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Dynamic ^{123}I-MIBG SPECT reflects sympathetic nervous integrity and predicts clinical outcome in patients with chronic heart failure

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^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) is useful for assessment of the severity and prognosis of patients with chronic heart failure (CHF). To examine ^{123}I-MIBG kinetics in the early phase soon after tracer injection, we performed dynamic single photon emission computed tomography (SPECT) in 76 patients with CHF and 17 control subjects. The consecutive 15 images of 2 min-dynamic SPECT were acquired for 30 min after injection. From 0 to 4 min, a significant amount of radioactivity existed in the blood pool, thus we calculated washout rate of ^{123}I-MIBG from 4 to 30 min (%WR-E). Patients were followed up with an end-point of cardiac death or re-hospitalization for 16 months (6–30 months). As the NYHA functional class advanced, %WR-E increased (control, NYHA class I, II, and III: 9 ± 4%, 10 ± 5%, 12 ± 5%, and 17 ± 5%*, respectively, *$p < 0.01$ vs. all other groups). Significant correlation was found between %WR-E and conventional WR from 30 min to 240 min ($r = 0.606$, $p < 0.0001$). %WR-E was positively correlated with left ventricular end-diastolic dimension ($r = 0.372$, $p < 0.01$) and was inversely correlated with left ventricular fractional shortening ($r = -0.316$, $p < 0.02$). The normal upper limit of %WR-E was defined as mean + 2SD value of 17 control subjects (17.1%). Patients with abnormally rapid %WR-E levels had a higher cardiac event rate than those with normal %WR-E levels (57% vs. 12%, $p < 0.0001$). These data suggest that washout rate of ^{123}I-MIBG in the early phase from 4 min to 30 min (%WR-E) reflects cardiac sympathetic nervous integrity and is useful to evaluate the severity and prognosis of patients with CHF. The present results indicate a potential role of dynamic SPECT in shortening the ^{123}I-MIBG imaging protocol.

Key words: ^{123}I-MIBG, heart failure, prognosis

INTRODUCTION

SYMPATHETIC nervous activation characterized by elevated plasma level, increased spillover, and decreased cardiac store of norepinephrine plays an important role in the pathophysiology of congestive heart failure.[1] Since sympathetic nervous overactivity closely relates to the prognosis, assessing cardiac autonomic status is clinically important in the management of patients with chronic heart failure.[2,3] Iodine-123-metaiodobenzyl-guanidine (^{123}I-MIBG) has been used to evaluate cardiac sympathetic nervous distribution and function, since MIBG shares many cellular uptake and storage properties with norepinephrine.[4–7] The washout of ^{123}I-MIBG from the heart, possibly reflecting cardiac adrenergic nervous activity, is accelerated in patients with heart failure.[8–11] A number of studies have demonstrated that ^{123}I-MIBG imaging provides powerful diagnostic and prognostic information in patients with chronic heart failure.[12–15]

In cardiac ^{123}I-MIBG imaging, the initial image is usually taken at 15–30 min after the tracer injection.[8–15] Washout rate of ^{123}I-MIBG is calculated from myocardial counts in the early (15–30 min) and delayed (180–240

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Table 1 Characteristics of study subjects

	Control (n = 17)	Chronic heart failure (n = 76)
Age (yrs)	58 ± 16	63 ± 15
Men/women	11/6	47/29
NYHA (I/II/III)	NA	18/34/24
Echocardiography		
LAD (mm)	33 ± 5	45 ± 9*
LVEDD (mm)	43 ± 6	53 ± 11*
FS (%)	42 ± 7	28 ± 11*
^{123}I-MIBG scintigraphy		
Early H/M ratio	1.90 ± 0.15	1.79 ± 0.28*
Delay H/M ratio	1.98 ± 0.22	1.69 ± 0.30*
Conventional washout rate (%)	15 ± 6	25 ± 7*

LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; FS, fractional shortening; H/M, heart to mediastinum ratio.
*p < 0.01 vs. control subjects

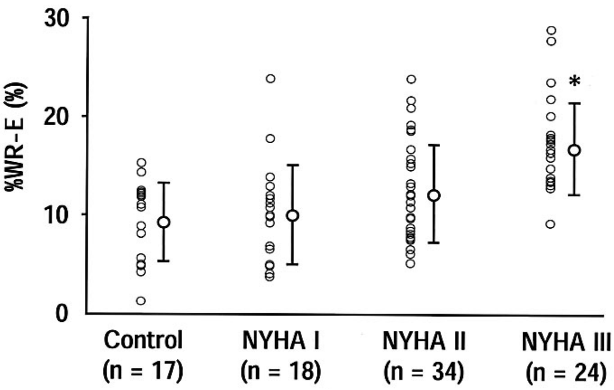

Fig. 1 Relationship between washout rate of ^{123}I-MIBG in the acute phase (%WR-E) and NYHA functional class. *p < 0.01 vs. all other groups

min) images, and the timing for image acquisition may affect the calculation of ^{123}I-MIBG washout, especially in patients with severe heart failure and rapid washout of ^{123}I-MIBG. The purpose of this study was to examine ^{123}I-MIBG kinetics in the acute phase soon after tracer injection using dynamic single photon emission computed tomography (SPECT). We compared ^{123}I-MIBG washout in the acute phase obtained from dynamic SPECT with clinical features, echocardiographic findings and prognostic outcome in patients with chronic heart failure.

METHODS

Subjects and study protocol

We studied 76 patients with chronic heart failure who were admitted to the Yamagata University Hospital. Written informed consent was obtained from all patients, and the Institutional Review Board on human research approved the study protocol. There were 47 men and 29 women with a mean age of 63 ± 15 years. We used 17 normal subjects with normal coronary arteries, 11 men and 6 women with a mean age of 58 ± 16 years, as a control. The etiologies of chronic heart failure were idiopathic dilated cardiomyopathy in 24, valvular heart disease in 16, ischemic cardiomyopathy in 12, hypertensive heart disease in 9, tachycardia-induced cardiomyopathy in 9, and others in 6 patients. The characteristics of the study subjects are summarized in Table 1. There were 18 patients with New York Heart Association (NYHA) functional class I, 34 patients with class II, and 24 patients with class III. Patients were given angiotensin-converting enzyme inhibitors (n = 32), angiotensin II receptor blockers (n = 12), β-blockers (n = 26), diuretics (n = 34), digitalis (n = 23), and vasodilators (n = 12). Echocardiography was performed on the day of admission to measure left ventricular dimensions at end-systole and end-diastole, left ventricular fractional shortening, and left atrial dimension.

Patients were prospectively followed during a mean follow-up period of 16 months (range 4–30 months). The end points were cardiac death, defined as death from progressive heart failure or sudden cardiac death, and progressive heart failure requiring re-hospitalization. Only patients with a follow-up period greater than 6 months were analyzed (n = 64).

Dynamic ^{123}I-MIBG SPECT imaging

We performed dynamic ^{123}I-MIBG SPECT within 1 week after admission. A dose of 111 MBq of ^{123}I-MIBG (Daiichi Radioisotope Laboratories, Tokyo, Japan) was rapidly administered with 20 m*l* saline under resting supine conditions after an overnight fast. All images were acquired using a three-head rotating gamma camera equipped with a low-energy, high-resolution collimator (Multispect 3, Siemens Medical Systems, Chicago IL, USA) as previously reported.[16,17] Data acquisition was performed in the continuous rotation mode, in which the three detector heads make an alternating motion in a 120-degree range with a cycle of 2 min.[18,19] The 15 consecutive 2 min-dynamic SPECT images were obtained for 30 min after the tracer injection. Energy discrimination was provided by a 15% window centered on the 159 eV photopeak. The data were stored on a 64 × 64 matrix. Data processing was performed on a nuclear medicine computer system (ICON, Siemens). A series of contiguous transaxial images of 6 mm thickness were reconstructed by means of a filtered back-projection algorithm without attenuation correction. These transaxial images were then reoriented in the short axis and vertical long axis of the left ventricle.

The serial short axis images were reconstructed, and regions of interest were defined for the entire left ventricle and left ventricular cavity on the short axis image.[18,19] The radioactivities in the regions of interest were plotted as a function of time for every 2 min, and the time-activity

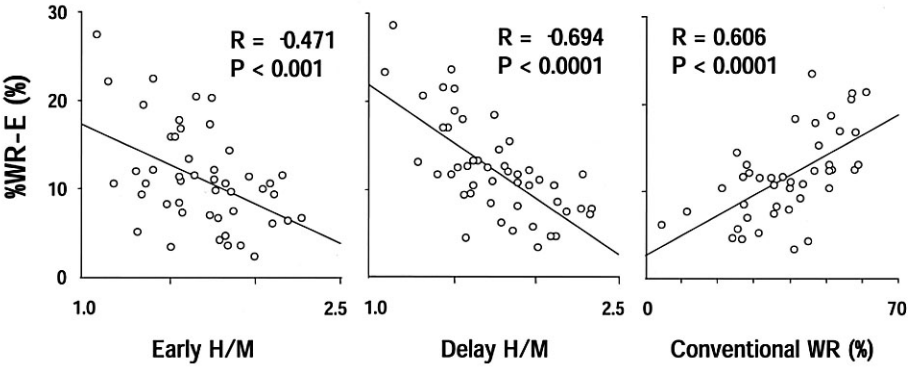

Fig. 2 Correlations of ^{123}I-MIBG washout rate in the acute phase (%WR-E) with heart-to-mediastinum (H/M) ratios in early and delayed images and conventional washout rate of ^{123}I-MIBG from 30 min to 240 min.

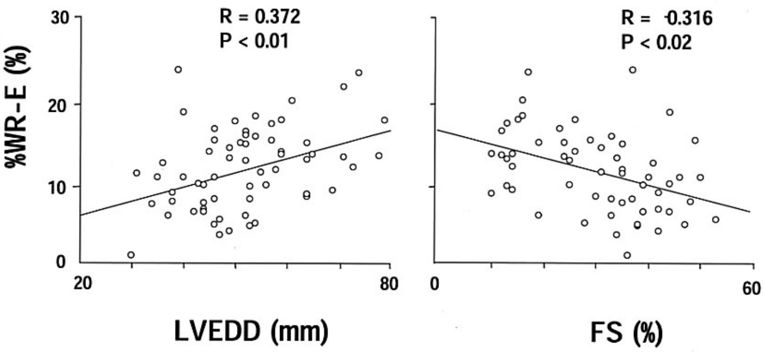

Fig. 3 Correlations of ^{123}I-MIBG washout rate in the acute phase (%WR-E) with echocardiographic findings. LVEDD, left ventricular end-diastolic dimension; FS, fractional shortening.

curves from 0 to 30 min were generated for the entire left ventricle and left ventricular cavity. The time-activity curve for the left ventricular myocardium was obtained by subtracting the time activity curve of the left ventricular cavity from that of the entire left ventricle.[18,19]

A significant amount of radioactivity existed in the blood pool soon after tracer injection on 0–2 and 2–4 min images. Therefore, the washout rate of ^{123}I-MIBG from 4–6 to 28–30 min images (%WR-E) was calculated with physical decay correction as (myocardial counts at 4–6 min – myocardial counts at 28–30 min) × 100/myocardial counts at 4–6 min (%). The analyses of %WR-E were repeated in 12 patients by the same observer and by the second observer on a separate day to determine intra- and inter-observer variability. The calculation of %WR-E was reliable because excellent correlations were obtained from the repeated analyses ($r = 0.97$, $p < 0.0001$ by the same observer, $r = 0.95$, $p < 0.0001$ by the second observer).

After dynamic data acquisition, 5 min-anterior planar imaging was carried out at 30 min and 240 min after the ^{123}I-MIBG injection. The heart-to-mediastinum (H/M) ratios of ^{123}I-MIBG uptake at 30 min (early H/M) and at 240 min (delay H/M) were calculated. Conventional washout rate from the myocardium (30–240 min) was calculated as [(H – M) at 30 min – (H – M) at 240 min] × 100/(H – M) at 30 min (%), where H is the mean counts/pixel in the left ventricle and M is mean counts/pixel in the upper mediastinum.[10,11,15–17]

Statistics

All values are expressed as mean ± SD. Comparison of the mean values of the two groups was made by the unpaired Student t test. %WR-E values among NHYA functional classes were compared by one-way ANOVA followed by the Scheffe's test. A p value less than 0.05 was considered statistically significant. Survival curves were created by the Kaplan-Meier method to determine the time-dependent cumulative cardiac event free rates in patients stratified into 2 groups based on %WR-E values and were analyzed by a log rank test. Statistical potentials of independent predictors in univariate analysis were determined using the Cox proportional hazard model, and statistical significance was analyzed by the chi-square test.

RESULTS

As shown in Table 1, left ventricular fractional shortening

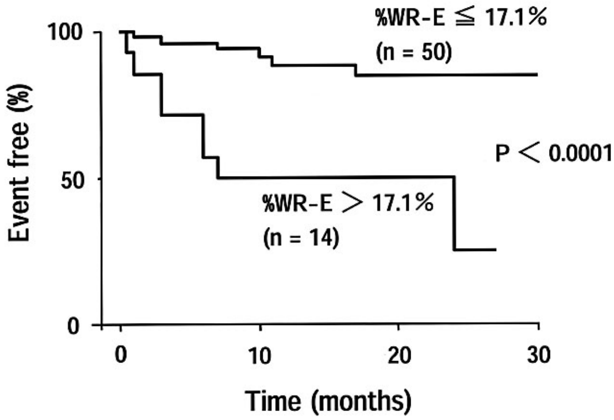

Fig. 4 Cardiac event free rates and washout rate of ^{123}I-MIBG in the acute phase (%WR-E). Survival curves were created by a Kaplan-Meier method and analyzed by a log rank test.

Table 2 Cox proportional hazard analysis

Variables	Chi-square	P value
%WR-E (%) (4 min–30 min)	4.829	0.0280
Conventional washout rate (%) (30 min–240 min)	0.953	0.3290
Delay heart-to-mediastinum ratio	0.561	0.4538

%WR-E, washout rate in the acute phase

obtained from echocardiography was lower in patients with chronic heart failure than in control subjects ($p < 0.01$). Left ventricular end-diastolic dimension and left atrial dimension were larger in chronic heart failure compared to control subjects ($p < 0.01$). H/M ratios at early and delayed images were lower in patients with heart failure than in control ($p < 0.01$), and conventional washout rate (30 min to 240 min) of ^{123}I-MIBG from the myocardium was faster in heart failure than in control ($p < 0.01$) as reported in previous studies.[15–17]

Initial cardiac ^{123}I-MIBG counts were not different between patients with chronic heart failure and control subjects (9394 ± 2301 vs. 8673 ± 2511 counts). %WR-E ranged from 4% to 27% in chronic heart failure patients. %WR-E was higher in patients with chronic heart failure than in control subjects. The relationship between the %WR-E and the severity of heart failure was examined in Figure 1. As the severity of NYHA functional class advanced, %WR-E increased (control, NYHA class I, II, and III: 9 ± 4%, 10 ± 5%, 12 ± 5%, and 17 ± 5%*, respectively, *$p < 0.01$ vs. all other groups).

We examined the correlations between %WR-E and conventional scintigraphic parameters such as H/M ratios and conventional washout rate as shown in Figure 2. %WR-E was inversely correlated with early H/M ($r = -0.471$, $p < 0.0001$) and delay H/M ($r = -0.694$, $p < 0.0001$), and was positively correlated with conventional washout rate from 30 to 240 min ($r = 0.606$, $p < 0.0001$). %WR-E was positively correlated with left ventricular end-diastolic dimension ($r = 0.372$, $p < 0.01$) and was inversely correlated with left ventricular fractional shortening ($r = -0.316$, $p < 0.02$) as shown in Figure 3. These data suggest that %WR-E reflects functional severity of chronic heart failure.

Patients were followed-up with an end-point of cardiac death, sudden cardiac death or re-hospitalization due to worsening heart failure. Patients were stratified into two groups on the basis of the normal upper limit value of %WR-E (17.1%, mean + 2SD value of 17 normal control subjects). The incidence of ischemic cardiomyopathy tended to be higher in patients with rapid %WR-E than in those with normal %WR-E (29% vs. 12%). During a mean follow-up period of 16 months (range 6 to 30 months), 14 cardiac events were observed in 64 patients (22%). All 14 events were re-hospitalizations due to worsening heart failure. Cumulative event free curves were constructed by the Kaplan-Meier method as shown in Figure 4. Cardiac event rate was higher in patients with rapid %WR-E than in those with normal %WR-E (57% vs. 12%, $p < 0.0001$). %WR-E, delayed H/M ratio, and conventional washout rate (30–240 min) were entered into the multivariate Cox proportional hazard model. As shown in Table 2, the Cox regression analysis revealed that %WR-E was the only independent predictor of cardiac events (chi-square = 4.829, $p = 0.0280$).

DISCUSSION

We demonstrated in the present study that myocardial ^{123}I-MIBG washout rate was enhanced from the early phase soon after tracer injection in patients with chronic heart failure. ^{123}I-MIBG washout rate in the early phase (%WR-E) correlated well with the functional severity of heart failure and provided useful prognostic information for patients' clinical outcome.

A number of studies have reported that washout of ^{123}I-MIBG from the heart, which may reflect cardiac adrenergic nervous activity, is accelerated in patients with heart failure.[8,10,11] In addition, recent studies have shown that ^{123}I-MIBG is useful not only for determining the severity and prognosis of heart failure patients, but also for estimating the application and effect of β-blocker therapy.[20–22] ^{123}I-MIBG is taken up by adrenergic nerves at the presynaptic site.[4–7] Therefore, initial uptake of ^{123}I-MIBG reflects cardiac adrenergic nervous distribution and the ability of presynaptic neurons to take up norepinephrine. Washout rate of ^{123}I-MIBG from the heart reflects cardiac adrenergic nervous activity. It has been reported that the washout rate of ^{123}I-MIBG is a powerful predictor of patient prognosis.[10,11,15] It has also been demonstrated that the level of cardiac ^{123}I-MIBG uptake, expressed as a heart to mediastinum (H/M) ratio, is closely related to mortality in patients with congestive heart failure.[12–14] However, it is still controversial which parameter derived from cardiac ^{123}I-MIBG imaging, either washout or H/M ratios, is the more independent and powerful predictor of patient prognosis. The timing for the data acquisition is critical for the analysis of washout rate from early images (20–30 min) to delayed images (180–240 min). In the present study, rapid washout of ^{123}I-MIBG from the failing myocardium was observed in the early phase soon after tracer injection. These data suggest that the delay in early image acquisition may underestimate washout rate of ^{123}I-MIBG, especially in patients with severe congestive heart failure. This may be one of the reasons accounting for the fact that washout rate of ^{123}I-MIBG is less useful to predict prognosis of heart failure patients than H/M ratios.

In the present study, %WR-E correlated well with the functional severity of heart failure, determined according to NYHA functional class, left ventricular end-diastolic dimension, and left ventricular fractional shortening. We also demonstrated that %WR-E provided prognostic information for patients' clinical outcome. Furthermore, %WR-E was the only independent predictor of cardiac events among ^{123}I-MIBG parameters. These data suggest that %WR-E reflects the functional severity of heart failure and enhanced adrenergic nervous activity in patients with chronic heart failure as conventional ^{123}I-MIBG washout rate does. Therefore, these data indicate that it is possible to shorten the ^{123}I-MIBG imaging protocol by replacing the delayed imaging taken at 180–240 min after tracer injection with dynamic SPECT.

CONCLUSION

Washout rate of ^{123}I-MIBG in the acute phase (%WR-E) obtained from dynamic SPECT is useful to evaluate the severity and prognosis of patients with chronic heart failure, and may be a new parameter to reflect sympathetic nervous function and integrity.

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