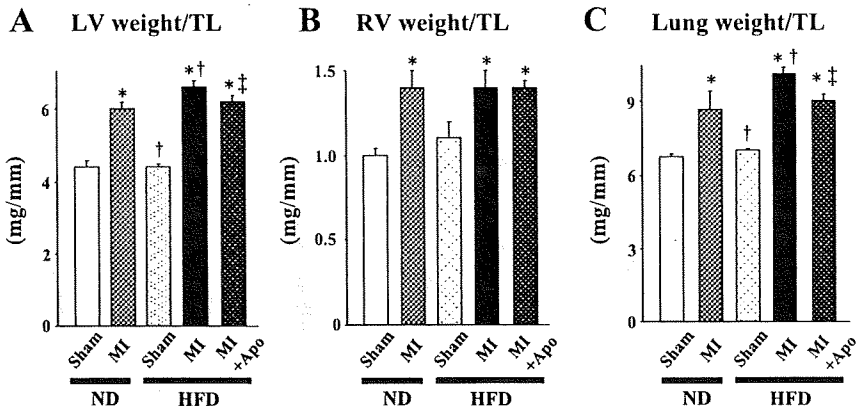

Fig. 3. Left ventricle (LV) weight/tibial length (TL) (*A*), right ventricle (RV) weight/TL (*B*), and lung weight/TL (*C*) in ND + sham (n = 10), ND + MI (n = 15), HFD + sham (n = 11), HFD + MI (n = 13), and HFD + MI + apocynin (Apo: n = 11) mice. Data are means ± SE. $P < 0.05$ vs. ND + sham (*), ND + MI (†), and HFD + MI (‡).

mental results are also supported by the clinical findings that patients with diabetes have a worse outcome after MI than that of patients without diabetes despite similar coronary patency rate and baseline LV ejection fraction (13, 15). Furthermore, in the clinical study of patients with HF, diabetes reduced long-term survival independent of the etiology of HF and baseline LV ejection fraction (42). The poor prognosis in patients with diabetes has been shown to be related with the progression of HF (1, 39, 44). In contrast, previous animal studies have shown that the HFD feeding to rats did not affect cardiac function following MI (26, 32). These differences might be due to differences in the species examined (mice vs. rats), the type of feed used (unsaturated vs. saturated fat), and the severity of diabetes.

The adverse effects of HFD-induced type 2 diabetes on LV remodeling were not a result of the expansion of MI size, because the infarct size was not altered at either 24 h or 28 days after the induction of MI. Furthermore, its effects were not due to the effects on hemodynamics, because blood pressure and heart rate were not altered. Importantly, HFD feeding itself did not affect cardiac function assessed by echocardiographic and hemodynamic measurements (Table 2). Furthermore, HFD feeding did not cause LV hypertrophy in our model. Histomorphometric analysis of LV sections showed that myocyte cross-sectional area and collagen volume fraction did not alter in HFD + sham mice (Fig. 4). A previous study by Park et al. (29) showed that fractional shortening was decreased and LV posterior wall thickness was increased in C57BL/6 mice fed on HFD for 20 wk. However, there were no significant alterations in fractional shortening, even after 10 and 15 wk of HFD feeding in their study. Therefore, the reason why cardiac function was preserved in HFD + sham mice might be due to the short duration of HFD feeding (8 wk) in the present study. These results suggest that HFD exacerbated LV remodeling in the absence of superimposed cardiac injury induced by diabetes.

Another important finding of the present study was that the exacerbation of post-MI LV remodeling and failure with type 2 diabetes was inhibited by an inhibitor of NAD(P)H oxidase activation, apocynin (Figs. 2 and 3 and Table 2), without affecting glucose intolerance (Table 1). NAD(P)H oxidase activity was increased, and ROS production was further enhanced in noninfarcted myocardium from HFD + MI mice compared with ND + MI mice (Fig. 5). Treatment of HFD + MI mice with apocynin normalized NAD(P)H oxidase activity and concomitantly ameliorated the increased ROS production (Fig. 5), which improved LV remodeling and failure to the level of ND + MI (Figs. 2 and 3 and Table 2), whereas apocynin itself did not have such effects on cardiac function in sham and ND + MI mice. The development of the post-MI remodeling process has been

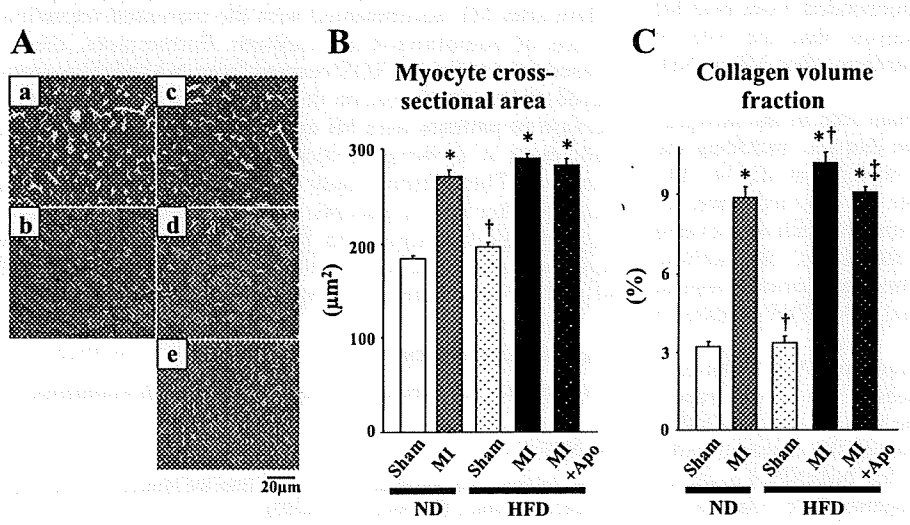

Fig. 4. Representative high-power photomicrographs (*A*) of LV cross sections stained with Masson's trichrome from ND + sham (*a*), ND + MI (*b*), HFD + sham (*c*), HFD + MI (*d*), and HFD + MI + Apo (*e*) mice. Scale bar, 10 μm. Summary data of myocyte cross-sectional area (*B*) and collagen volume fraction (*C*) in 5 groups of mice (n = 6 for each). Data are means ± SE. $P < 0.05$ vs. ND + sham (*), ND + MI (†), and HFD + MI (‡).

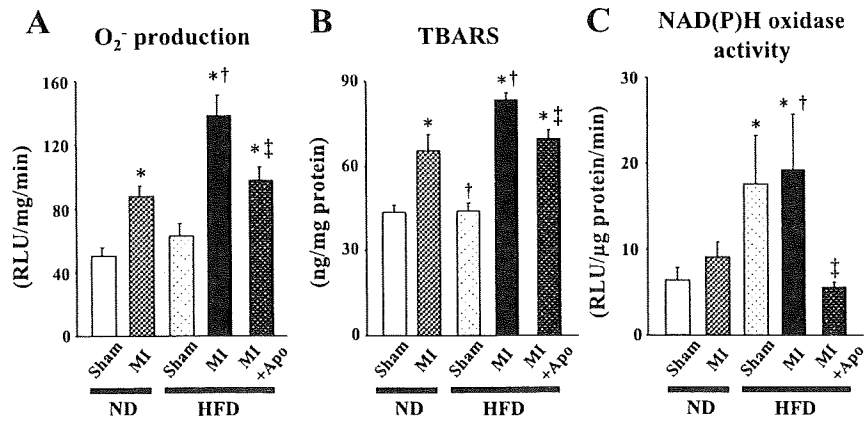

Fig. 5. O_2^- production (*A*, $n = 4$ for each), thiobarbituric acid reactive substances (TBARS; *B*, $n = 4$ for ND + sham and $n = 5$ for other groups), and NAD(P)H oxidase activity (*C*, $n = 4$ for each) in LV from 5 groups of mice. Data are expressed as means ± SE. $P < 0.05$ vs. ND + sham (*), ND + MI (†), and HFD + MI (‡).

known to be caused by several mechanisms, including the increased interstitial fibrosis, myocyte hypertrophy, and apoptosis of noninfarcted regions (43). The present study demonstrated that the HFD-induced type 2 diabetes was associated with an increase in interstitial fibrosis, and apocynin, indeed, ameliorated these changes (Fig. 4).

A previous report demonstrated that NAD(P)H oxidase-mediated oxidative stress was enhanced in noninfarcted myocardium after MI in rabbits (31). Furthermore, Doerries et al. (7) reported that a deficiency of the NAD(P)H oxidase subunit $p47^{phox}$ prevented LV remodeling and failure after MI and reduced cardiomyocyte hypertrophy, apoptosis, and interstitial fibrosis. In contrast, a study by Frantz et al. (10) did not indicate a protective effect of a deficiency of the NAD(P)H oxidase subunit $gp91^{phox}$ on LV remodeling and failure after MI. Thus, the role of NAD(P)H oxidase in these processes is still controversial. In the present study, oxidative stress was enhanced in noninfarcted myocardium after MI compared with sham in ND-feeding mice (Fig. 5, *A* and *B*). However, there was no difference in NAD(P)H oxidase activity between two groups (Fig. 5*C*). Moreover, treatment of ND-feeding MI mice with apocynin did not affect the increased production of ROS as well as cardiac remodeling and failure. These data suggest that ROS in the noninfarcted myocardium are produced from other sources than NAD(P)H oxidase. Based on our previous studies, they are produced in the mitochondria from post-MI heart (41). Therefore, our data suggest that the role of NAD(P)H oxidase is small in myocardium after MI in ND-feeding mice.

NAD(P)H oxidase plays an important role in the development of the diabetes-associated organ damage, including the vascular dysfunction and the renal impairment (2, 14, 33). Although the mechanisms responsible for this activation remain to be determined, the various stimuli, such as elevated plasma glucose, insulin, and free fatty acids, can activate NAD(P)H oxidase in vitro (18, 45). Therefore, these biological abnormalities may activate myocardial NAD(P)H oxidase in HFD mice.

The specificity of apocynin for inhibiting NAD(P)H oxidase activation is a matter of debate. A recent report indicated that its action might not be specific for NAD(P)H oxidase (16). In this in vitro study using the cultured cells, the inhibitory action of apocynin for NAD(P)H oxidase activation was restricted to myeloperoxidase (MPO)-expressing leukocytes and not demonstrated in MPO-free vascular cells. However, the administrated and activated apocynin in in vivo situations could inhibit the activation of NAD(P)H oxidase even in MPO-free skeletal muscle in the present study. Apocynin was first reported to inhibit the production of ROS by activated neutrophils (38). In that study, apocynin was shown to inhibit the translocation of $p47^{phox}$ and $p67^{phox}$, cytosolic components of NAD(P)H oxidase. It has been shown to inhibit the translocation of $p47^{phox}$ also in nonphagocte cells (28) and in vivo (21). More importantly, it has been widely used in isolated tissues and in vivo (5, 12, 19, 22, 31). Moreover, we demonstrated that ROS production was increased in ND + MI mice compared with ND mice. In contrast, NAD(P)H oxidase activity was comparable between two groups. Treatment with apocynin in ND + MI mice did not decrease ROS production. Therefore, we concluded that apocynin at the concentration used in the present study acted as an inhibitor of NAD(P)H oxidase activation rather than as a nonspecific antioxidant. However, to evaluate the exact contribution of NAD(P)H oxidase and obtain the direct evidence for a role of this ROS production in this setting, further studies through gene manipulation are needed.

The present study demonstrated that type 2 diabetes induced by HFD feeding exacerbated LV remodeling and failure after MI, accompanied with the increased interstitial fibrosis of noninfarcted myocardium. Furthermore, the increased production of ROS derived from NAD(P)H oxidase played an important role on this exacerbation. An explosive increase of patients with MI and HF associated with type 2 diabetes is a growing medical problem in industrialized countries. The present study may well explain the poor outcome after MI in patients with type 2 diabetes. Therefore, therapies designed to regulate oxidative stress are expected to be beneficial in the treatment of patients with MI and HF associated with type 2 diabetes.

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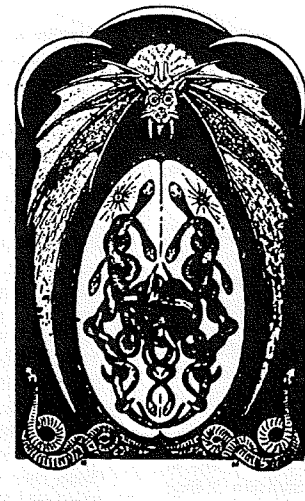

Iodine-123-Metaiodobenzylguanidine Imaging Can Predict Future Cardiac Events in Heart Failure with Preserved Ejection Fraction Patients

Shigehiko Katoh, M.D., Tetsuro Shishido, M.D., Satoshi Nishiyama, M.D., Takanori Arimoto, M.D., Daisuke Kutsuzawa, M.D., Hiroki Takahashi, M.D., Takehiko Miyashita, M.D., Takuya Miyamoto, M.D., Joji Nitobe, M.D., Tetsu Watanabe, M.D., and Isao Kubota, M.D.

Department of Cardiology, Pulmonology, and Nephrology,
Yamagata University School of Medicine, Yamagata, Japan

A short title: ^{123}I-MIBG in HF with preserved EF

Tables 4 and Figures 3

Address for correspondence: Tetsuro Shishido, M.D.
Department of Cardiology, Pulmonology, and Nephrology
Yamagata University School of Medicine
2-2-2 Iida-Nishi, Yamagata, Japan 990-9585
E-mail: tshishid@med.id.yamagata-u.ac.jp
Phone: +81-23-628-5302 Fax: +81-23-628-5305

Abstract

Background: Iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) has been used to assess function of the cardiac sympathetic nervous system in patients with chronic heart failure. The usefulness of ^{123}I-MIBG imaging for evaluating heart failure with preserved ejection fraction (HFPEF) patients has not been established.

Methods: We performed ^{123}I-MIBG scintigraphy and echocardiography, and measured plasma brain natriuretic peptide (BNP) level of consecutive 128 heart failure patients with left ventricular ejection fraction (LVEF) ≥50% (71 men, mean age 66 ± 14 years) who admitted to our hospital. Patients were divided into 2 groups by New York Heart Association (NYHA) functional Class.

Results: ^{123}I-MIBG delayed heart to mediastinum (H/M) ratio was significantly lower, and washout rate (WR) was higher in patients with HFPEF in increased with advancing NYHA functional Class (NYHA functional Class I, II vs. III: 1.89 ± 0.34 vs. 1.52 ± 0.37, $p < 0.0001$. 26.2 ± 13.5% vs. 46.1 ± 18.7%, $p < 0.0001$. respectively). On the other hand, ^{123}I-MIBG WR was not correlated with LVEF, and was weak correlation with plasma BNP level ($R = 0.201$, $p = 0.0327$). Moreover, patients with high ^{123}I-MIBG WR show poor clinical outcome ($p = 0.0004$).

Conclusions: ^{123}I-MIBG imaging provides independent prognostic information in patients with HFPEF.

Key words: cardiac imaging, sympathetic nervous system, washout rate, preserved ejection fraction

Introduction

Activation of sympathetic nervous system plays an important role in the progression of heart failure (HF) [1-3]. There is a correlation between the severity of HF and serum norepinephrine (NE) levels [4-6]. Cardiac imaging with Iodine-123-metaiodobenzyl guanidine (^{123}I-MIBG), an analogue of NE, is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with HF. A number of studies have been reported that ^{123}I-MIBG imaging provides powerful diagnostic and prognostic information especially in HF patients with reduced left ventricular (LV) systolic function [7-11].

Recently, 30-50% of the patients with congestive HF without reduced LV systolic function, is commonly referred to as HF with preserved ejection fraction (HFPEF) [12-16] and HFPEF is increasingly recognized as a common problem. Although morbidity and mortality rates in HFPEF are high [12, 13, 17], most of the previous studies have focused on systolic HF, and clinical usefulness of ^{123}I-MIBG scintigraphy to predict adverse outcome has not been yet established for HFPEF. Therefore, the aim of the present study was to examine whether ^{123}I-MIBG imaging could reliably risk stratify patients with HFPEF.

Methods

Study Subjects

We performed ^{123}I-MIBG scintigraphy and measured plasma levels of brain natriuretic peptide (BNP) in consecutive 368 patients who admitted to the Yamagata University Hospital for the treatment of worsening HF, for the diagnosis and pathophysiologic investigations of HF, and for the therapeutic evaluations of HF from April 2002 to December 2009 and 128 HF patients with LV ejection fraction (EF) ≥50% (71 men, 57 women, mean age 66 ± 14 years) were enrolled in this study [15, 18, 19]. The diagnosis of HF was made by 2 senior cardiologists using the generally accepted Framingham criteria and information including a history of dyspnea and symptomatic exercise intolerance with signs of pulmonary congestion, or peripheral edema, the presence of moist rales on auscultation, or documentation of left ventricular dysfunction by chest x-ray or echocardiography [20]. In the present study, patients were divided by New York Heart Association (NYHA) functional Class when ^{123}I-MIBG scintigraphy was performed. Twenty five subjects without HF, who were performed ^{123}I-MIBG scintigraphy, were served as control. Those subjects were diagnosed as normal by physical examinations, electrocardiogram, chest x-ray, and echocardiography. Written informed consent was given by all patients, and the Institutional Review Board of the Yamagata University approved the study protocol.

No patients had clinical symptoms or signs suggestive acute coronary syndrome or acute

myocarditis in the 3 months preceding admission. None had taken tricyclic antidepressants, serotonin reuptake inhibitors, and steroidal anti-inflammatory drugs [9, 10, 21]. Patients with renal insufficiency characterized by a serum creatinine level > 2.0 mg/dL were excluded from the present study [22-25]. Coronary arteriography was performed to diagnose ischemic HF and during the hospitalization, all ischemic heart disease patients were not performed revascularization.

^{123}I-MIBG Imaging

We performed ^{123}I-MIBG imaging before discharge (on mean 11 days after admission) in stable condition. A dose of 111 Mbq of ^{123}I-MIBG (FUJIFILM RI Pharma Co, Ltd, Tokyo, Japan) was administered with 20 mL saline while resting supine condition after an overnight fast. All images were acquired using a 256 × 256 matrix and a 3-head rotating gamma camera equipped with a low-energy, high-resolution collimator (Multi-spect 3, Siemens Medical Systems, Chicago, IL) as previously reported [9, 10, 26, 27]. Five min-anterior planar imaging was carried out at 30 minutes and 240 minutes after the ^{123}I-MIBG injection. The planar ^{123}I-MIBG images were analyzed by a region-of-interest (ROI) technique to obtain semiquantitative parameters for tracer distribution. The ^{123}I-MIBG count densities of the heart (H) and the mediastinum (M) were calculated from the 30 minutes and 240 minutes images [9, 10, 26, 27]. The heart to mediastinum (H/M) ratios of ^{123}I-MIBG uptake at 30 minutes (early H/M) and at 240 minutes (delayed H/M) were calculated as previously reported. Washout rate from the myocardium was calculated as 〔(H-M) at

30 minutes – (H-M) at 240 minutes] × 100/(H-M) at 30 minutes (%) [11].

Echocardiography and Blood Examination

We performed conventional M-mode and 2-dimensional echocardiographic studies using standard techniques within 3 days of the day when ^{123}I-MIBG scintigraphy was performed. A sample of venous blood was obtained from study subjects within 3 days of the day when ^{123}I-MIBG scintigraphy was performed. Glomerular filtration rate (GFR) was estimated from the modification of diet in renal disease formula [28].

Endpoints and Follow-up

Patients were prospectively followed for a mean period of 1026 days. The end points were (1) cardiac death, defined as death from worsening HF or sudden cardiac death, and (2) worsening HF requiring readmission. Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was established by the attending physician. Patients were contacted after the initial presentation by telephone interview performed by trained researchers.

Statistical Analysis

Results are expressed as mean ± SD for continuous variables and as percentages of the total number of patients for categorical variables. Skewed variables are expressed as medians and

interquartile ranges. Significance between 2 groups was determined by unpaired Student's t-test for continuous variables and by chi-square test for categorical variables. If data were not distributed normally, the Mann-Whitney U test was used. A p value < 0.05 was considered significant. Univariate and multivariate analyses with the Cox proportional hazard regression model were used to determine significant predictors of cardiac events. The cardiac event-free curve was computed according to the Kaplan-Meier method and compared using the log-rank test. Statistical analysis was performed with a standard statistical program package (Stat View version 5.0; SAS Institute Inc., Cary, North Carolina).

Results

Clinical Characteristics of Study Subjects

Clinical characteristics including ^{123}I-MIBG scintigraphic, biochemical, and echocardiographic findings at stable condition before discharge, and medications of the 128 HFPEF patients and 25 control subjects enrolled in the study are shown in Table 1. There were 29 patients with NYHA functional Class I, 78 patients with NYHA functional Class II, and 21 patients with NYHA functional Class III, when ^{123}I-MIBG imaging was performed. Hypertension, hyperlipidemia, diabetes mellitus, and current smokers were identified in 74 (59%), 33 (26%), 27 (21%), and 29 (23%) patients, respectively. The etiologies of HF were identified as idiopathic dilated cardiomyopathy in 11 (9%) patients, ischemic HF in 11 (9%), including 4 old myocardial infarction and 5 ischemic heart disease and all ischemic heart disease patients were not performed revascularization during the hospitalization, and hypertensive heart disease in 44 (34%), hypertrophic cardiomyopathy in 15 (12%), arrhythmia induced HF in 21 (16%), and others in the remaining 26 (20%). Median plasma level of BNP was 163 pg/mL (range 61.8-341 pg/mL) in patients with HFPEF at stable conditon.

Early and delayed H/M ratios were significantly lower and WR was significantly higher in patients with HFPEF than in control subjects (Table 1).

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

As shown in Figure 1a and 1b, ^{123}I-MIBG delayed H/M ratio was significantly lower, and WR was higher in patients with HFPEF in increased with advancing NYHA functional Class (NYHA functional Class I and II vs. NYHA functional Class III: 1.89 ± 0.34 vs. 1.52 ± 0.37, $p < 0.0001$. $26.2 \pm 13.5\%$ vs. $46.1 \pm 18.7\%$, $p < 0.0001$. respectively).

Clinical Characteristics of HFPEF Patients Between Low WR Group and High WR Group

We divided patients with HFPEF into 2 groups by cut off value of ^{123}I-MIBG WR (24.2%) from Receiver operated characteristic (ROC) curve: low WR group (<24.2%, n = 51) and high WR group (≥24.2%, n = 77). Clinical characteristics were compared between patients with the low and high ^{123}I-MIBG WR groups (Table 2). The complication of diabetes mellitus was more in the high WR group than in the low WR group. NYHA functional Class was more severe in the high WR group than in the low WR group. In the etiologies of HF, hypertensive heart disease was more in patients with the high WR group than in the low WR group. BNP was significantly higher, and estimated GFR was significantly lower in the high WR group than in the low WR group. Early and delayed H/M ratios were significantly lower, and WR was significantly higher in the high WR group than in the low WR group. In echocardiographic LVEF, there was no significant difference between the 2 groups in Table 2.

Comparison of ^{123}I-MIBG WR with BNP and LVEF

^{123}I-MIBG WR was weakly correlated with BNP (R = 0.201, p = 0.0327) and was not correlated with LVEF by a simple linear regression analysis (Figure 2a and 2b). ROC curves for ^{123}I-MIBG WR, BNP and delayed H/M ratio were constructed. The area under the ROC of ^{123}I-MIBG WR was larger than that of BNP or delayed H/M ratio (0.7163 vs. 0.6477 or 0.6936), suggesting that ^{123}I-MIBG WR was superior to BNP or delayed H/M ratio to predict adverse cardiac events. The sensitivity and specificity to detect future cardiac events were 82.1% and 55.7% by ^{123}I-MIBG WR, 61.5% and 68% by BNP, 53.6% and 82.3% by delayed H/M ratio, respectively.

Prognosis of Subjects and ^{123}I-MIBG WR Value

There were 46 cardiac events (4 cardiac deaths and 42 rehospitalizations) during a follow-up period in all patients with HFPEF. Cumulative event-free survival curves were illustrated by the Kaplan-Meier method and compared by a log-rank test (Figure 3). Cardiac event-free rate was significantly lower in the high WR group than in the low WR group (53.2 % vs. 80.4%, log-rank test p = 0.0004).

In the present study, if the patients with HFPEF were divided into 2 groups by cut off level of plasma BNP (180.7 pg/mL) from ROC curve, cardiac event-free rate was also significantly lower in the high plasma BNP group than in the low plasma BNP group by Kaplan-Meier analysis (log-rank test p = 0.0112) (data not shown).

The univariate Cox proportional hazards analysis to predict cardiac events for ^{123}I-MIBG WR and other variables are shown in Table 3. An increase of 1SD (16.2%) in ^{123}I-MIBG WR value was a significant variable (hazard ratio: 2.01, 95% CI: 1.52-2.65, $p < 0.0001$). Furthermore, NYHA functional Class, an increase of 1 SD in the uric acid, $\log_{10}$BNP, echocardiographic LAD, and LVEDD were significantly related to cardiac events. However, LVEF was not related to cardiac events in the univariate Cox proportional hazard analysis (Table 3).

Those variables with p values of less than 0.05 were entered into the multivariate Cox proportional hazard regression analysis, ^{123}I-MIBG WR was an independent predictor of cardiac events among those variables (Table 4.)

Discussion

In the present study, we found several new findings with respect to prognostic value for HFPEF patients using ^{123}I-MIBG scintigraphy. ^{123}I-MIBG WR and delayed H/M ratio can classify the patients with HFPEF by NYHA functional Class. (1) ^{123}I-MIBG WR was significantly higher, and delayed H/M ratio was lower in patients with HFPEF in increased with advancing NYHA functional Class. (2) In patients with HFPEF, cardiac event-free rate was significantly lower in the high ^{123}I-MIBG WR group than in the low ^{123}I-MIBG WR group by Kaplan-Meier analysis. (3) In patients with HFPEF, multivariate analysis showed that $\log_{10}$BNP was not an independent predictor, but ^{123}I-MIBG WR was an independent predictor for subsequent cardiac events. Furthermore, ^{123}I-MIBG WR was not correlated with LVEF and showed extremely weak correlation with plasma BNP level.

A number of studies have established that ^{123}I-MIBG imaging provides diagnostic and prognostic information in HF patients with reduced LV systolic function [7-11]. Epidemiologic studies have implicated an important relationship between hypertension and pathogenesis of HFPEF. Grassi et al. have reported that sympathetic activation was markedly potentiated in patients with hypertension depended on an arterial baroreflex impairment [29]. However, there are still few reports which were clinically examined the relationship between cardiac sympathetic activation and LV diastolic dysfunction. It was reported that serum NE level was similar in diastolic HF and

systolic HF and was markedly increased compared to normal subjects [30]. Moreover, in animal model there are several reports that NE was an important factor in the development of diastolic dysfunction [31, 32].

It is suggested that rennin-angiotensin system (RAS) is associated with cardiac sympathetic activation. In humans, RAS inhibition controls hypertension and regresses LV hypertrophy [33]. In animal models of LV hypertrophy, RAS activity is upregulated and increased myocardial tissue angiotensin I conversion impairs diastolic function [33]. It was reported that activation of RAS was associated with NE release from cardiac sympathetic nerve endings in HF [34]. Therefore, there is a possibility that ^{123}I-MIBG findings assessed cardiac stress induced by RAS.

In the present study, we showed the impact of ^{123}I-MIBG findings on detecting abnormalities of the myocardial adrenergic nervous system in patients with HFPEF as in those with reduced LV systolic function. From the results of the present study, it is expected that ^{123}I-MIBG findings may be an indication for treatment of HFPEF.

Several studies have been reported about relationships between the cardiac nervous system and HFPEF [16, 35, 36]. One of these studies, however, was investigated in smaller populations and one of them was a report in hypertrophic cardiomyopathy patients and one of them was a report of an improvement in ^{123}I-MIBG findings at 6 months after candesartan treatments.

Grewal et al. reported that plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and BNP were strong independent predictors of cardiac events in patients with HFPEF [37]. In the

present study, cardiac event-free rate was also significantly lower in the high plasma BNP group than in the low plasma BNP group by Kaplan-Meier analysis (data not shown). In multivariate Cox proportional hazards analysis, however, log_{10}BNP was not independent predictor for future cardiac events in our study. As for the extremely weak-relationship between plasma BNP level and ^{123}I-MIBG WR, it is known that plasma BNP level is increased by LV overload like congestive HF [38, 39], and meanwhile, ^{123}I-MIBG scintigraphic findings directly reflects cardiac sympathetic nerve activity and ongoing myocardial damage [7-10]. In the above-mentioned conditions, it may mean BNP is a useful diagnostic and predictive marker for patients with HF at a point of the HF term, whereas ^{123}I-MIBG imaging is a useful tool for assessing and predicting HF patients in longer term of HF. Therefore, it seems that not plasma level of BNP but ^{123}I-MIBG WR was an independent predictor for future cardiac events in multivariate analysis. From these findings, it seems that to reduce rising cardiac sympathetic nerve activity, by using β-blockers, is a beneficial therapy in patients with HFPEF. Future investigation is needed.

Study Limitations

Several potential limitations should be considered with respect to these findings. We defined that study subjects were HF patients with LVEF ≥50% [15, 18], therefore a number of them were maybe diastolic HF patients, but we did not get sufficient diastolic parameters by echocardiography, such as

E/E' ratio (in the present study, we measured E/E' ratio from only 28 HFPEF patients). We measured E/A ratio and E wave deceleration time by echocardiography, which might have some variation in treatments for congestive HF, so they could not be powerful indicators of diastolic HF [12, 40].

In the present study, there were some variations in the etiologies of HFPEF compared to other study. Tsuchihashi-Makaya et al. recently showed the etiologies of 429 Japanese HFPEF in their report [17]. They reported that the prevalence of HFPEF was 26% and the etiologies of HFPEF were identified as idiopathic dilated cardiomyopathy in 5%, ischemic HF in 25%, hypertensive HF in 44%, hypertrophic cardiomyoprthy in 10% and others in 36%. In the present study, the number of dilated cardiomyopathy was slightly larger and that of hypertensive HF was slightly smaller than in their study. One possible explanation is that this study was in a single university hospital and the patients with pure hypertensive heart disease were little.

It was, however, important and interesting that we followed future cardiac events in patients with HFPEF approximately 3 years.

Conclusions

The value of ^{123}I-MIBG WR was increased, and delayed H/M ratio was decreased in patients with HFPEF. ^{123}I-MIBG WR was independently associated with an increased risk for

cardiac events. These findings indicate that the value of ^{123}I-MIBG WR is a novel promising marker to provide useful prognostic information for clinical outcomes in patients with HFPEF.