Spironolactone Improves Cardiac Sympathetic Nerve Activity and Symptoms in Patients with Congestive Heart Failure

Shu Kasama, MD[1]; Takuji Toyama, MD[1]; Hisao Kumakura, MD[2]; Yoshiaki Takayama, MD[2]; Shuichi Ichikawa, MD[2]; Tadashi Suzuki, MD[1]; and Masahiko Kurabayashi, MD[1]

[1]Second Department of Internal Medicine, Gunma University School of Medicine, Maebashi, Japan; and [2]Kitakanto Cardiovascular Hospital, Gunma, Japan

We evaluated whether spironolactone would improve cardiac sympathetic nerve activity and symptoms in patients with congestive heart failure (CHF). **Methods:** Thirty patients with CHF (left ventricular ejection fraction [LVEF] $<$ 40%; mean, 30% $\pm$ 9%) were treated with an angiotensin-converting enzyme inhibitor, a loop diuretic, and, in most cases, digoxin. Fifteen patients (group A) were assigned to additionally receive spironolactone (12.5–50 mg/day), and the remaining 15 patients (group B) continued their current regimen. Patients were studied before and 6 mo after treatment. The delayed heart-to-mediastinum count ratio (H/M ratio), delayed total defect score (TDS), and washout rate (WR) were determined from ^{123}I-meta-iodobenzylguanidine (MIBG) images. LVEF was determined by echocardiography, and New York Heart Association (NYHA) functional class was estimated. **Results:** Before treatment, LVEF, TDS, H/M ratio, WR, and NYHA functional class were similar in both groups. With treatment, LVEF did not significantly improve in either group. However, after treatment in group A, TDS decreased from 37 $\pm$ 9 to 25 $\pm$ 13 (P = 0.0001), H/M ratio increased from 1.62 $\pm$ 0.20 to 1.83 $\pm$ 0.27 ($P < 0.0001$), and WR decreased from 51 $\pm$ 9 to 40 $\pm$ 15 ($P < 0.001$). In group B, these parameters did not significantly change. NYHA functional class improved in both groups (in group A, from 3.3 $\pm$ 0.5 to 1.7 $\pm$ 0.5 [$P < 0.0001$]; in group B, from 3.3 $\pm$ 0.5 to 2.4 $\pm$ 0.6 [P = 0.01]); this was a significantly greater improvement in group A than in group B ($P < 0.01$). **Conclusion:** Spironolactone improves cardiac sympathetic nerve activity and symptoms in patients with CHF.

Key Words: radionuclide imaging; heart failure; aldosterone

J Nucl Med 2002; 43:1279–1285

Since the Randomized Aldactone Evaluation Study (RALES) (*1*) showed the effectiveness of spironolactone, this drug has often been used as a treatment for patients with severe congestive heart failure (CHF). Aldosterone is important in the pathophysiology of CHF (*2–5*). Aldosterone promotes retention of sodium, loss of magnesium and potassium, myocardial and vascular fibrosis, baroreceptor dysfunction, vascular damage and arterial compliance, sympathetic activation, and parasympathetic inhibition (*5–9*). RALES reported that the addition of spironolactone (an aldosterone-receptor blocker) reduced the risk of death from cardiac causes, hospitalization for cardiac causes, and the combined endpoint of death from cardiac causes among patients who had severe left ventricular systolic dysfunction and who were receiving standard therapy including an angiotensin-converting enzyme inhibitor. Spironolactone also improved the symptoms of heart failure, as measured by changes in the New York Heart Association (NYHA) functional class.

Myocardial imaging with ^{123}I-meta-iodobenzylguanidine (MIBG), an analog of norepinephrine, is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with CHF (*10–16*). However, there are no reports on cardiac ^{123}I-MIBG scintigraphy evaluating the effects of chronic spironolactone therapy in patients with CHF. This study was performed to determine whether spironolactone can improve cardiac sympathetic nerve activity and symptoms in patients with severe CHF.

MATERIALS AND METHODS

Study Population

Thirty patients, 17 men and 13 women (mean age, 69 $\pm$ 13 y; age range, 42–88 y), with CHF were included in the study. A detailed history and physical examination were obtained. Chest radiography, standard electrocardiography, echocardiography, and ^{201}Tl and ^{123}I-MIBG scintigraphy were performed on all patients. Patients were in NYHA functional class III or IV at the time of enrollment and had echocardiographic left ventricular ejection fraction (LVEF) $<$ 40% (mean, 30% $\pm$ 9%). The causes of CHF were old myocardial infarction (n = 16), idiopathic dilated cardiomyopathy (n = 8), and valvular disease (n = 6). All patients were being treated with an angiotensin-converting enzyme inhib-

Received Jan. 9, 2002; revision accepted Jun. 4, 2002.

For correspondence or reprints contact: Shu Kasama, MD, Second Department of Internal Medicine, Gunma University School of Medicine, 3-39-15, Shouwa-machi, Maebashi, Gunma 371-0034, Japan.

E-mail: s-kasama@bay.wind.ne.jp

itor and a loop diuretic. Treatment with digitalis and vasodilators was allowed, but potassium-sparing diuretics were not permitted (Table 1).

Patients were excluded from the study if they had primary operable valvular heart disease, congenital heart disease, unstable angina, recent acute myocardial infarction, primary hepatic failure, or active cancer.

Study Protocol

Fifteen patients (group A) were randomized to additionally receive spironolactone (12.5–50 mg/day), and the remaining 15 patients (group B) continued their current drug regimen. We performed a series of examinations before and 6 mo after treatment. In this study, no patient received a β-blocker.

^{123}I-MIBG Imaging

The ^{123}I-MIBG was obtained commercially (Daiichi Radioisotope Laboratories, Tokyo, Japan). Patients were injected intravenously with ^{123}I-MIBG (111 MBq) while upright. Anterior planar imaging and SPECT were performed beginning at 15 min and were repeated 4 h later. SPECT was performed with a dedicated single-head imaging system (Millennium MPR; General Electric Medical Systems, Waukesha, WI). The energy, uniformity, and linearity were constantly corrected. Images were acquired for 40 s each at 32 steps over a 180° orbit and were recorded at a digital resolution of 128 × 128 from the anterior planar ^{123}I-MIBG image.

From anterior planar delayed ^{123}I-MIBG images, the heart-to-mediastinum count ratio (H/M ratio) was determined (Fig. 1). Washout rate (WR) was calculated by the following: {([H] − [M])early − ([H] − [M])delayed}/([H] − [M])early × 100 (%), where [H] = mean count per pixel in the left ventricle and [M] = mean count per pixel in the upper mediastinum. In our laboratory, the normal value of the delayed H/M ratio is from 2.00 to 2.80, and the normal value of WR is from 22% to 32%.

The myocardial delayed SPECT images for each patient were divided into 20 segments (Fig. 2). The short-axis images at the basal, middle, and apical ventricular levels were divided into 6 segments. The apical segment of the vertical long-axis image was divided into 2 segments. Regional tracer uptake was assessed semiquantitatively using 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.

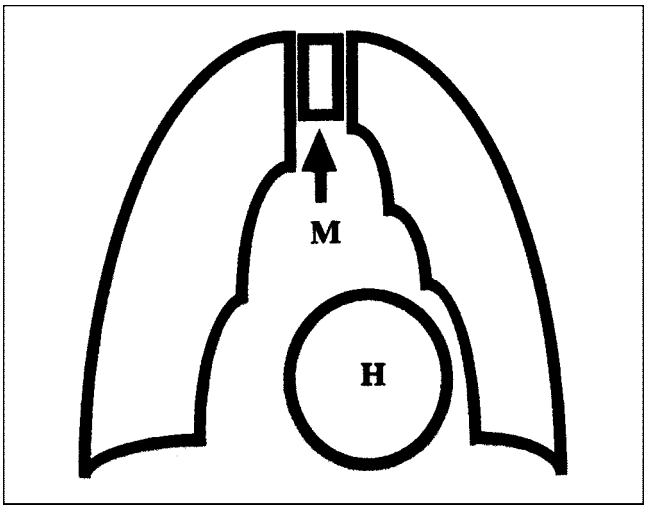

FIGURE 1. Cardiac ^{123}I-MIBG uptake was quantified as H/M ratio 4 h after injection, using regions of interest positioned over heart (H) and upper mediastinum (M).

Interobserver variability was determined in a masked manner by 2 independent observers. The interobserver correlation was represented by $r = 0.90$ ($P < 0.001$).

Echocardiography

Echocardiographic measurement was performed using standard methods. LVEF was calculated using the modified Simpson method (*17*).

Statistical Analysis

Statistical analysis was performed using StatView (Abacus Concepts, Berkeley, CA) for Macintosh (Apple Computer, Inc., Cupertino, CA). Unpaired t and χ^2 tests were used to compare the 2 groups. All values are reported as mean ± SD. $P < 0.05$ was considered statistically significant.

TABLE 1
Demographics and Clinical Characteristics

Demographic/ characteristic	Group A (n = 15)	Group B (n = 15)	P
Age	73 ± 12	65 ± 13	NS
Sex (male/female)	8/7	9/6	NS
LVEF (%)	34 ± 5	34 ± 5	NS
NYHA functional class			
III	10	11	NS
IV	5	4	NS
Diagnosis			
OMI	8	8	NS
DCM	4	4	NS
Valvular disease	3	3	NS

NS = not statistically significant; OMI = old myocardial infarction; DCM = idiopathic dilated cardiomyopathy.

RESULTS

The hemodynamic characteristics of the 2 groups did not significantly differ. Before treatment, LVEF, TDS, H/M ratio, WR, and NYHA functional class were similar in both groups. LVEF is reported in Table 2. The baseline value did not significantly differ from the value after 6 mo of treatment in either group.

TDS, H/M ratio, and WR are reported in Table 3. In group A, the TDS decreased significantly after 6 mo (25 ± 13) from the baseline value (37 ± 9) ($P = 0.0001$). In the segmental analysis of TDS, though it tended to improve the uptake of the inferior wall, the improvement was not statistically significant. The H/M ratio increased significantly after 6 mo (1.83 ± 0.27) from the baseline (1.62 ± 0.20) ($P < 0.0001$). The WR decreased significantly after 6 mo (40 ± 15) compared with baseline (51 ± 9) ($P < 0.001$). In contrast, in group B, there were no significant differences between baseline and values after 6 mo of treatment. Furthermore, after 6 mo of treatment, the WR of group A was

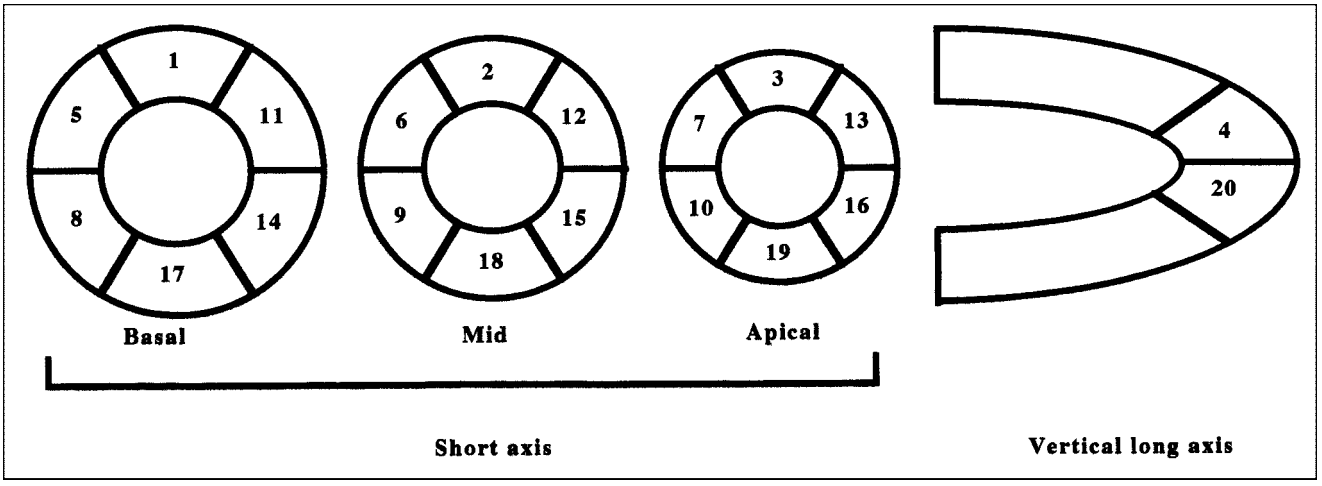

FIGURE 2. Segmentation scheme used to quantitate regional ^{123}I-MIBG uptake.

TABLE 2
Changes in LVEF and NYHA Functional Class in Patients with Heart Failure

Patient no.	Sex	Age (y)	LVEF (%)		NYHA functional class	
			BSL	6M	BSL	6M
Group A						
1	F	80	20	24	4	2
2	M	56	38	40	4	1
3	F	87	36	38	3	2
4	M	74	30	36	3	2
5	F	75	36	32	3	2
6	F	73	38	46	3	1
7	F	84	39	39	3	2
8	M	61	28	32	4	1
9	F	80	40	38	3	2
10	M	79	33	32	3	2
11	F	78	38	36	4	2
12	M	46	31	32	3	1
13	M	87	36	41	4	2
14	M	66	32	30	3	2
15	M	65	36	42	3	1
Mean		73 ± 12	34 ± 5	36 ± 6	3.3 ± 0.5	1.7 ± 0.5*
Group B						
1	F	88	36	43	3	2
2	M	74	38	40	4	3
3	M	62	32	30	3	2
4	F	57	37	40	3	3
5	M	69	32	27	3	2
6	F	62	30	24	3	3
7	M	64	34	42	4	3
8	M	57	33	26	3	2
9	M	42	36	28	3	1
10	F	46	30	35	3	3
11	F	84	28	26	4	3
12	M	58	40	48	3	3
13	F	78	38	36	3	2
14	M	71	40	36	4	2
15	M	63	24	32	3	2
Mean		65 ± 13	34 ± 5	34 ± 7	3.3 ± 0.5	2.4 ± 0.6†

*$P < 0.0001$ vs. BSL and $P < 0.01$ vs. group B.
†$P = 0.01$ vs. BSL.
BSL = baseline; 6M = after 6 months of therapy.

TABLE 3
Changes in TDS, H/M Ratio, and WR for ^{123}I-MIBG Imaging in Patients with Heart Failure

Patient no.	TDS		H/M ratio		WR	
	BSL	6M	BSL	6M	BSL	6M
Group A						
1	33	22	1.42	1.62	49	43
2	43	35	1.55	1.91	43	24
3	46	24	1.54	1.88	52	26
4	38	37	1.81	1.92	45	45
5	46	43	1.59	1.72	46	38
6	44	31	1.48	1.48	55	48
7	39	33	1.35	1.62	68	59
8	44	20	1.8	1.98	42	33
9	20	6	1.98	2.09	42	39
10	40	48	1.42	1.39	75	76
11	45	32	1.38	1.53	47	50
12	34	12	1.74	1.94	44	24
13	28	8	1.9	2.46	49	33
14	41	22	1.59	1.9	49	25
15	20	4	1.68	1.97	54	30
Mean	37 ± 9	25 ± 13*	1.62 ± 0.20	1.83 ± 0.27†	51 ± 9	40 ± 15‡
Group B						
1	44	46	1.45	1.29	42	68
2	40	41	1.66	1.38	43	75
3	35	32	1.96	1.95	44	42
4	29	22	2.05	2.04	33	36
5	30	32	1.76	1.62	44	49
6	28	30	1.87	1.74	37	35
7	41	34	1.48	1.68	48	40
8	42	40	1.44	1.29	43	58
9	37	33	1.63	1.6	54	52
10	41	36	1.48	1.65	48	59
11	21	31	1.77	1.62	49	58
12	23	33	1.72	1.66	51	55
13	24	18	1.98	1.68	33	49
14	27	33	1.84	1.69	54	52
15	23	30	1.86	2.1	47	31
Mean	32 ± 8	33 ± 7	1.73 ± 0.20	1.67 ± 0.24	45 ± 7	51 ± 12

*$P = 0.0001$ vs. BSL.
†$P < 0.0001$ vs. BSL.
‡$P < 0.001$ vs. BSL and $P < 0.05$ vs. group B.
BSL = baseline; 6M = after 6 months of therapy.

significantly lower than that of group B ($P < 0.05$). Representative ^{123}I-MIBG images before and after spironolactone treatment are shown in Figures 3 and 4.

The NYHA functional class of the patients is shown in Table 2 and Figure 5. Patients in both groups showed improvement after 6 mo of treatment compared with baseline (in group A, from 3.3 ± 0.5 to 1.7 ± 0.5 [$P < 0.0001$]; in group B, from 3.3 ± 0.5 to 2.4 ± 0.6 [$P = 0.01$]). After treatment, the NYHA functional class of patients in group A was better than that in group B ($P < 0.01$).

DISCUSSION

Aldosterone causes myocardial and vascular fibrosis (*18,19*), direct vascular damage (*9*), and baroreceptor dysfunction (*7*) and prevents myocardial uptake of norepinephrine (*5,20*). RALES (*1*) found that spironolactone reduced the risk of death in patients with CHF from cardiac causes. Spironolactone may prevent myocardial fibrosis by blocking aldosterone; myocardial fibrosis may predispose patients to variation in ventricular-conduction times and, hence, to reentry ventricular arrhythmias (*20–23*). Spironolactone may also prevent sudden death by increasing myocardial uptake of norepinephrine (*1*). Thus, we examined whether cardiac MIBG imaging was useful for evaluating increasing myocardial uptake of norepinephrine.

Cardiac MIBG, an analog of norepinephrine, is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with CHF (*10–16*). Several reports have suggested that β-blocker therapy can improve cardiac sympathetic nerve activity by cardiac MIBG scin-

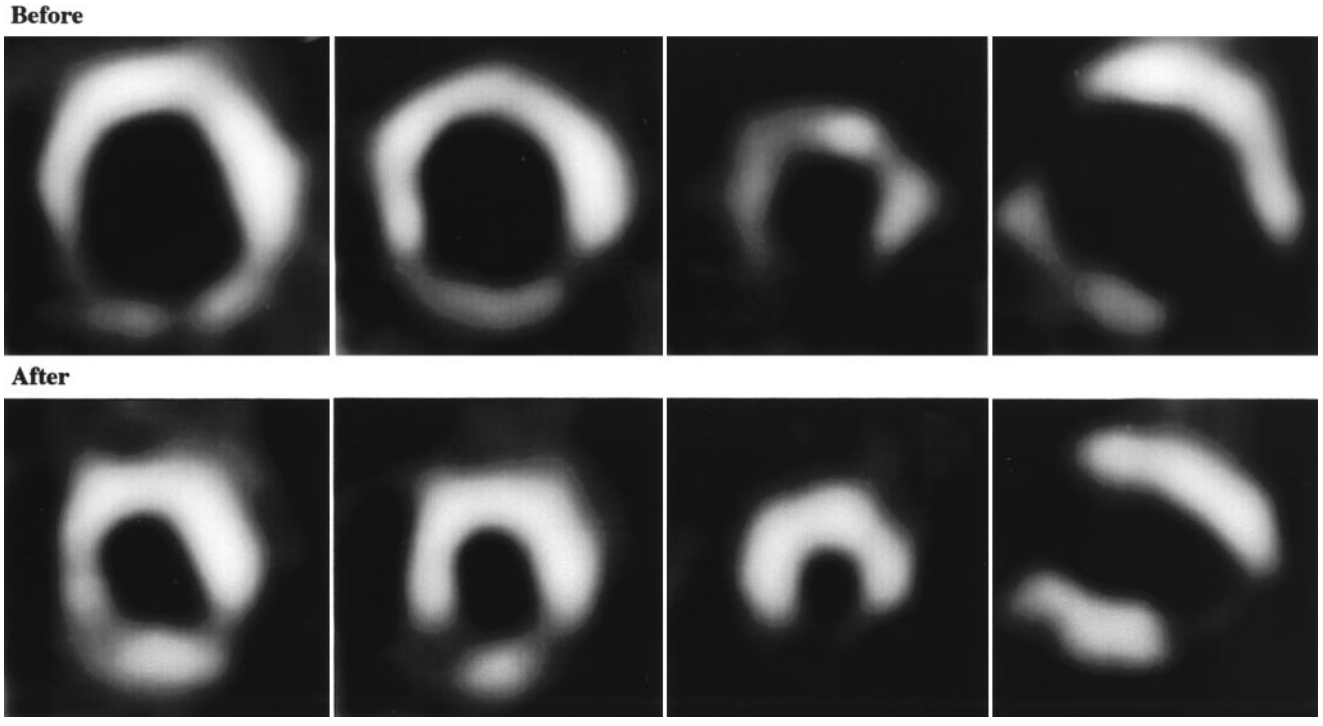

FIGURE 3. Representative SPECT ^{123}I-MIBG images before and after spironolactone treatment in dilated cardiomyopathy.

tigraphy in patients with CHF (*24–27*). In this study, the TDS, H/M ratio, and WR of cardiac MIBG scintigraphy improved in the spironolactone treatment group as opposed to the control group. However, there was no significant difference in the recovery of cardiac function before and after treatment in either group. β-blocker treatment improves both cardiac MIBG scintigraphy and cardiac function by echocardiography (*24,27*). Thus, spironolactone may lack some of the beneficial actions of β-blockers: increased myocardial energy for synthetic and reparative processes and improved diastolic relaxation, filling, and compliance (*28–30*). Instead, spironolactone may be effective by increasing myocardial uptake of norepinephrine.

Tsutamoto et al. (*31*) reported that spironolactone could improve cardiac function in patients with CHF. However, that study included patients with mild to moderate nonischemic CHF. In contrast, our study included many patients with CHF due to old myocardial infarction; therefore, spironolactone might not recognize the improvement in cardiac function. Correlation between cardiac sympathetic nerve activity and cardiac function in patients with idiopathic dilated cardiomyopathy has been reported (*32*). However, that study also excluded patients with old myocardial infarction and thus seemed to be different from our study. Because of the results of our study and the other 2 studies, we consider that spironolactone treatment could not improve cardiac function in patients with CHF due to old myocardial infarction because the infarcted areas had already undergone irreversible necrosis after the treatment.

In this study, delayed MIBG images were used to obtain TDS and H/M ratio. There are 2 types of norepinephrine or MIBG uptake. Uptake-1 (neuronal uptake), which takes place even if the concentration of norepinephrine or MIBG is low, depends on sodium and adenosine triphosphate 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 unaffected by tricyclic agents (*33–35*). Early images result from both uptake-1 and uptake-2 (*36,37*), whereas delayed images involve less of uptake-2 and therefore show the status of cardiac sympathetic nerve activity more accurately. For these reasons, we used delayed MIBG imaging in this study. Several reports suggest that WR is the most clinically useful for severity and improvement of CHF (*38,39*). Increased norepinephrine turnover at cardiac sympathetic nerve endings may decrease the uptake in delayed images such that the increase in turnover, that is, the increase in the WR, reflects CHF severity. In this study, all 3 parameters (delayed TDS, delayed H/M ratio, and WR) improved with spironolactone. We infer that spironolactone increases myocardial uptake of norepinephrine as a mechanism for CHF improvement.

CONCLUSION

Spironolactone improves cardiac sympathetic nerve activity and symptoms in patients with CHF.

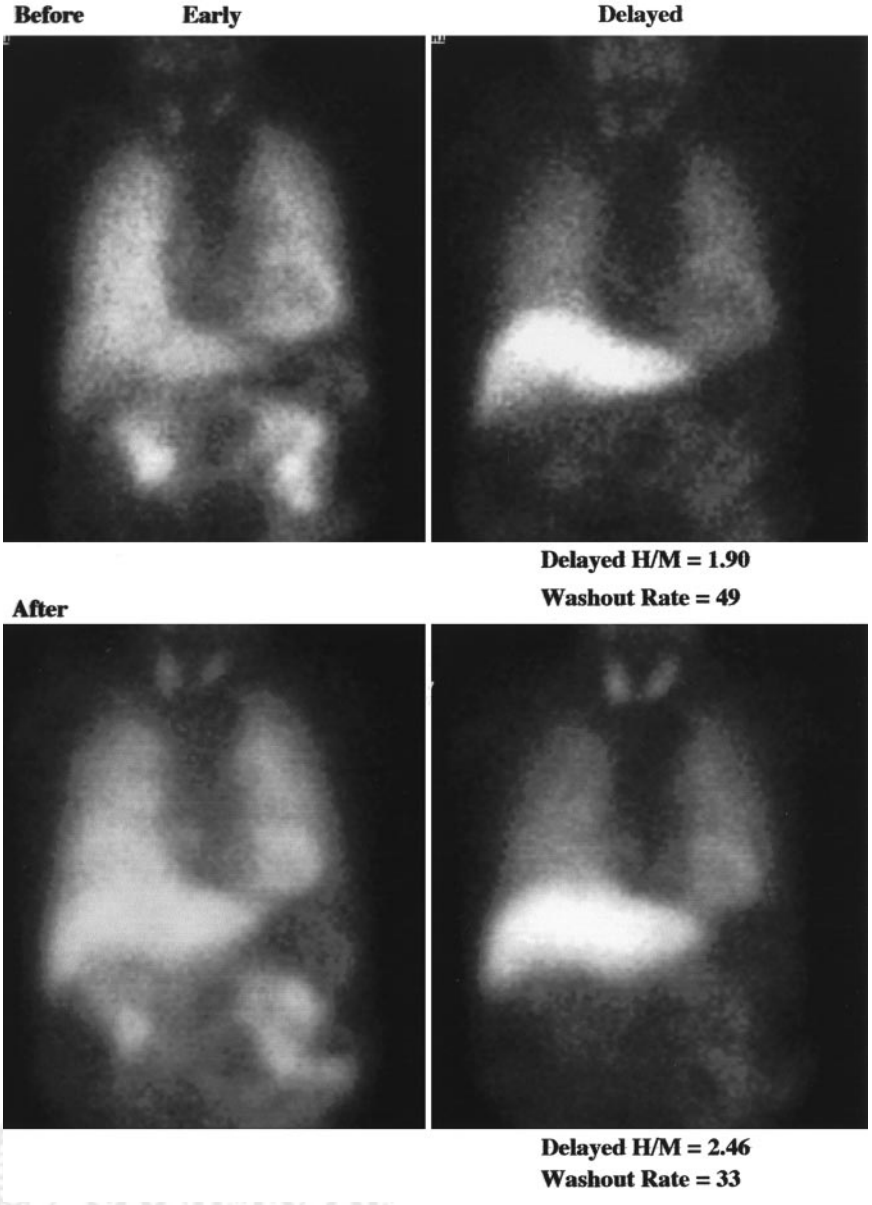

FIGURE 4. Representative anterior planar ^{123}I-MIBG images before and after spironolactone treatment in dilated cardiomyopathy. In this example, delayed H/M ratio increased from 1.90 to 2.46, and WR decreased from 49 to 33.

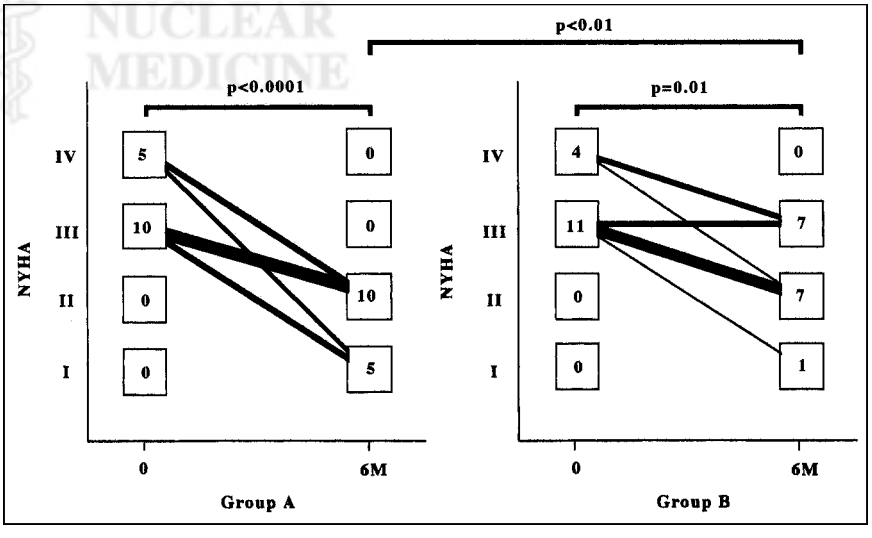

FIGURE 5. Changes in NYHA functional class during treatment in the 2 groups. 6M = after 6 mo of therapy.

REFERENCES

1. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med.* 1999;341:709–717.
2. Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. *Circulation.* 1981;63:645–651.
3. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. *Circulation.* 1990;82:1730–1736.
4. Weber KT, Villarreal D. Aldosterone and antialdosterone therapy in congestive heart failure. *Am J Cardiol.* 1993;71:3A–11A.
5. Barr CS, Lang CC, Hanson J, Arnott M, Kennedy N, Struthers AD. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *Am J Cardiol.* 1995;76:1259–1265.
6. MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. *Cardiovasc Res.* 1997;35:30–34.
7. Wang W. Chronic administration of aldosterone depresses baroreceptor reflex function in the dog. *Hypertension.* 1994;24:571–575.
8. Duprez DA, De Buyzere ML, Rietzschel ER, et al. Inverse relationship between aldosterone and large artery compliance in chronically treated heart failure patients. *Eur Heart J.* 1998;19:1371–1376.
9. Rocha R, Chander PN, Khanna K, Zuckerman A, Stier CT Jr. Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. *Hypertension.* 1998;31:451–458.
10. Henderson EB, Kahn JK, Corbett JR, 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.
11. Yamakado K, Takeda K, Kitano T, et al. Serial change of iodine-123 metaiodobenzylguanidine (MIBG) myocardial concentration in patients with dilated cardiomyopathy. *Eur J Nucl Med.* 1992;19:265–270.
12. Simmons WW, Freeman MR, Grima EA, Hsia TW, Armstrong PW. Abnormalities of cardiac sympathetic function in pacing-induced heart failure as assessed by [^{123}I]metaiodobenzylguanidine scintigraphy. *Circulation.* 1994;89:2843–2451.
13. Merlet P, Valette H, Dubois-Rande JL, et al. Iodine 123-labeled metaiodobenzylguanidine imaging in heart disease. *J Nucl Cardiol.* 1994;1:S79–S85.
14. Schofer J, Spielmann R, Schuchert A, Weber K, Schluter 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.
15. Glowniak JV, Turner FE, Gray LL, Palac RT, Lagunas-Solar MC, Woodward WR. Iodine-123 metaiodobenzylguanidine imaging of the heart in idiopathic congestive cardiomyopathy and cardiac transplants. *J Nucl Med.* 1989;30:1182–1191.
16. Merlet P, Valette H, Dubois-Rande JL, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med.* 1992;33:471–477.
17. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2:358–367.
18. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium: fibrosis and renin-angiotensin-aldosterone system. *Circulation.* 1991;83:1849–1865.
19. Brilla CG, Pick R, Tan LB, Janicki JS, Weber KT. Remodeling of the rat right and left ventricles in experimental hypertension. *Circ Res.* 1990;67:1355–1364.
20. Struthers AD. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. *J Card Fail.* 1996;2:47–54.
21. Klug D, Robert V, Swynghedauw B. Role of mechanical and hormonal factors in cardiac remodeling and the biologic limits of myocardial adaptation. *Am J Cardiol.* 1993;71:46A–54A.
22. Brilla CG, Matsubara LS, Weber KT. Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. *J Mol Cell Cardiol.* 1993;25:563–575.
23. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. *Lancet.* 1994;343:327–329.
24. Fukuoka S, Hayashida K, Hirose Y, et al. Use of iodine-123 metaiodobenzylguanidine myocardial imaging to predict the effectiveness of beta-blocker therapy in patients with dilated cardiomyopathy. *Eur J Nucl Med.* 1997;24:523–529.
25. Kakuchi H, Sasaki T, Ishida Y, Komamura K, Miyatake K. Clinical usefulness of ^{123}I meta-iodobenzylguanidine imaging in predicting the effectiveness of beta blockers for patients with idiopathic dilated cardiomyopathy before and soon after treatment. *Heart.* 1999;81:148–152.
26. Suwa M, Otake Y, Moriguchi A, et al. Iodine-123 metaiodobenzylguanidine myocardial scintigraphy for prediction of response to beta-blocker therapy in patients with dilated cardiomyopathy. *Am Heart J.* 1997;133:353–358.
27. Toyama T, Aihara Y, Iwasaki T, et al. Cardiac sympathetic activity estimated by ^{123}I-MIBG myocardial imaging in patients with dilated cardiomyopathy after beta-blocker or angiotensin-converting enzyme inhibitor therapy. *J Nucl Med.* 1999;40:217–223.
28. Alderman J, Grossman W. Are beta-adrenergic-blocking drugs useful in the treatment of dilated cardiomyopathy? *Circulation.* 1985;71:854–857.
29. Packer M. Pathophysiological mechanisms underlying the effects of beta-adrenergic agonists and antagonists on functional capacity and survival in chronic heart failure. *Circulation.* 1990;82(2 suppl):I77–I88.
30. Sato H, Hori M, Ozaki H, et al. Exercise-induced upward shift of diastolic left ventricular pressure-volume relation in patients with dilated cardiomyopathy: effects of beta-adrenoceptor blockade. *Circulation.* 1993;88:2215–2223.
31. Tsutamoto T, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *J Am Coll Cardiol.* 2001;37:1228–1233.
32. Parthenakis FI, Prassopoulos VK, Koukouraki SI, et al. Segmental pattern of myocardial sympathetic denervation in idiopathic dilated cardiomyopathy: relationship to regional wall motion and myocardial perfusion abnormalities. *J Nucl Cardiol.* 2002;9:15–22.
33. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jacques S Jr. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med.* 1987;28:1620–1624.
34. 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.
35. 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.
36. Kline RC, Swanson DP, Wieland DM, et al. Myocardial imaging in man with I-123 meta-iodobenzylguanidine. *J Nucl Med.* 1981;22:129–132.
37. Nakajo M, Shimabukuro K, Yoshimura H, et al. Iodine-131 metaiodobenzylguanidine intra- and extravesicular accumulation in the rat heart. *J Nucl Med.* 1986;27:84–89.
38. Momose M, Kobayashi H, Iguchi N, et al. Comparison of parameters of ^{123}I-MIBG scintigraphy for predicting prognosis in patients with dilated cardiomyopathy. *Nucl Med Commun.* 1999;20:529–535.
39. 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(suppl):183P.