Short Cardiac Iodine-123-Metaiodobenzylguanidine Imaging Protocol in Heart Failure

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Background For assessment of cardiac sympathetic nervous activity, the conventional protocol for iodine-123-metaiodobenzylguanidine (^{123}I -MIBG) imaging requires several hours.

Methods and Results To establish whether it is possible to shorten the conventional ^{123}I -MIBG imaging protocol, anterior planar imaging was performed in 42 heart failure (HF) patients at 5, 15 and 180 min. The washout rate of ^{123}I -MIBG from 5 to 15 min (WR5-15 min) was calculated as a novel index. WR5-15 min closely correlated with the conventional washout rate and inversely correlated with the heart to mediastinum ratio. Univariate Cox analysis revealed that rapid WR5-15 min, augmented plasma B-type natriuretic peptide level, and decreased left ventricular ejection fraction (LVEF) were predictors for cardiac events. Multivariate analysis showed WR5-15 min and LVEF were independent predictors. The cardiac event rate was markedly higher (73%) in patients when both WR5-15 min and LVEF were abnormal.

Conclusions WR5-15 min obtained from anterior planar imaging is useful for evaluating the severity of HF and clinical outcome, and may shorten the cardiac ^{123}I -MIBG scintigraphy protocol. (Circ J 2008; 72: 1106–1111)

Key Words: Heart failure; ^{123}I -MIBG imaging

Despite the many life-prolonging therapies that are available for patients with heart failure (HF), the disease still has an adverse prognosis.^{1–3} Progression of HF often occurs, even in the absence of overt clinical events, because HF evokes the activation of multiple neuro-humoral factors, such as rennin–angiotensin–aldosterone, catecholamines, and the natriuretic peptides.⁴ Physiological findings and several noninvasive examinations, including left ventricular ejection fraction (LVEF) and B-type natriuretic peptide (BNP), for cardiac status have emerged as strong predictors of risk among patients presenting with HF and are now routinely available to clinicians.^{5–16}

We and others have characterized the prognostic value of cardiac sympathetic function assessed by iodine-123-metaiodobenzylguanidine (^{123}I -MIBG) in HF^{5,9,17–20} but despite the clinical utility of ^{123}I -MIBG imaging being established, it is not used widely enough to be considered part of routine medical management, mainly because the conventional cardiac ^{123}I -MIBG imaging protocol requires several hours, which is a contraindication in some patients.

In the present study, we examined whether it is possible to shorten the conventional ^{123}I -MIBG imaging protocol.

Methods

Study Subjects

We performed ^{123}I -MIBG scintigraphy and measured plasma levels of BNP in 42 consecutive patients (30 men, 12 women, mean age 67 ± 12 years) who admitted to the Ishinomaki Red Cross Hospital for treatment of worsening chronic HF. All patients suffered from symptoms of HF, with pulmonary congestion on admission chest X-ray. Written informed consent was given by all patients, and the Institutional Review Board on Human Research approved the study protocol.

We performed conventional M-mode and 2-dimensional echocardiographic studies using standard techniques on the same day as ^{123}I -MIBG scintigraphy, after conventional medical treatment for HF. No patients had experienced clinical symptoms or signs suggestive of acute myocardial infarction, unstable angina, or acute myocarditis in the year preceding the index admission. None had taken tricyclic antidepressants and serotonin reuptake inhibitors. Coronary angiography was performed to diagnose ischemic HF.

^{123}I -MIBG Imaging

We performed ^{123}I -MIBG imaging before discharge when the patients were in a stable condition. A dose of 111 MBq of ^{123}I -MIBG (Daiichi Radioisotope Laboratories Co, Tokyo, Japan) was administered with 10 ml saline while resting supine after an overnight fast. All images were acquired using a 256×256 matrix and a gamma-camera with a large field of view and a low-energy, high-resolution collimator (Siemens E.CAM; Siemens Medical Systems, Inc, IL, USA). After the ^{123}I -MIBG injection, 4-min anterior planar imaging was carried out. The planar ^{123}I -MIBG images were analyzed by a region-of-interest (ROI) technique to obtain semi-quantitative parameters for tracer distribution. To assess the

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Fig 1. Protocol of iodine-123-metaiodobenzylguanidine (¹²³I-MIBG) imaging used in the present study. We calculated the washout rate of ¹²³I-MIBG from 5 to 15 min (WR5-15 min) from the heart to mediastinum (H/M) ratio at 5 min and 15 min. WR15-180 min, washout rate of ¹²³I-MIBG from 15 to 180 min

Table 1 Clinical Background of the Patients With Heart Failure

	All patients (n=42)	Cardiac events (n=12)	No-cardiac events (n=30)	p value
Age (years)	67±12	69±10	67±13	0.6765
Sex (M/F)	30/12	8/4	22/8	0.6657
NYHA functional class (II/III)	18/24	3/9	15/15	0.1391
Etiology				0.5838
Dilated cardiomyopathy	15 (36%)	5 (42%)	10 (33%)	
Ischemic heart failure	14 (33%)	4 (33%)	10 (33%)	
Hypertensive heart disease	5 (12%)	1 (8%)	4 (13%)	
Valvular heart disease	4 (10%)	2 (17%)	2 (7%)	
Other	4 (10%)	0 (0%)	4 (13%)	
Hypertension	15 (36%)	6 (50%)	9 (30%)	0.2217
Diabetes mellitus	14 (33%)	5 (42%)	9 (30%)	0.4687
Hyperlipidemia	10 (24%)	3 (25%)	7 (23%)	0.9088
Atrial fibrillation	14 (33%)	4 (33%)	10 (33%)	0.9999
LVEF (%)	38±14	32±14	41±13	0.0504
BNP (pg/ml)	444±432	668±632	358±288	0.0332
¹²³ I-MIBG imaging				
H/M 5 min	2.29±0.37	2.31±0.51	2.28±0.30	0.7913
H/M 15 min	2.36±0.37	2.30±0.49	2.38±0.32	0.5280
H/M 180 min	2.15±0.42	1.99±0.41	2.21±0.42	0.1356
WR5-15 min (%)	6.8±2.6	8.6±1.9	6.1±2.5	0.0038
WR15-180 min (%)	29.0±8.8	33.5±7.1	27.1±8.8	0.0326
Medications				
ACEI and/or ARBs	38 (90%)	12 (100%)	26 (87%)	0.1836
-blockers	27 (64%)	7 (58%)	20 (67%)	0.6106
Calcium-channel blockers	15 (36%)	3 (25%)	12 (40%)	0.3594
Spironolactone	12 (29%)	5 (42%)	7 (23%)	0.2348
Loop diuretics	27 (64%)	10 (83%)	17 (57%)	0.1032
Digoxin	18 (43%)	7 (58%)	11 (37%)	0.1999

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; ¹²³I-MIBG, iodine-123-metaiodobenzylguanidine; H/M, heart to mediastinum; WR, washout rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker.

global myocardial kinetics of ¹²³I-MIBG, the ROI was drawn manually over the whole heart and a rectangular ROI over the upper mediastinum was used as a reference background region. The ¹²³I-MIBG count densities of the heart (H) and the mediastinum (M) were calculated from the 5-, 15- and 180-min images. The heart to mediastinum (H/M) ratio of ¹²³I-MIBG uptake at 5 min (H/M 5 min), 15 min (H/M 15 min) and 180 min (H/M 180 min) were calculated as previously reported.^{17,18,21,22} The washout rate of ¹²³I-MIBG from 5 to 15 min and 15 to 180 min (WR5-15 min and WR15-180 min) from the myocardium was calculated as (H at 5 min – H at 15 min) × 100 / H at 5 min (%) and (H at 15 min – H at 180 min) × 100 / H at 15 min (%), respectively (Fig 1). The analyses of WR5-15 min were repeated in 12 patients by the same observer and by a second observer on a separate day to determine intra- and interobserver variability, respectively. The calculated WR5-15 min was reliable, because excellent correlations were obtained from the repeated analyses (R=0.97, p<0.001 by the same observer, R=0.95, p<0.001 by the second observer).

BNP Assay

A sample of venous blood was obtained from the study subjects on the day of ¹²³I-MIBG scintigraphy. The plasma level of BNP was measured by an immunoradiometric assay using a commercially available kit (Shionoria™ BNP, Shionogi Co, Osaka, Japan).

Endpoints and Follow-up

Patients were prospectively followed for a median period of 382 days. The end points were (1) cardiac death, defined as death from progressive HF or sudden cardiac death, and (2) progressive HF requiring hospitalization. All patients were monitored for at least 6 months.

Statistical Analysis

All values are expressed as mean ± SD. Significance between 2 groups (with or without cardiac events) and New York Heart Association (NYHA) class II vs class III was determined by unpaired Student's t-test for continuous variables and by chi-square test for discrete variables. Values of p<0.05 were considered significant. Univariate and multivariate analyses with the Cox proportional hazard regression

Table 2 Results of Univariate Analysis for Predicting Cardiac Events

	HR	95% CI of HR	p value
Age, per 1-year increase	1.009	0.961–1.058	NS
Male	0.731	0.220–2.429	NS
NYHA functional class, II vs III	0.366	0.099–1.358	NS
Presence of			
Hypertension	2.095	0.669–6.555	NS
Diabetes mellitus	1.515	0.478–4.799	NS
Hyperlipidemia	0.952	0.257–3.526	NS
LVEF, per 1% increase	0.947	0.899–0.999	0.0445
BNP, per 1 pg/ml increase	1.002	1.000–1.003	0.0061
¹²³ I-MIBG imaging			
H/M 5 min [#]	0.767	0.246–2.391	NS
H/M 15 min [#]	1.333	0.422–4.208	NS
H/M 180 min [#]	1.864	0.561–6.196	NS
WR5-15 min [*]	15.237	1.961–118.412	0.0092
WR15-180 min [*]	2.098	0.631–6.974	NS

[#]Inflamedian level vs supramedian level, ^{*}supramedian level vs inflamedian level.

CI, confidence interval; HR, hazard ratio; NS, no significance. Other abbreviations see in Table 1.

model were used to determine significant predictors of cardiac events. The receiver-operating characteristic (ROC) curves were constructed to illustrate various cut-off values to determine optimal sensitivity and specificity. Kaplan-Meier survival curves determined the time-dependent cumulative cardiac-event-free rates in patients stratified into 2 or 3 groups based on the values for WR5-15 min, BNP, and LVEF were analyzed by a log rank test.

Results

Clinical Characteristics of Study Subjects and Patients With Cardiac Events

Clinical characteristics, including ¹²³I-MIBG scintigraphic and biochemical findings, of the 42 patients enrolled in the study are shown in Table 1: 18 patients had NYHA functional class II and 24 had class III. The etiologies of HF were identified as idiopathic dilated cardiomyopathy in 15 (36%) patients, ischemic HF in 14 (33%), hypertensive heart disease in 5 (12%), valvular heart disease in 4 (10%) and others in the remaining 4 (10%). Hypertension, diabetes mellitus, and hyperlipidemia were identified in 15 (36%), 14 (33%), and 10 (24%) patients, respectively. H/M 5 min, H/M 15 min and H/M 180 min were 2.29±0.37 (range 1.18–3.14), 2.36±0.37 (range 1.18–2.94) and 2.15±0.42 (range 0.98–3.30), respectively. WR5-15 min and WR15-180 min were 6.8±2.6% (range 2.2–15.1%) and 29.0±8.8% (range 14.3–49.5%) in patients with HF. Mean plasma level of BNP was 444±432 pg/ml (range 40–1,990 pg/ml) in patients with HF.

The patients were followed up for a median period of 382 days with regard to cardiac events. During follow-up, 9 patients were rehospitalized because of worsening congestive HF; 2 patients died because of progression of HF and 1 patient died of sudden cardiac death. Only 1 patient died of non-cardiac disease (renal bleeding). The comparison of the clinical characteristics of patients with or without cardiac events is shown in Table 1. Patients with cardiac events had lower LVEF and higher levels of BNP than those without cardiac events. The WR5-15 min and WR15-180 min were faster in patients with cardiac events than in those without cardiac events.

Fig 2. Washout rate of iodine-123-metaiodobenzylguanidine (¹²³I-MIBG) from 5 to 15 min (WR5-15 min) in the study population. NYHA, New York Heart Association.

Relationships Between ¹²³I-MIBG Imaging Parameters and NYHA Functional Class

H/M 15 min did not differ between NYHA classes II and III (2.41±0.27 vs 2.32±0.43, p=0.42). H/M 180 min was lower in patients with NYHA class III than in those in class II (2.02±0.39 vs 2.31±0.43, p=0.0263). WR15-180 min of ¹²³I-MIBG was faster in patients with NYHA class III compared with class II (31±9 vs 26±8%, p=0.0347). Of the novel parameters, H/M 5 min did not differ between NYHA classes II and III (2.23±0.26 vs 2.29±0.44, p=0.9798). WR5-15 min was faster in patients with NYHA class III compared with class II (7.8±2.5 vs 5.4±1.9%, p=0.002) as shown Fig 2.

Correlations Between Our New Index and Conventional Parameters

We examined the correlations between WR5-15 min (our novel index) and conventional scintigraphic parameters such as H/M ratio and WR15-180 min (Fig 3). WR5-15 min inversely correlated with H/M 15 min (R=−0.49, p=0.0012), H/M 180 min (R=−0.72, p<0.001), and was positively well correlated with WR15-180 min (R=0.76, p<0.001). WR5-15 min also positively correlated with the plasma level of BNP (R=0.42, p<0.01).

Prognostic Value of ¹²³I-MIBG Imaging, BNP and LVEF

Univariate Cox analysis showed that WR5-15 min, BNP, and LVEF were significantly related to subsequent cardiac events (Table 2). The cut-off values for WR5-15 min, BNP, and LVEF were determined from the largest sum of sensitivity plus specificity on each ROC curve. The optimal cut-off values were 6.4% for WR5-15 min, 260 pg/ml for BNP, and 30% for LVEF. The cardiac event rate was higher in patients with a fast WR5-15 min (≥6.4%) than in those with a relatively slow value (<6.4%) (Fig 4A). Cardiac events occurred more often in patients with elevated BNP level (≥260 pg/ml) than in those with low levels (<260 pg/ml) (Fig 4B). Patients with severe reductions in left ventricular (LV) systolic function had high cardiac event rate as shown in Fig 4C. Multivariate analysis showed that only WR5-15 min (hazard ratio (HR) 9.789; 95% confidence interval (CI) 1.145–83.704; p=0.0372) and LVEF (HR 5.401; 95% CI 1.397–20.883; p=0.0145) remained as independent

Fig 3. Correlations between the washout rate of iodine-123-metaiodobenzylguanidine from 5 to 15 min (WR5-15 min) and general MIBG parameters and the plasma level of B-type natriuretic peptide (BNP). H/M, heart to mediastinum.

prognostic factors of cardiac events.

Identification of Subgroups of Patients With High Risk

Stratification of patients on the basis of the combined cut-off values of WR5-15 min (6.4%) and LVEF (30%) is shown in Fig 5. The cardiac event rate in patients with WR5-15 min $\geq 6.4\%$ and LVEF $\leq 30\%$ was 73%. The cardiac event rate was 31% in patients with WR5-15 min $\geq 6.4\%$ or LVEF $\leq 30\%$. Notably, no cardiac events occurred in patients with

Table 3 Results of Multivariate Analysis for Predicting Cardiac Events

	HR	95%CI of HR	p value
WR5-15 min, $\geq 6.4\%$	9.789	1.145–83.704	0.0372
LVEF, $\leq 30\%$	5.401	1.397–20.883	0.0145
BNP, ≥ 260 pg/ml	0.792	0.202–3.107	NS

Abbreviations see in Tables 1,2.

Fig 4. (A) Washout rate of iodine-123-metaiodobenzylguanidine (^{123}I -MIBG) from 5 to 15 min (WR5-15 min) and all cardiac events in patients with heart failure. (B) Plasma levels of B-type natriuretic peptide (BNP) and cardiac events in patients with heart failure. (C) Left ventricular ejection fraction (LVEF) and cardiac events in patients with heart failure. Survival curves were created by Kaplan-Meier method.

Fig 5. Kaplan-Meier analysis of cardiac-event-free survival in patients with heart failure stratified into normal, either abnormality, or both abnormalities groups, based on the combination of the washout rate of iodine-123-metaiodobenzylguanidine (^{123}I -MIBG) from 5 to 15 min (WR5-15 min) and left ventricular ejection fraction (LVEF). Normal group: WR5-15 min $<6.4\%$ and LVEF $>30\%$; either abnormality group: WR5-15 min $\geq 6.4\%$ or LVEF $\leq 30\%$; and both abnormalities group: WR5-15 min $\geq 6.4\%$ and LVEF $\leq 30\%$.

WR5-15 min $<6.4\%$ and LVEF $>30\%$.

Discussion

This study has 2 interesting findings. (1) Our novel index, WR5-15 min, was augmented by NYHA functional class. WR5-15 min significantly correlated with conventional ^{123}I -MIBG parameters such as WR15-180 min and H/M ratio. (2) Multivariate analysis showed WR5-15 min was an independent predictor for subsequent cardiac events. WR5-15 min provided additional prognostic information to that given by LVEF in patients with HF. These findings support the clinical effectiveness of a short ^{123}I -MIBG imaging protocol, which also reduces the burden on the patient with HF.

Assessing cardiac autonomic status is clinically important in the management of patients with HF, because sympathetic nervous activation causes excessive ventricular afterload, downregulation of α -adrenergic receptors, tachycardiac interference with ventricular filling, HF progression, and increased mortality.²³ We and others have demonstrated that several parameters of ^{123}I -MIBG imaging, such as H/M ratio and conventional washout rate, provide promising information for the assessment of patients with HF^{5,9,17,18,20} but the long protocol for such imaging may limit this efficacious examination in some clinical settings. We recently demonstrated that washout of ^{123}I -MIBG occurred 4 min after tracer injection and was already augmented in the early stage of HF, even in patients in NYHA functional classes I and II.¹⁷ In the present study, we evaluated ^{123}I -MIBG washout in the very early phase using anterior planar imaging, which is a simple and widely available method. Rapid ^{123}I -MIBG washout from 5 to 15 min was observed in patients with cardiac events; in fact, the WR5-15 min advanced with NYHA functional class. As shown Fig 3, WR5-15 min inversely correlated with H/M 180 min and positively correlated with WR15-180 min. WR5-15 min also positively correlated with the plasma level of BNP. These findings suggest that WR5-15 min reflects the functional severity of HF. Rapid ^{123}I -MIBG washout in the very early phase may be a feature of failing myocardium, although the mechanism is still not apparent from our results. However, neither the number of patients nor the cardiac hard events were large enough and the follow-up period was not long enough,

compared with previous studies,^{5,9,17,18,20} so the prognostic relevance of WR5-15 min remains conjectural.

It is now widely recognized that many patients with signs and symptoms of HF have preserved LVEF.^{24,25} The overall mortality and rate of HF hospitalization in patients with systolic dysfunction or preserved systolic function are very similar.²⁵ On the other hand, LVEF is an important predictor of fatal and nonfatal cardiovascular outcomes, including HF hospitalization, sudden death and HF death, in those with a severe reduction of LV systolic function.¹⁶ In agreement with those results, the rate of cardiac events was markedly higher in patients with severe systolic dysfunction as shown in Fig 4.

We and others have documented the rationale for combined evaluation of cardiac nervous assessment and biomarkers for risk stratification of patients with HF.^{18,20} We can detect high-risk patients with HF using a sole adverse factor, whereas the predictive power to detect low-risk patients is insufficient. In the present study cardiac events occurred in some patients stratified into the low-risk group (Fig 4). Combined assessment may contribute to a more precise stratification of low-risk patients compared with a single assessment. Interestingly, no cardiac events occurred in patients with both preserved WR5-15 min and LVEF.

Study Limitations

Several potential limitations should be considered with respect to these findings. First, the patients were treated with medications that may have affected cardiac MIBG uptake, such as α -adrenergics, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, and spironolactone.^{22,26,27} Second, we also acknowledge the fact that other MIBG parameters (WR15-180 min and H/M 180 min), and BNP did not predict cardiac events independently in the present study. Presumably, our results do not apply to severe HF because 43% of the patients were in NYHA class II. Additionally, the number of patients and the number of adverse cardiac accidents were not large enough. Only 2 patients died from progressive HF and 1 patient died suddenly. In this respect, a large-scale completely prospective study is needed to further assess the prognostic value of a short ^{123}I -MIBG imaging protocol. Third, the washout curve of cardiac ^{123}I -MIBG was steeper in the very early phase compared with the late phase.⁷ A slight time lag in

image acquisition may affect the calculation of ¹²³I-MIBG washout in the very early phase, because the SD of WR5-15 min was relatively large compared with that for WR15-180 min.

Conclusions

WR5-15 min obtained with anterior planar imaging is useful to evaluate the severity and clinical outcome of HF. We may be able to shorten the ¹²³I-MIBG imaging protocol and thus lighten the patient's burden with this novel process.

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