

# Cardiac Sympathetic Activity Estimated by $^{123}\text{I}$ -MIBG Myocardial Imaging in Patients with Dilated Cardiomyopathy After $\beta$ -Blocker or Angiotensin-Converting Enzyme Inhibitor Therapy

Takuji Toyama, Yasushi Aihara, Tsutomu Iwasaki, Akira Hasegawa, Tadashi Suzuki, Ryozo Nagai, Keigo Endo, Hiroshi Hoshizaki, Shigeru Oshima and Koichi Taniguchi

Second Department of Internal Medicine, Division of Nuclear Medicine, Gunma University School of Medicine; Gunma Prefectural Cardiovascular Center, Maebashi, Japan

Impaired cardiac sympathetic activity can be evaluated by  $^{123}\text{I}$ -metaiodobenzylguanidine (MIBG) imaging. **Methods:** We studied the significance of MIBG imaging for 24 patients (age  $58 \pm 12$  y) with dilated cardiomyopathy (DCM). We compared 12 patients (group A) treated with metoprolol (dose from 30–60 mg/d) with 12 patients treated with angiotensin-converting enzyme (ACE) inhibitors. Patients were studied before treatment, after 5 mo of treatment (only in group A) and after 1 y of treatment. Cardiac MIBG uptake was assessed as the heart-to-mediastinum activity ratio (H/M) and total defect score (TDS) from anterior planar and SPECT MIBG images, which were acquired in 4 h after tracer injection. New York Heart Association (NYHA) class and left ventricular ejection fraction (LVEF) calculated by echocardiography were also assessed. **Results:** TDS decreased in both groups (in group A, from  $30 \pm 7$  through  $23 \pm 9$  to  $18 \pm 10$ ;  $P < 0.01$ , in group B, from  $30 \pm 6$  to  $24 \pm 8$ ;  $P < 0.01$ ) and H/M was increased in both groups (in group A, from  $1.87 \pm 0.31$  through  $2.03 \pm 0.28$  to  $2.14 \pm 0.29$ ;  $P < 0.01$ , in group B, from  $1.82 \pm 0.28$  to  $1.94 \pm 0.26$ ;  $P < 0.05$ ). But TDS and H/M were more improved in group A than in group B ( $P < 0.05$ ). LVEF was significantly increased in only group A (from  $38 \pm 6$  through  $43 \pm 8$  to  $49\% \pm 9\%$ ;  $P < 0.01$ ). NYHA improved in both groups (in group A, from mean 2.5 through 2.1 to 1.8;  $P < 0.01$ , in group B, from mean 2.6 to 2.1;  $P < 0.05$ ) but was more improved in group A than in group B ( $P < 0.05$ ). **Conclusion:** Cardiac function, symptom and cardiac sympathetic activity evaluated by MIBG images improved after the  $\beta$ -blocker therapy more than with the treatment that used ACE inhibitors.

**Key Words:**  $^{123}\text{I}$ -metaiodobenzylguanidine;  $\beta$ -blocker; angiotensin-converting enzyme inhibitor; dilated cardiomyopathy

*J Nucl Med* 1999; 40:217–223

**T**he prognosis of patients with idiopathic dilated cardiomyopathy (DCM) remains poor. Vasodilator drugs have

been used to treat congestive heart failure. Disturbances in the neurohormonal system, such as activation of the renin-angiotensin-aldosterone system, are well known (1) and treatment with angiotensin-converting enzyme (ACE) inhibitors has been very successful (2). Furthermore, an activated sympathetic nervous system has other characteristics of congestive heart failure and, although short-term beneficial results have been achieved with inotropic drugs (3,4), long-term trials (5–7) have not been successful. To protect the failing heart by reducing adrenergic overstimulation, researchers recently administered a  $\beta$ -adrenergic blocking agent (8,9). However, both drugs were still not compared.

$^{123}\text{I}$ -metaiodobenzylguanidine (MIBG) imaging has been used to study cardiac sympathetic activity. Cardiac MIBG uptake is disturbed in patients with DCM in comparison with normal subjects (10,11). Cardiac uptake and left ventricular ejection fraction (LVEF) are correlated (10,11), and MIBG imaging can be a useful prognostic marker in patients with DCM (11). This study was undertaken to examine the significance of MIBG imaging in patients with DCM and to compare  $\beta$ -blocker treatment with ACE inhibitor treatment.

## MATERIALS AND METHODS

### Study Population

Between 1993 and 1996, we placed 24 consecutive patients with DCM in metoprolol or enalapril treatments, in addition to conventional treatment for heart failure. All patients had experienced at least one episode of heart failure that required short-term hospitalization. They were all symptomatic at the start of  $\beta$ -blocker or ACE inhibitor. Patients were New York Heart Association (NYHA) functional class II and III and had echocardiographic LVEFs under 50%.

Twenty-four patients, 10 women and 14 men (mean age  $58 \pm 12$  y, range 32–74 y) with DCM entered the study. Twelve patients, 5 women and 7 men (mean age  $59 \pm 10$  y, initial mean heart rate  $68 \pm 9$  bpm, initial mean blood pressure  $89 \pm 7$  mm Hg) were treated with  $\beta$ -blocker and 12 patients, 5 women and 7 men (mean

Received Sep. 22, 1997; revision accepted May 27, 1998.

For correspondence or reprints contact: Takuji Toyama, MD, Gunma Prefectural Cardiovascular Center, 3–12, Kameizumi-machi, Maebashi, Gunma, 371, Japan.

age  $56 \pm 13$  y, initial mean heart rate  $71 \pm 9$  bpm, initial mean blood pressure  $91 \pm 10$  mm Hg) were treated with ACE inhibitors. Patients were randomly assigned.

All patients underwent coronary angiographies that showed normal coronary arteries. In all patients, acute or chronic myocarditis was excluded by the findings of left ventricular endomyocardial biopsy. None of the patients was suspected of alcohol abuse. In both groups, background medications included diuretics and digoxin.

### Study Protocol

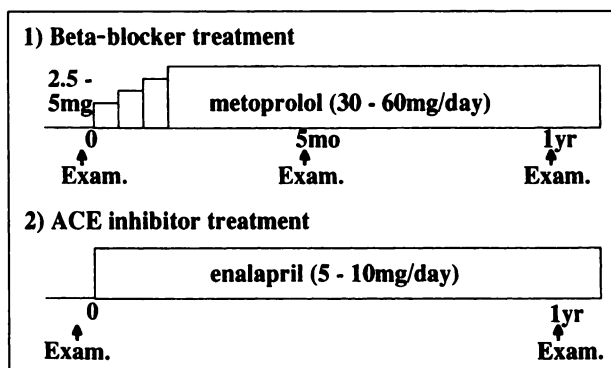
Figure 1 shows the study protocol. In patients treated with  $\beta$ -blocker, the initial metoprolol dose was 2.5–5 mg/d. Three to 5 mo later, the dose was increased to a maintenance dose of 30–60 mg/d. We performed a series of examinations before treatment, 5 mo later and on 1 y of treatment. In patients treated with ACE inhibitor, we started medication with 5–10 mg/d of enalapril. We performed a series of examinations before and after 1 y of treatment.

### MIBG and TI Imagings

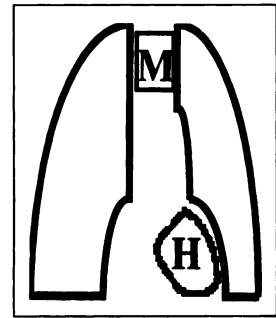
The MIBG was obtained commercially (Daiichi-radioisotope-laboratories, Chiba, Japan). The patients were injected intravenously with 111 MBq (3 mCi) MIBG while in an upright position. Anterior planar and SPECT imagings were performed beginning at 15 min and were repeated 4 h later. SPECT imaging was performed with a dedicated three-detector imaging system (PRISM 3000; Picker International, Cleveland, OH). The detectors were constantly corrected for energy, uniformity and linearity. Projection images were acquired for 20 s each at  $3^\circ$  increments over  $360^\circ$  orbits and were recorded at a digital resolution of  $64 \times 64$ . Immediately after this acquisition, the patients were injected intravenously with 111 MBq (3 mCi) TI in the upright position and imaging began 15 min later. TI SPECT imaging was acquired for 20 s each at  $3^\circ$  increments over  $360^\circ$  orbits. Energy discrimination was provided by a 20% window around the 159-keV photo-peak of  $^{123}\text{I}$  and a 20% window around the 72-keV photo-peak of TI.

From anterior planar delayed MIBG images, the heart-to-mediastinum (H/M) activity ratio was obtained (Fig. 2). Washout rate was calculated by the following:  $(\text{H/M})_{\text{early}} - (\text{H/M})_{\text{delayed}} / (\text{H/M})_{\text{early}} \times 100$ .

The myocardial SPECT image of each patient was divided into 20 segments (Fig. 3). The short axis image at basal, middle and apical ventricular levels was divided into six segments. The apical segment of the vertical long axis image was divided into two segments. Regional tracer uptake was scored semiquantitatively



**FIGURE 1.** Diagram of study protocol. ACE = angiotensin-converting enzyme.



**FIGURE 2.** Anterior planar image was obtained 15 min and 4 h after MIBG intravenous injection. Cardiac MIBG uptake was quantified as H/M activity ratio, using regions of interest positioned over heart (H) and over upper mediastinum (M).

with a 4-point scoring system (0 = normal uptake; 1 = mildly reduced uptake; 2 = moderately reduced uptake; 3 = severely reduced uptake). The total defect score (TDS) was calculated as the sum of the scores for all 20 segments.

### M-Mode Echocardiography

Echographic measurements were performed with standard recommendations (12). Left ventricular end-diastolic and end-systolic dimensions were recorded and the LVEF was calculated by the Teicholz method (13).

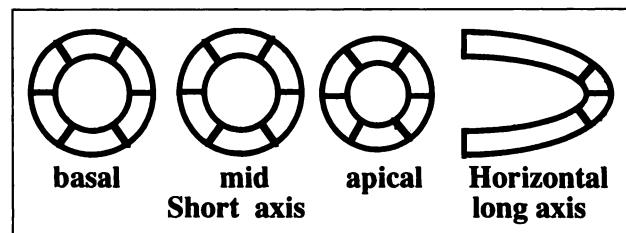
### Data Analysis and Statistics

Statistical analysis was performed with the STATVIEW program (Berkeley, CA) run on a Macintosh computer. Specific comparisons of parameters were made with paired 2-tailed *t* tests or analyses of variance (ANOVAs). Unpaired 2-tailed *t* tests were used to make comparisons between ACE inhibitors and  $\beta$ -blocker groups. All values were expressed as mean  $\pm$  SD, and  $P < 0.05$  was considered statistically significant.

### RESULTS

The TDS on delayed MIBG image is shown in Table 1 and Figure 4. In patients treated with  $\beta$ -blocker, the TDS significantly decreased after 5 mo ( $23 \pm 9$ ) ( $P < 0.05$ ) and further decreased after 1 y of treatment ( $18 \pm 10$ ) ( $P < 0.01$ ) in comparison with the baseline ( $30 \pm 7$ ). In patients treated with ACE inhibitors, the TDS also significantly decreased after 1 y of treatment ( $24 \pm 8$ ) in comparison with the baseline ( $30 \pm 6$ ). The TDS on TI images did not change significantly in either group (Table 1).

H/M ratio on delayed MIBG image is shown in Table 1 and Figure 5. In patients treated with  $\beta$ -blocker, the H/M ratio significantly increased after 5 mo ( $2.03 \pm 0.28$ ) ( $P < 0.05$ ) and further increased after 1 y of treatment ( $2.14 \pm 0.29$ ) ( $P < 0.01$ ) in comparison with the baseline ( $1.87 \pm 0.31$ ). In patients treated with ACE inhibitors, the H/M ratio also significantly increased after 1 y of treatment ( $1.94 \pm 0.26$ )



**FIGURE 3.** Diagram of segmentation scheme used for regional MIBG and TI uptake.

**TABLE 1**  
MIBG and TI Data

Patient no.	Sex	Age (y)	TDS (MIBG)			H/M Ratio			Washout rate (%)			TDS (TI)		
			BSL	5 mo	1 y	BSL	5 mo	1 y	BSL	5 mo	1 y	BSL	5 mo	1 y
<b>β-blocker treatment group</b>														
1	F	59	19	19	8	2.78	2.7	2.93	27	26	10	4	4	4
2	M	67	22	19	19	2.01	2.3	2.13	33	35	26	7	7	7
3	M	72	40	36	36	1.66	1.87	1.84	59	55	55	9	6	3
4	F	63	32	25	19	1.98	2.1	2.39	56	39	30	10	6	9
5	F	58	36	36	32	1.78	1.8	2.12	38	38	41	12	8	13
6	F	57	31	21	15	1.79	2	2.05	40	36	26	10	10	8
7	M	64	33	33	26	1.65	1.65	2.03	35	45	15	11	13	6
8	F	59	28	23	13	1.88	2.12	2.3	45	45	41	9	9	5
9	M	53	28	25	15	1.7	1.71	1.88	57	55	44	6	5	3
10	M	60	24	17	10	1.86	1.96	1.97	31	36	34	6	6	4
11	M	32	44	15	5	1.63	2.09	2.08	30	28	29	2	2	2
12	M	68	26	7	12	1.76	2.07	1.96	48	44	29	6	2	5
Mean		59 ± 10	30 ± 7	23 ± 9*	18 ± 10††	1.87 ± 0.31	2.03 ± 0.28*	2.14 ± 0.29†§	42 ± 11	40 ± 9	32 ± 12†§	8 ± 3	7 ± 3	6 ± 3
<b>ACE-inhibitor treatment group</b>														
1	F	53	35		32	1.58		2.13	39		34	16		20
2	M	52	40		32	1.65		1.71	65		46	17		14
3	M	74	30		25	1.71		1.8	55		47	8		11
4	F	63	36		28	1.75		1.8	55		36	13		8
5	F	38	20		13	1.54		1.86	38		40	12		8
6	M	63	39		34	1.55		1.68	50		48	19		19
7	M	69	31		27	1.77		1.92	29		41	17		11
8	M	71	27		30	1.78		1.74	60		56	13		14
9	M	38	23		17	2.37		2.33	22		35	4		0
10	F	61	27		25	1.7		1.68	70		73	6		6
11	M	49	26		12	2.3		2.33	35		34	3		1
12	F	37	25		16	2.1		2.3	45		35	4		1
Mean		56 ± 13	30 ± 6		24 ± 8†	1.82 ± 0.28		1.94 ± 0.26†	47 ± 15		44 ± 12	11 ± 6		9 ± 7

\**P* < 0.05 vs. BSL.  
†*P* < 0.01 vs. BSL.  
‡*P* < 0.01 vs. 5 mo.  
§*P* < 0.05 vs. 5 mo.  
TDS = total defect score; H/M = heart-to-mediastinum; BSL = baseline; 5 mo = 5 mo of study; 1 y = 1 y of study; ACE = angiotensin-converting enzyme.

(*P* < 0.05) in comparison with the baseline (1.82 ± 0.28). Furthermore, after 1 y of treatment, the H/M ratio of patients treated with β-blocker was higher than that of patients treated with ACE inhibitors (*P* < 0.05).

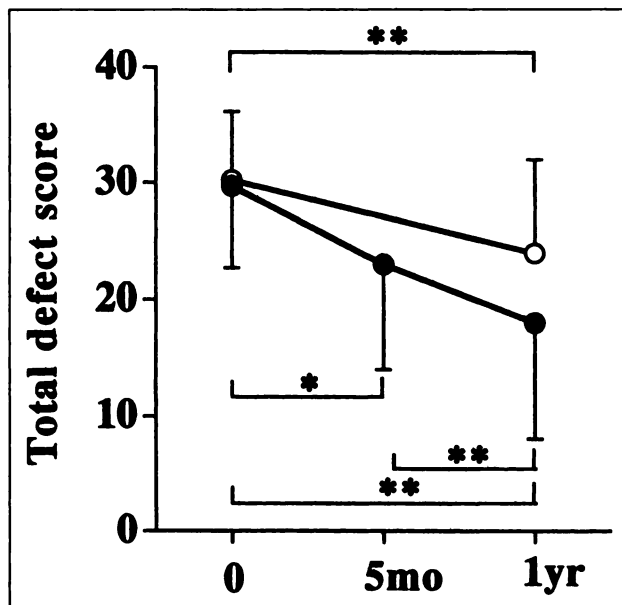
The washout rate of MIBG image is shown in Table 1. In patients treated with β-blocker, the washout rate significantly decreased at 1 y (32% ± 12%) (*P* < 0.05) in comparison with the baseline (42% ± 11%) and after 5 mo of treatment (40% ± 9%), but in patients treated with ACE inhibitors, the washout rate tended to decrease from 47% ± 6% to 44% ± 12% but was not significant.

The left ventricular end-diastolic dimension did not change significantly in either group (Table 2). However, after 1 y of treatment, the end-diastolic dimension (58 ± 6 mm) of patients treated with β-blocker was significantly lower (66 ± 9 mm) than that of patients treated with ACE inhibitors (*P* < 0.05).

The left ventricular end-systolic dimension is shown in

Table 2. In patients treated with β-blocker, the end-systolic dimension significantly decreased at 5 mo (45 ± 6 mm) (*P* < 0.01) and further decreased after 1 y of treatment (43 ± 6 mm) (*P* < 0.01) in comparison with the baseline (49 ± 5 mm), but patients treated with ACE inhibitors showed no significant change after treatment (to 55 ± 10 mm from 53 ± 6 mm). Furthermore, after 1 y of treatment, the end-systolic dimension of patients treated with β-blocker was significantly lower than that of patients treated with ACE inhibitors (*P* < 0.05).

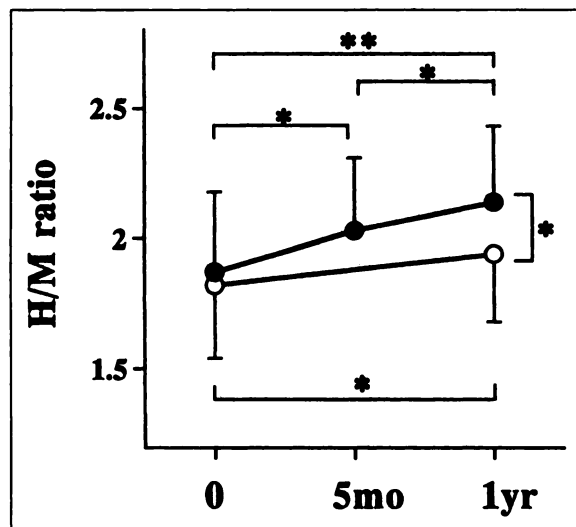
The LVEF is shown in Table 2 and Figure 6. In patients treated with β-blocker, the LVEF significantly increased after 5 mo (43% ± 8%) (*P* < 0.05) and further increased after 1 y of treatment (49% ± 9%) (*P* < 0.01) in comparison with the baseline (38% ± 6%), but patients treated with ACE inhibitors showed no significant change after treatment (to 34% ± 11% from 33% ± 7%). Furthermore, after 1 y of treatment, LVEF of patients treated with β-blocker was



**FIGURE 4.** Line graph shows TDS of delayed MIBG image between two groups. Data are mean  $\pm$  SD values. Filled circles represent  $\beta$ -blocker treatment group; unfilled circles, ACE-inhibitor treatment group. \* $P < 0.05$ ; \*\* $P < 0.01$ .

significantly higher than that of patients treated with ACE inhibitors ( $P < 0.01$ ).

The NYHA class is shown in Table 2 and Figure 7. Patients treated with  $\beta$ -blocker showed improvement after 5 mo and further improvement after 1 y of treatment in comparison with the baseline. Patients treated with ACE inhibitors were also improved after 1 y of treatment in comparison with the baseline. Furthermore, after 1 y of treatment, the NYHA class of patients treated with  $\beta$ -blocker was better than that of patients treated with ACE inhibitors.



**FIGURE 5.** Line graph shows H/M activity ratio of delayed MIBG image between two groups. Data are mean  $\pm$  SD values. Filled circles represent  $\beta$ -blocker treatment group; unfilled circles, ACE-inhibitor treatment group. \* $P < 0.05$ ; \*\* $P < 0.01$ .

## DISCUSSION

Myocardial scintigraphy with MIBG, an analog of norepinephrine, has been reported to provide images that reflect the sympathetic function (14,15). MIBG uptake was considered useful for evaluation of the severity of heart failure, and H/M ratio or TDS was demonstrated to correlate with LVEF. Later, MIBG came to be used not only for evaluation of the severity but for prognostication and evaluation of the therapeutic effect (11). In this study, we investigated its utility in evaluation of the effects of  $\beta$ -blocker and ACE inhibitor treatments and compared the effect of these two types of drugs on dilated cardiomyopathy.

In evaluation of the therapeutic effect, improvement of TDS was more marked in the  $\beta$ -blocker treatment group than in the ACE inhibitor group at 1 y after initiation of treatment, and H/M ratio was significantly higher for the  $\beta$ -blocker treatment group at 1 y. In heart function, left ventricular end-diastolic dimension, end-systolic dimension and LVEF improved significantly in the  $\beta$ -blocker treatment group; while not showing significant changes in the ACE inhibitor group, the  $\beta$ -blocker treatment group compared favorably with the ACE inhibitor group in these values at 1 y. This indicated that the recovery of cardiac function correlated well with the improvement of MIBG uptake. The improvement of MIBG uptake was not shown by heart function data in the ACE inhibitor group, but it was reflected on the cardiac symptoms, which suggested that the improvement not captured by heart function tests was demonstrated by MIBG.

Delayed MIBG images were used to obtain TDS and H/M ratio in this study. There are two types of norepinephrine or MIBG uptake. Uptake-1 (neuronal uptake), which takes place even if the concentration of epinephrine or MIBG is low, depends on sodium and ATP and is suppressed by tricyclic antidepressants. Uptake-2 (extraneuronal uptake), which takes place only when the concentration is high, represents a diffusion system and is hardly suppressed by tricyclic agents (16-18). We judged that early images resulted from both uptake-1 and uptake-2 (14,19), whereas delayed images involved less uptake-2 so that they showed the state of cardiac sympathetic nerves more accurately. Further, because the neuronal accumulation of MIBG reached peak at 4 h after its administration, the neuronal norepinephrine uptake function would be evaluated accurately if MIBG imaging was performed at just that time (19). For these reasons, we used delayed MIBG imaging in this study. In respect to the extent of involvement of the uptake-2 factor, however, studies in heart transplant cases revealed that there was a 10-fold difference in MIBG uptake between patients with transplanted heart and healthy subjects, which implies that MIBG uptake strongly depends on uptake-1 (neuronal uptake) in human hearts (20). It was reported that myocardial MIBG uptake in early images was also specific to sympathetic nerves and nearly all early images resulted from uptake-1 (21). If so, why do delayed images reflect the severity of heart failure more accurately than early images?

**TABLE 2**  
Echocardiographic and NYHA Data

Patient no.	LVDD (mm)			LVDs (mm)			LVEF (%)			NYHA		
	BSL	5 mo	1 y	BSL	5 mo	1 y	BSL	5 mo	1 y	BSL	5 mo	1 y
<b>β-blocker treatment group</b>												
1	50	50	53	41	39	43	37	44	39	2	2	2
2	61	61	63	50	47	47	37	46	49	3	2	2
3	62	55	52	48	43	40	44	42	46	2	2	2
4	56	56	53	47	46	41	35	35	45	2	2	1
5	55	54	55	42	41	38	47	48	58	2	2	2
6	64	62	62	52	47	47	37	48	48	3	2	2
7	61	59	61	51	42	47	34	55	45	3	2	2
8	67	68	63	59	60	54	25	25	30	3	3	2
9	58	47	46	45	36	31	42	46	61	2	2	1
10	67	67	65	53	50	47	42	49	53	3	2	2
11	65	62	61	54	48	47	35	45	45	3	2	2
12	54	54	57	44	44	37	38	38	64	2	2	1
Mean	60 ± 5	58 ± 6	58 ± 6*	49 ± 5	45 ± 6†	43 ± 6*†	38 ± 6	43 ± 8‡	49 ± 9†§	2.5 ± 0.5	2.1 ± 0.3‡	1.8 ± 0.5*
<b>ACE-inhibitor treatment group</b>												
1	64		67	56		60	26		22	3		2
2	64		76	58		66	20		27	3		2
3	60		65	51		58	31		23	2		2
4	64		66	54		54	33		37	3		3
5	57		59	47		48	36		38	3		3
6	65		76	55		70	32		17	3		2
7	72		78	62		65	29		34	3		2
8	61		62	50		54	37		27	2		2
9	61		60	50		46	37		46	2		1
10	70		73	60		60	30		36	3		3
11	59		56	46		43	44		46	2		2
12	56		50	44		35	43		53	2		1
Mean	63 ± 5		66 ± 9	53 ± 6		55 ± 10	33 ± 7		34 ± 11	2.6 ± 0.5		2.1 ± 0.7*

\*P < 0.05 vs. ACE group.

†P < 0.01 vs. BSL.

‡P < 0.05 vs. BSL.

§P < 0.01 vs. ACE group.

||P < 0.05 vs. 5 mo.

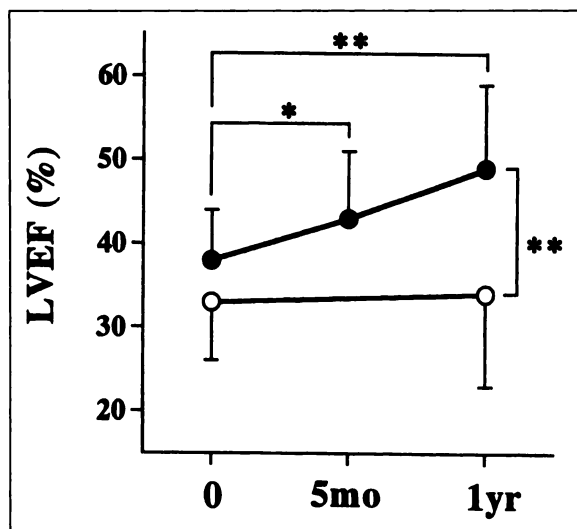
NYHA = New York Heart Association; LVDD = Left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; LVEF = left ventricular ejection fraction; BSL = baseline; ACE = angiotensin-converting enzyme; 5 mo = 5 mo of study; 1 y = 1 y of study.

The answer may be that an increase in norepinephrine turnover at cardiac sympathetic nerve endings led to the decrease in the uptake in late images, so that the increase in turnover, that is, the increase in washout rate, was reflected on the severity. In fact, there are several reports that the severity and improvement of heart failure correlated with the degree and improvement of washout rate (22). In this study, the improvement of washout rate was not obtained at 5 mo but it was confirmed at 1 y in the β-blocker treatment group. Here too, the improvement of norepinephrine turnover seemed to have contributed to the improvement of uptake in late images.

Mechanism of the action of β-blocker on dilated cardiomyopathy includes the following: (a) increased myocardial energy available for synthetic and reparative processes; (b) improved diastolic relaxation, filling and compliance; (c) inhibition of sympathetically mediated vasoconstriction via

prostaglandins and renin release; (d) protection against catecholamine-induced myocardial damage and necrosis; and (e) upregulation of β-adrenergic receptors, allowing restoration of catecholamine responsiveness (23–25). Several authors reported that β-blocker treatment for dilated cardiomyopathy produced improvement of the cardiac function as well as symptoms and prognosis. ACE inhibitors were also reported to have improved the symptoms, cardiac function and prognosis in congestive heart failure (26,27). Though β-blockers were sometimes used without ACE inhibitors (28), the two agents were usually used in combination with each other (24,29–32). Thus, it is not clear which was more responsible for the improvement of cardiac function, and comparison of the two agents has not been reported.

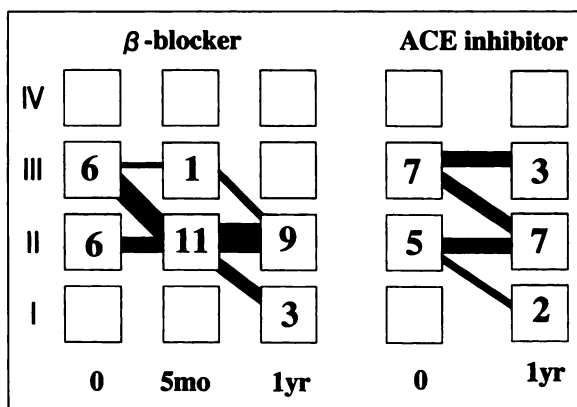
In this study, we used β<sub>1</sub>-selective blocking agent metoprolol. Recently, the differences of responses to dilated cardiomyopathy between β<sub>1</sub>-selective blocking agent and



**FIGURE 6.** Line graph shows LVEF between two groups. Data are mean  $\pm$  SD values. Filled circles represent  $\beta$ -blocker treatment group; unfilled circles, ACE-inhibitor treatment group. \* $P < 0.05$ ; \*\* $P < 0.01$ .

nonselective  $\beta$ -blocking agent. Gilbert et al. (33) reported that there were no significant differences in hemodynamic effects between the nonselective  $\beta$ -blocking agent carvedilol and the  $\beta_1$ -selective blocking agent metoprolol active-treatment groups, and metoprolol was associated with an increase in cardiac  $\beta$ -receptor density, whereas carvedilol did not change cardiac  $\beta$ -receptor expression. That study means carvedilol lets cardiac function recover without upregulation of  $\beta$ -adrenergic receptors.

It has been reported that, in ACE inhibitor treatment for congestive heart failure, enalapril improved hemodynamics (33), symptoms (34) and mortality rate (7,19). In many of these studies, enalapril dosage was increased up to 20 mg (26,27). In this study, ACE inhibitor dosage was not stepped up and its maximum dose may have been insufficient, which might account for the inadequate improvement of the cardiac function. Although we have skipped follow-up at 5



**FIGURE 7.** Flow chart of NYHA functional classification during treatment between two groups. ACE = angiotensin-converting enzyme.

mo in the ACE inhibitor group, data at 1 y suggested that marked changes could not have been expected at 5 mo.

This study shows that cardiac sympathetic function in patients with dilated cardiomyopathy slightly improved with ACE inhibitor treatment. About the relation between cardiac sympathetic function and ACE inhibitor treatment in patients with dilated cardiomyopathy, Spinale et al. (36) reported using a dog's model of dilated cardiomyopathy caused by rapid ventricular pacing. Concomitant ACE inhibitor with chronic tachycardia reduced left ventricular chamber dilation and improved myocyte contractile function and  $\beta$ -adrenergic responsiveness.

Our results indicate that  $\beta$ -blocker is more effective than ACE inhibitors in improving the cardiac function. The  $\beta_1$ -selective blocking agent metoprolol treatment seemed to have brought about recovery of the cardiac sympathetic activity more efficiently than ACE inhibitor treatment by upregulation of  $\beta$ -receptors, with the resulting improvement in the cardiac function. However, combined use of the two agents is desirable in a clinical situation.

## CONCLUSION

Cardiac function, symptom and cardiac sympathetic activity evaluated by MIBG images improved more after the  $\beta$ -blocking treatment than with the treatment that used ACE inhibitors.

## REFERENCES

- Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. *Ann Intern Med.* 1984;101:370-377.
- The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med.* 1987;316:1429-1435.
- Baim DS, McDowell AV, Cherniles J, et al. Evaluation of a new bipyridine inotropic agent-milrinone in patients with severe congestive heart failure. *N Engl J Med.* 1983;309:748-756.
- Maskin CS, Sinoway L, Chadwick B, Sonnenblick EH, Le Jemtel TH. Sustained hemodynamic and clinical effects of a new cardiotoxic agent, Win 47203, in patients with severe congestive heart failure. *Circulation.* 1983;67:1065-1070.
- Petein M, Levine TB, Cohn JN. Persistent hemodynamic effects without long-term clinical benefits in response to oral proximone (MDL 19,205) in patients with congestive heart failure. *Circulation.* 1986;73:230-236.
- DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R, for the Milrinone Multicenter Trial Group. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. *N Engl J Med.* 1989;320:677-683.
- Cohn JN. Inotropic therapy for heart failure: paradise postponed. *N Engl J Med.* 1989;320:729-731.
- Engelmeier RS, O'Connell JB, Walsh R, Rad N, Scanlon PJ, Gunnar R. 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.
- Anderson JL, Lutz JR, Gilbert EM, et al. A randomized trial of low-dose beta-blockade therapy for idiopathic dilated cardiomyopathy. *Am J Cardiol.* 1985;55:471-475.
- Schofer J, Spielmann R, Schbert A, Weber K, Schluter M. Iodine-123 metaiodobenzylguanidine scintigraphy: a noninvasive method to demonstrate myocardial adrenergic system disintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol.* 1988;12:1252-1258.
- Merlet P, Valette H, Dubois-Randé JL, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med.* 1992;33:471-477.
- Sahn DJ, DeMaria A, Kissio J, Weyman A. Recommendations regarding quantitation in M-Mode echocardiography: result of a survey of echocardiographic measurements. *Circulation.* 1978;58:1072-1083.

13. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence or absence of asynergy. *Am J Cardiol.* 1976;37:7.
14. Kline RC, Swanson DP, Wieland DM, et al. Myocardial imaging in man with I-123 meta-iodobenzyl guanidine. *J Nucl Med.* 1981;22:29–132.
15. Wieland DM, Brown LE, Rogers WL, et al. Myocardial imaging with a radioiodinate norepinephrine storage analog. *J Nucl Med.* 1981;22:22–31.
16. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jaques S Jr. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med.* 1987;28:1620–1624.
17. Tobes MC, Jaques S JR, Wieland DM, Sisson JC. Effect of uptake one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. *J Nucl Med.* 1985;26:897–907.
18. Gasnier B, Roisin MP, Scherman D, Coornaert S, Desplanches G, Henry JP. Uptake of meta-iodobenzylguanidine by bovine chromaffin granule membranes. *Mol Pharmacol.* 1986;29:275–280.
19. Nakajo M, Shimabukuro Y, Yoshimura H, et al. Iodine-131 metaiodobenzylguanidine intra- and extravascular accumulation in the rat heart. *J Nucl Med.* 1986;27:84–89.
20. Glowniak JV, Turner FE, Palac RT, Lagunas-Solar MC, Woodward WR. Iodine-123-metaiodobenzylguanidine imaging of the heart on idiopathic congestive cardiomyopathy and cardiac transplants. *J Nucl Med.* 1989;30:1182–1191.
21. Dae MW, Marco TD, Botvinick EH, et al. Scintigraphic assessment of MIBG uptake in globally denervated human and canine hearts-Implications for clinical studies. *J Nucl Med.* 1992;33:1444–1450.
22. Nishimura T, Morozumi T, Hori M. I-123 MIBG scintigraphy for the estimation of the beta-blocker therapy in patients with dilated cardiomyopathy: a multicenter trial [abstract]. *J Nucl Med.* 1996;37:183P.
23. Alderman J, Grossman W. Are beta-adrenergic-blocking drugs useful in the treatment of dilated cardiomyopathy? *Circulation.* 1985;71:854–857.
24. Woodley SL, Gilbert EM, Anderson JL, et al. Beta-blockade with bucindololin heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. *Circulation.* 1991;84:2426–2441.
25. Yamada T, Fukunami M, Ohmori M, et al. Which subgroup of patients with dilated cardiomyopathy would benefit from long-term beta-blocker therapy? *J Am Coll Cardiol.* 1993;21:628–633.
26. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991;325:293–302.
27. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med.* 1991;325:303–310.
28. Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long-term beta-blockade in dilated cardiomyopathy. *Circulation.* 1989;80:551–563.
29. Erlebacher JA, Bhardwaj M, Suresh A, Leber GB, Goldweit RS. Beta-blocker treatment of idiopathic and ischemic dilated cardiomyopathy in patients with ejection fraction  $\leq$ 20%. *Am J Cardiol.* 1993;71:1467–1469.
30. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet.* 1993;342:1441–1446.
31. Bristow MR, O'Connell JB, Gilbert EM, et al. Dose-response of chronic beta-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. *Circulation.* 1994;89:1632–1642.
32. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The cardiac insufficiency bisoprolol study (CIBIS). *Circulation.* 1994;90:1765–1773.
33. Gilbert EM, Abraham WT, Olsen S, et al. Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. *Circulation.* 1996;94:2817–2825.
34. Ader R, Chatterjee K, Ports T, Brundage B, Hiramatsu B, Parmley W. Immediate and sustained hemodynamic and clinical improvement in chronic heart failure by an oral angiotensin-converting enzyme inhibitor. *Circulation.* 1980;61:931–937.
35. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory congestive heart failure. *J Am Coll Cardiol.* 1988;62:41A-45A.
36. Spinale FG, Holzgrefe HH, Mukherjee R, et al. Angiotensin-converting enzyme inhibition and the progression of congestive cardiomyopathy. Effects on left ventricular and myocyte structure and function. *Circulation.* 1995;92:562–578.