cardiomyopathy. Echocardiography and iodine-123-MIBG myocardial scintigraphy were performed in 35 patients of dilated cardiomyopathy with normal sinus rhythm. Mean myocardial MIBG uptake in the patient group at early and delayed images were significantly lower than those in normal control subjects (10.6 ± 1.1, 9.8 ± 1.2 vs 12.4 ± 1.0, 12.1 ± 1.0, $p<0.01$). There were, however, no significant differences of mean MIBG uptake in the lung and mediastinum between the two groups ($p>0.05$). There were no significant correlations between myocardial MIBG uptake, expressed as the ratio of heart/mediastinum MIBG activity at delayed image, and left ventricular systolic and diastolic functional parameters {left ventricular ejection fraction, left ventricular end-diastolic dimension, peak velocity of early diastolic filling (E velocity), deceleration time of E wave, cardiac output, left ventricular end-diastolic pressure}. In conclusion, the myocardial uptake of MIBG is decreased in patients with dilated cardiomyopathy assessed by iodine-123-MIBG myocardial scintigraphy. There were, however, no significant correlations between myocardial MIBG uptake and left ventricular systolic and diastolic functional parameters derived from echocardiography.

Key Words: Myocardial metaiodobenzylguanidine uptake, left ventricular systolic and diastolic function, dilated cardiomyopathy

INTRODUCTION

The prognosis of patients with dilated cardiomyopathy is poor, with a 1-year mortality between 15 and 30%.[1] Cardiac transplantation emerged as an alternative treatment for the most severe patients who have no other option.[2-4] Unfortunately, a discrepancy exists between the number of candidates for heart transplantation and the availability of donors. Several studies have demonstrated a variety of prognostic parameters using invasive or noninvasive diagnostic approaches.[5-8] Recently, the restrictive filling pattern, indicating severe diastolic dysfunction, was shown to be the best clinical predictor for cardiac deaths in patients with congestive heart failure and dilated cardiomyopathy.[1,9] Merlet et al. demonstrated that cardiac metaiodobenzylguanidine (MIBG) uptake assessed by iodine-123-MIBG myocardial scintigraphy and radionuclide left ventricular ejection fraction were the only predictors for survival in patients with congestive heart failure.[10,11] Thus, Doppler echocardiography and iodine-123-MIBG myocardial scintigraphy are regarded as useful non-invasive diagnostic modalities in assessing the prognosis in these patients. However, the relationship between myocardial MIBG uptake and echocardiographic variables reflecting left ventricular systolic and diastolic functions has not been well investigated. We analyzed cardiac MIBG imaging in patients with dilated cardiomyopathy and assessed the relation between left ventricular systolic

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and diastolic functional parameters derived from echocardiography and myocardial MIBG uptake.

MATERIALS AND METHODS

Subjects

Thirty-five patients (17 men and 18 women, mean age: 53.6±14.3) were included in this study. Ten healthy subjects served as controls. The diagnosis was based on a diagnostic procedure, including two-dimensional echocardiography, coronary angiography and left ventriculography. The diagnostic criteria were as follows: an enlarged left ventricle (M-mode echocardiographic left ventricular end-diastolic dimension >55 mm) with decreased systolic function (ejection fraction <45% by echocardiography), exclusion of ischemic heart disease, no history of hypertension, no clinical or histologic evidence of myocarditis or any other primary cause of cardiomyopathy, and no primary valvular disorder. The duration and severity of symptoms according to the New York Heart Association functional classification were assessed on the day of echocardiographic examination.

Radionuclide ventriculography (RVG)

ECG-gated RVG was performed to assess the regional myocardial contractility and to measure left ventricular ejection fraction (LVEF). An injection of 1 mg of pyrophosphate, 20 mci (740 MBq) of Tc-99m-pertechnate was administered to the antecubital vein 30 minutes later. Anterior, left anterior oblique (LAO) and lateral views at preset 1000 K counts were obtained. R-R interval was divided into 24 frames. The LVEF was measured manually by drawing a ROI over the left ventricle on LAO view. The regional wall motion was assessed visually.

Iodine-123-MIBG scintigraphy

Before scintigraphy, 100 mg of potassium iodide solution was given for at least 5 consecutive days (2 days before and 3 days after the scintigraphy) to block thyroid uptake. All medications were discontinued 24 hours before scintigraphy. The thirty minutes and 4 hours after injection of 3 mCi (111 MBq) of iodine-123-MIBG (Daiich Lab, Japan), planar and

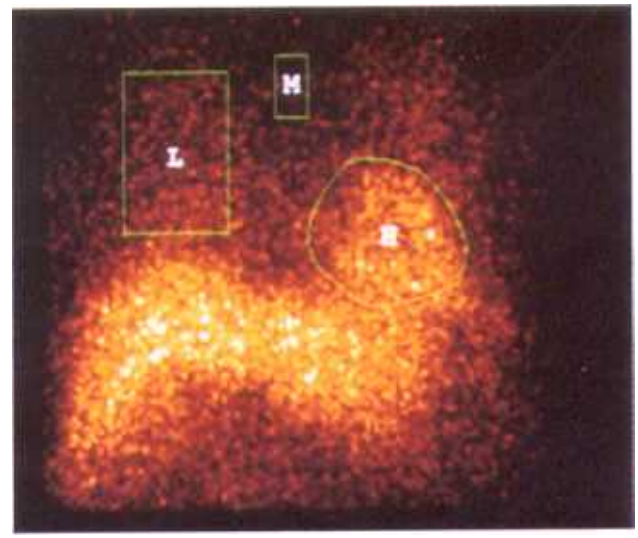

Fig. 1. Anterior planar image of iodine-123-MIBG scintigraphy. Regions of interest were drawn over the lung (L), mediastinum (M), and the heart (H). Mean counts per pixel in each of the areas were obtained, and heart to mediastinal activity ratios were calculated.

SPECT images were obtained. Planar anterior views were acquired at a preset count of 200K on a dual-headed gamma camera equipped with low energy high resolution parallel-hole collimators (ADAC, Milpitas, USA) in 64×64 matrices. A 20% of energy window centered on 159 KeV was used for imaging. SPECT images were obtained at 40 sec/view with 5.6 degree of angular increment and projection data were reconstructed by the filtered back projection method using a butterworth filter (Nyquist frequency 0.35 cycle/cm, order No.5). Short axis, vertical long axis and horizontal long axis views were then obtained by reorientation of transaxial images. SPECT findings were assessed visually to evaluate the presence of adrenergic neuronal damage. On planar views, the region of interest (ROI) was drawn over the lung, mediastinum and heart (Fig. 1). MIBG uptake of the heart, lung and mediastinum was measured as a count per pixel. Mean MIBG uptake was expressed as (early uptake+delayed uptake)/2. The heart-to-lung (H/L) and heart-to-mediastinal (H/M) activity ratios were also calculated from early and delayed images.

Echocardiographic analysis

M-mode, two-dimensional and pulsed wave Doppler echocardiographic examinations were performed

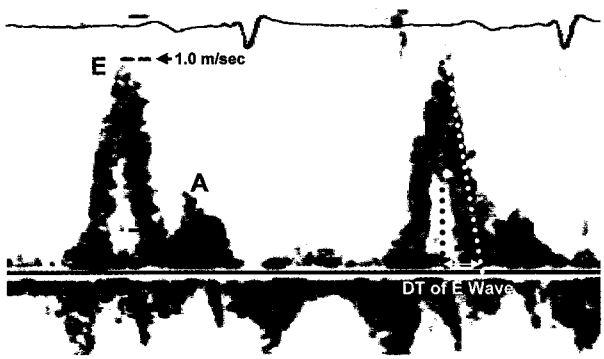

Fig. 2. Pulsed-wave Doppler recording of mitral inflow velocity. Mitral inflow velocity has two components, E and A, in sinus rhythm. DT of mitral inflow is interval from peak velocity of early filling velocity (E) to time it reaches baseline. A denotes peak velocity of mitral inflow during atrial contraction; DT, deceleration time of E wave.

with a Hewlett-Packard model SONOS 1,000 or 1,500 ultrasound imager, using 2.5 MHz phased-array transducer (Hewlett-Packard Co., Palo Alto, California). All examinations were recorded on videotape, and calculations were made directly on screen by computerized planimetry. Recordings were obtained from the parasternal and apical views, while measurements of the left ventricular end-diastolic and end-systolic dimensions, left ventricular fractional shortening and ejection fraction were made according to the recommendations of the American Society of Echocardiography.[12] Pulsed wave Doppler recordings at the tip of both mitral leaflets were obtained from the apical four-chamber view. From velocity tracings, the following variables were obtained: peak early (E) and late (A) transmitral filling velocities (cm/s) and their ratios, the time-velocity integral of the E and A waves (cm), and the deceleration time of E wave (Fig. 2). The isovolumic relaxation time (from aortic valve closure to the beginning of transmitral flow) were also measured. Mitral regurgitation was graded semiquantitatively from grade 1 to 4 by color Doppler flow mapping.[13]

Right heart catheterization, coronary angiography and endomyocardial biopsy

Right heart catheterization was performed using a wedge balloon catheter (Arrow Inc., Reading, PA). Pulmonary capillary wedge, pulmonary artery, right ventricle and right atrial pressures were also measured. Coronary angiography was performed using the Judkins technique. Significant coronary artery disease was defined as a diameter stenosis $>30\%$. Endomyocardial biopsy was performed after coronary angiography in patients who gave informed consent for this additional procedure. Three to 5 biopsy specimens were obtained from the right side of the interventricular septum using a 5.4 Fr biopsy forceps (Cordis Corporation, Miami, FL), and examined by qualitative and quantitative light and electron microscopy.

Analysis of 24 hour collected urine for catecholamine

24-hour urinary norepinephrine and epinephrine were measured by high performance liquid chromatography.

Statistics

All data are expressed as mean$\pm$SD. The two-tailed Student's t-test was used to compare MIBG uptake between patients with dilated cardiomyopathy and the control group. Bivariate correlation analysis was used to evaluate the correlation between myocardial MIBG uptake and echocardiographic parameters. Statistical significance was accepted at the $p<0.05$ level.

RESULTS

Echocardiographic data

Left ventricular end-diastolic and end-systolic dimensions increased (69.4 ± 7.1 mm, 61.8 ± 7.8 mm, respectively) while fractional shortening and ejection fraction measured by M-mode echocardiography decreased ($11.1\pm4.7\%$, $23.7\pm8.0\%$, respectively) in the patient group. Severe mitral regurgitation (grade 3, 4) was detected in 5 patients. No mitral regurgitation was observed in 8 patients. Severe tricuspid regurgitation (grade 3, 4) was observed in 3 patients. Transmitral Doppler velocity recordings obtained from the patient group are also illustrated in Table 1. Two different groups can be identified according to the pattern of left ventricular filling; relaxation abnormality, which is characterized by prolonged deceleration time (DT) of early filling (E), reversed E/A ratio, and prolonged IVRT and restrictive hemo-

dynamics, which is characterized by shortened DT and increased E/A ratio.

Radionuclide ventriculography

Left ventricular ejection fraction was decreased in the patient group (25.5±9.2%). Regional wall motion abnormality was not observed in all patients.

Hemodynamic findings and myocardial biopsy results

Right heart catheterization was performed in 14 patients. Mean left ventricular end-diastolic pressure and mean pulmonary artery pressure were 19.7±6.4 mmHg and 24.5±9.1 mmHg, respectively (Table 2). Endomyocardial biopsy was performed in 9 patients. Light microscopic examination of biopsy specimens revealed various degrees of fibrosis and myocyte hypertrophy without inflammatory infiltrates or other pathognomonic findings.

24-hr urinary catecholamine measurements

Twenty-four hour urinary concentration of epinephrine and norepinephrine in the patient group were 23.9±30.6 ug and 80.8±120.8 ug, respectively.

Table 1. Echocardiographic Variables in Patient Group (N=35)

LVEDD (mm)	69.4±7.1
LVESD (mm)	61.8±7.8
LVEF (%)	23.7±8.0
LVFS (%)	11.1±4.7
MR grade I/II/III/IV	13/9/4/1
TR grade I/II/III/IV	16/4/2/1
E velocity (m/sec)	0.80±0.30
A velocity (m/sec)	0.56±0.28
E/A ratio	2.2±2.3
Deceleration time (msec)	178.8±91.2
IVRT (msec)	105.2±29.4

Values are mean±SD or number of subjects. A indicates peak velocity of late diastolic filling wave; E, peak velocity of early diastolic filling wave; IVRT, isovolumic relaxation time; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVFS, left ventricular fractional shortening; MR, mitral regurgitation; TR, tricuspid regurgitation.

Iodine-123-MIBG scintigraphy

Mean myocardial MIBG uptake in the patient group at early and delayed images were significantly lower than that in normal control subjects (10.6±1.1, 9.8±1.2 vs 12.4±1.0, 12.1±0.9, $p<0.01$). There were, however, no significant differences of mean MIBG uptake of lung and mediastinum between the two groups ($p>0.05$). The early and delayed heart/lung ratios in the patient group were significantly lower than those in normal control subjects (0.9±0.1, 1.0±0.1 vs 1.2±0.2, 1.3±0.1, $p<0.01$). The early and delayed heart/mediastinum ratios in patient group were also significantly lower than those in normal control subjects (1.6±0.2, 1.5±0.2 vs 2.0±

Table 2. Hemodynamic Variables in Patient Group (N=14)

PCWP (mmHg)	17.9±8.6
MPASP (mmHg)	36.3±12.7
MPADP (mmHg)	18.5±8.3
MPAMP (mmHg)	24.5±9.1
RVSP (mmHg)	38.9±12.2
RAP (mmHg)	7.8±6.1
LVEDP (mmHg)	19.7±6.4

LVEDP indicates left ventricular end-diastolic pressure. MPADP, main pulmonary artery diastolic pressure; MPASP, main pulmonary artery systolic pressure; MPAMP, main pulmonary artery mean pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVSP, right ventricular systolic pressure.

Table 3. Early and Delayed MIBG Uptake of Heart, Lung, and Mediastinum in Patients and Normal Control Groups

	Patient (N=35)	Control (N=10)	p value
Early Heart	10.6±1.1	12.4±1.0	0.006
Early Lung	11.8±1.5	10.5±1.1	0.100
Early mediastinum	6.5±0.6	6.8±1.3	0.407
Delay Heart	9.8±1.2	12.1±0.9	0.000
Delay Leung	10.2±1.1	10.3±1.2	0.716
Delay Mediastinum	6.3±0.5	6.8±1.1	0.163
Early H/L	0.9±0.1	1.2±0.2	0.015
Delay H/L	1.0±0.1	1.3±0.1	0.001
Early H/M	1.6±0.2	2.0±0.1	0.000
Delay H/M	1.5±0.2	2.0±0.1	0.000

H, heart; L, lung; M, mediastinum.

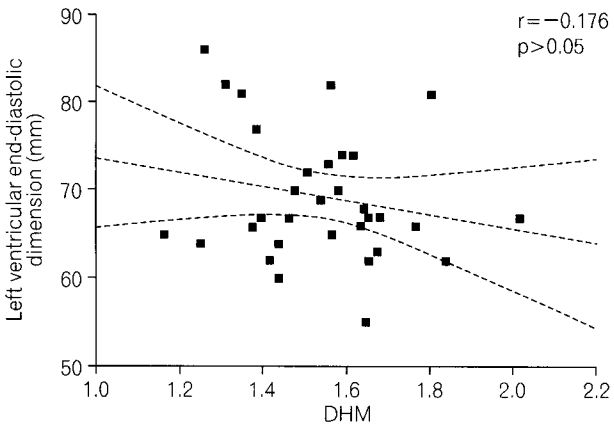

Fig. 3. Correlation between myocardial MIBG uptake (DHM) and left ventricular end-diastolic dimension determined by echocardiography.

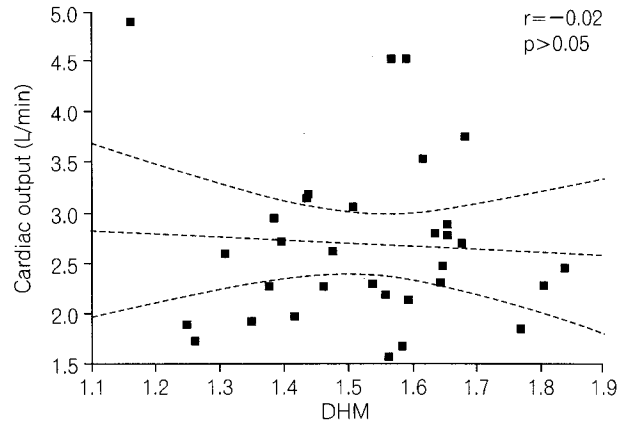

Fig. 4. Correlation between myocardial MIBG uptake (DHM) and cardiac output determined by Doppler echocardiography.

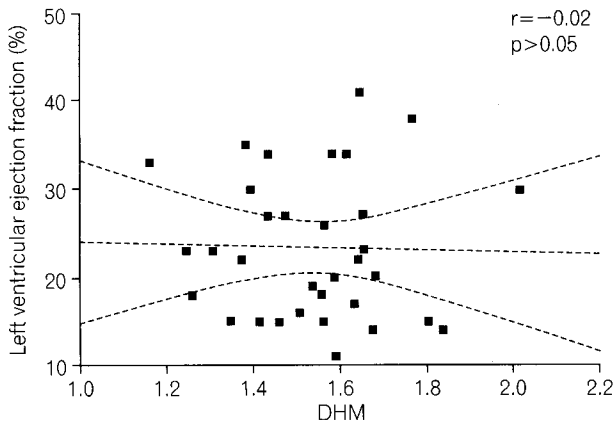

Fig. 5. Correlation between myocardial MIBG uptake (DHM) and left ventricular ejection fraction determined by radionuclide ventriculography.

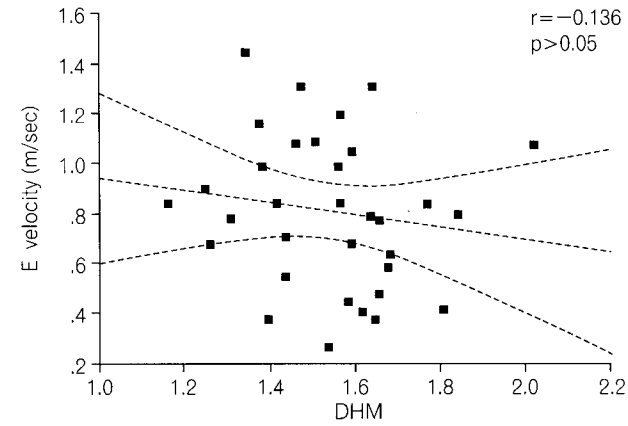

Fig. 6. Correlation between myocardial MIBG uptake (DHM) and E velocity.

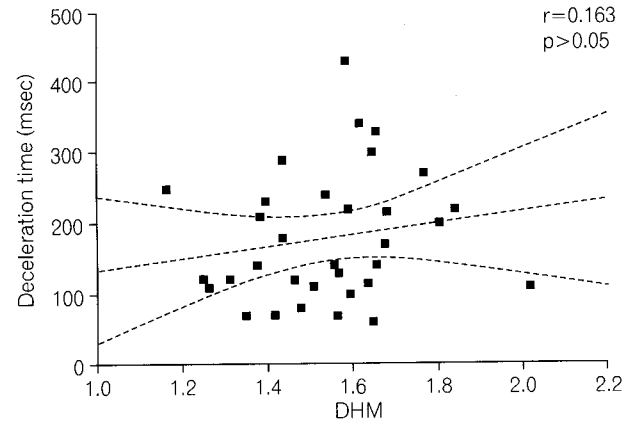

Fig. 7. Correlation between myocardial MIBG uptake (DHM) and deceleration time of E wave.

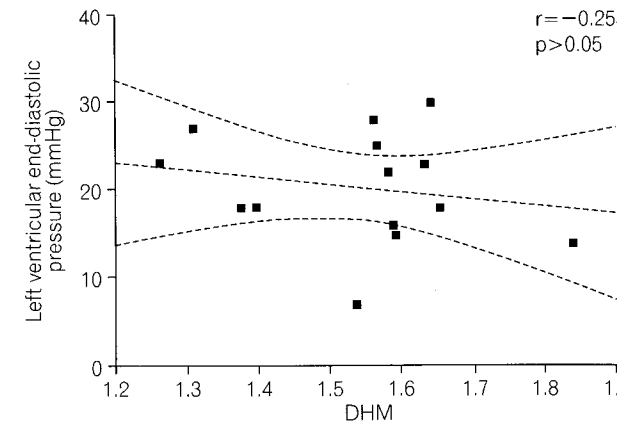

Fig. 8. Correlation between DHM and left ventricular end-diastolic pressure.

0.1, 2.0±0.1, $p<0.001$) (Table 3). The early and delayed heart/mediastinum ratios of patients with NYHA functional class 3 and 4 were significantly lower than those in patients with NYHA functional class 1 and 2 ($p<0.01$). There were, however, no significant differences of early and delayed heart/mediastinum ratios of MIBG uptake between the two groups separated by diastolic left ventricular filling pattern (relaxation abnormality vs restrictive hemodynamic).

Correlation between myocardial MIBG uptake and left ventricular functional parameters

There were no significant correlations between myocardial MIBG uptake, expressed as delayed heart/mediastinum ratio, and left ventricular end-diastolic dimension, cardiac output, left ventricular ejection fraction, E velocity, DT of E wave and left ventricular end-diastolic pressure (Fig. 3-8).

DISCUSSION

The principal findings of the present study were that (1) myocardial MIBG uptake was reduced in patients with dilated cardiomyopathy, and (2) there were no significant correlations between myocardial MIBG uptake, expressed as delayed heart/mediastinum ratio which is known as a strong predictor of prognosis, and left ventricular diastolic functional parameters derived from echocardiography, which are also independent prognostic indicators.

Previous investigations have shown that the prognosis of patients with congestive heart failure appears inversely related to the levels of circulating norepinephrine, which reflect the magnitude of neurohormonal activation.[14,15] Heart failure is a predominant clinical feature of dilated cardiomyopathy. Heart failure is accompanied by important disturbances of the autonomic nervous system.[16-21] Plasma norepinephrine, however, is derived from adrenergic activity throughout the body and is therefore not a specific index of cardiac adrenergic activity.[22-24] Microelectrodes in the superficial nerves innervating muscle or skin or recording potential effector responses to neurally-released norepinephrine can be used in the assessment of sympathetic function in humans.[25] Each of these methods, however, assesses different aspects of sympathetic function and has its advantages and limitations. Recently, a more direct, noninvasive and qualitative assessment of cardiac sympathetic nervous integrity has been possible with iodine-123-MIBG, a guanethidine analog that shares many neuronal transport and storage mechanisms with norepinephrine.[26-28] Abnormalities in myocardial MIBG uptake have been related to sympathetic denervation in the setting of left ventricular damage or dysfunction associated with myocardial infarction, or dilated cardiomyopathy.[29-31] Schofer et al. reported iodine-123-MIBG imaging in 31 patients with dilated cardiomyopathy and showed that the myocardial versus mediastinal MIBG activity ratio was related to myocardial norepinephrine concentration and to left ventricular ejection fraction.[32] Glowniak et al. reported decreased uptake of MIBG within the heart in patients with idiopathic congestive cardiomyopathy suggesting cardiac sympathetic nerve dysfunction.[30] Our data also demonstrated that myocardial MIBG uptake is reduced in patients with dilated cardiomyopathy and this is consistent with previous studies. However, in contrast to the study of Schofer et al.[32] there is only a weak correlation between left ventricular ejection fraction and myocardial MIBG uptake. The quantity of norepinephrine released by adrenergic nerve endings in the heart is, under ordinary circumstances, dependent on the adrenergic impulse traffic, and alterations in the frequency of nerve impulses modify the quantity of norepinephrine released and acting on beta-adrenergic receptors in the myocardium. This mechanism is the most important one which acutely modifies the position of the force-velocity and ventricular function curves under physiologic conditions. Simmons et al. demonstrated that the MIBG heart-to-lung ratio was positively correlated with left ventricular tissue norepinephrine content in a canine pacing-induced heart failure model.[33] However, no relation was found between plasma norepinephrine concentration and the heart/lung MIBG ratio. Although, no significant relation was found between myocardial MIBG uptake and systolic functional parameters, such as ejection fraction and cardiac output in our study, it can be speculated that left ventricular contractile reserve could be related to myocardial MIBG uptake. Therefore it is conceivable that myocardial MIBG uptake will be more closely related to left ventricular contractile reserve than with resting left ventricular systolic functional indices such

as ejection fraction. Further studies are needed to consolidate this issue.

Assessment of left ventricular diastolic function by Doppler echocardiographic analysis of the diastolic transmitral inflow have been regarded as a useful noninvasive diagnostic modality in predicting the prognosis of patients with congestive heart failure including dilated cardiomyopathy. Werner et al. reported that deceleration time and peak early Doppler velocity were the strongest predictors of survival as compared with systolic function and clinical status in a Cox proportional hazards analysis.[1] It has also been demonstrated that restrictive left ventricular filling pattern in patients with dilated cardiomyopathy is a powerful indicator of increased mortality risk.[9] Similar results were reported in patients with congestive heart failure.[34] However, myocardial MIBG uptake was not evaluated in these studies, thus an assessment of correlation between two variables, which had been known as independent prognostic factors, cannot be made. In this study, we analyzed the correlation between variables which were known to be related to the prognosis in congestive heart failure derived from two different noninvasive diagnostic modalities and demonstrated no significant relation between myocardial MIBG uptake and diastolic functional parameters derived from Doppler echocardiography. Imamura et al. assessed myocardial adrenergic activity using iodine-123-MIBG imaging in patients with heart failure from various causes and demonstrated that there was no correlation between myocardial MIBG washout and diastolic function.[35] In their study, diastolic function was analyzed by peak filling rate and time to peak filling rate derived from a time activity curve of gated radionuclide angiography.

In conclusion, the results from our study suggested that myocardial MIBG uptake, expressed as the ratio of heart/mediastinum MIBG activity at delayed image, reflects a different aspect of prognosis in patients with dilated cardiomyopathy, which is not closely related to left ventricular systolic and diastolic functional parameters.

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