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Ongoing myocardial damage relates to cardiac sympathetic nervous disintegrity in patients with heart failure

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Iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) has been used to assess the integrity and function of the cardiac sympathetic nervous system in patients with heart failure. Heart-type fatty acid binding protein (H-FABP) is released into the circulation when the myocardium is injured, and H-FABP has been recently used as a novel marker for the diagnosis of ongoing myocardial damage. ***Objective:*** The aim of the present study was to compare cardiac sympathetic nervous activity assessed by ^{123}I-MIBG imaging with serum levels of H-FABP in patients with heart failure. ***Methods:*** Fifty patients with chronic heart failure were studied. ^{123}I-MIBG imaging was carried out at 30 min (early) and 240 min (delayed) after the tracer injection. We measured serum levels of H-FABP using a sandwich enzyme linked immunosorbent assay. ***Results:*** Heart to mediastinum (H/M) ratios of ^{123}I-MIBG decreased and washout rate increased with higher New York Heart Association (NYHA) functional class. H-FABP, norepinephrine and brain natriuretic peptide (BNP) levels increased as the severity of NYHA class advanced. Delayed H/M ratio was significantly correlated with H-FABP ($r = -0.296$, $p = 0.029$) and BNP ($r = -0.335$, $p = 0.0213$). Myocardial washout rate of ^{123}I-MIBG was also correlated with H-FABP ($r = 0.469$, $p < 0.001$), norepinephrine ($r = 0.433$, $p = 0.005$), and BNP ($r = 0.465$, $p = 0.001$). ***Conclusions:*** These data suggest that cardiac sympathetic nervous activation was associated with ongoing cardiomyocyte damage characterized by an elevated serum level of H-FABP in patients with heart failure. ^{123}I-MIBG imaging is an appropriate approach to evaluate non-invasively not only cardiac sympathetic nervous activity, but also latent ongoing myocardial damage in the failing heart.

Key words: H-FABP, ^{123}I-MIBG imaging, heart failure

INTRODUCTION

ACTIVATION of the sympathetic nervous system plays an important role in the progression of congestive heart failure.[1–3] Iodine-123-metaiodobenzyl-guanidine (^{123}I-MIBG), an analogue of norepinephrine, has been developed and used to visualize cardiac sympathetic nervous distribution and function.[4–6] A number of studies have reported that ^{123}I-MIBG imaging provides powerful diagnostic and prognostic information in patients with heart failure.[7–13]

It has been reported that levels of multiple neurohumoral factors including norepinephrine and brain natriuretic peptide (BNP) are elevated in patients with heart failure and related to the severity of the disease.[14–16] On the other hand, heart-type fatty acid binding protein (H-FABP), a novel marker of ongoing myocardial damage, is a small cytosolic protein that binds long chain fatty acid and functions as the principle transporter of long chain fatty acid in the cardiomyocyte.[17–20] H-FABP is present abundantly in the myocardium, and is released into the circulation when the myocardium is injured. We have recently demonstrated that the serum H-FABP level is closely related to the severity of heart failure and predicts

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subsequent cardiac events independently of established prognostic variables in chronic heart failure.[20]

Although several previous reports have identified that ^{123}I-MIBG parameters are correlated with neurohumoral factors such as norepinephrine and BNP,[13,21–23] the relationship between cardiac sympathetic nervous activity and myocardial cell injury remains to be elucidated.[24] In the present study, we examined whether sympathetic nervous overactivity was accompanied by ongoing myocardial damage in patients with chronic heart failure. We compared parameters of ^{123}I-MIBG imaging with the serum level of H-FABP, a novel marker of cardiomyocyte damage, in patients with heart failure.

METHODS

Study subjects

We studied 50 patients (34 men and 16 women, mean age of 65 ± 14 years) with 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. Twenty-four age-matched normal subjects (17 men and 7 women, aged 64 ± 12 years) without heart failure comprised the control group. The characteristics of the patients are summarized in Table 1. The etiologies of heart failure were ischemic heart failure in 10 (20%) patients and non-ischemic heart failure in the remaining 40 (80%) patients. There were 26 patients with New York Heart Association (NYHA) functional class II and 24 patients with class III. No patients had clinical symptoms or signs suggestive of acute myocardial infarction, unstable angina, or acute myocarditis within the 3 months preceding admission. Patients with renal insufficiency determined by a serum creatinine level >1.5 mg/d*l* were excluded from the present study.

^{123}I-MIBG imaging

A dose of 111 MBq of ^{123}I-MIBG (Daiichi Radioisotope Laboratories, Tokyo, Japan) was administered with 20 m*l* saline under resting supine condition 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.[25–27] Five 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) rations of ^{123}I-MIBG uptake at 30 min (early H/M) and at 240 min (delayed H/M) were calculated (H: mean counts/pixel in the left ventricular myocardium, M: mean counts/pixel in the upper mediastinum) as previously reported.[25–27] Washout rate from the myocardium was calculated as [(H – M) at 30 min – (H – M) at 240 min] × 100/(H – M) at 30 min (%).

Table 1 Clinical background of patients with heart failure

	All patietns (n = 50)
Age (y.o.)	65 ± 14
Gender (male/female)	34/16
NYHA functional class (II/III)	26/24
Hypertension	25 (50%)
Diabetes mellitus	12 (24%)
Hyperlipidemia	5 (10%)
Current smoking	11 (22%)
Etiology	
Ischemic heart failure	10 (20%)
Non-ischemic heart failure	40 (80%)
Blood examination	
Norepinephrine (pg/m*l*)	578 ± 368
BNP (pg/m*l*)	504 ± 639
H-FABP (ng/m*l*)	5.2 ± 3.3
Echocardiography	
LVEDD (mm)	52 ± 11
LVEF (%)	47 ± 21
^{123}I-MIBG imaging	
Early H/M ratio	1.81 ± 0.26
Delayed H/M ratio	1.72 ± 0.28
Washout rate (%)	42.9 ± 9.9
Medications	
ACE inhibitors and/or ARBs	33 (66%)
β-blockers	22 (44%)
Ca channel blockers	6 (12%)
Spironolactone	12 (24%)
Loop diuretics	36 (72%)
Digoxin	20 (40%)
Aspirin	14 (28%)
Warfarin	15 (30%)
Statins	5 (10%)

NYHA, New York Heart Association; BNP, brain natriuretic peptide; H-FABP, heart-type fatty acid binding protein; LVEDD, left ventricular dimension at end-diastole; LVEF, left ventricular ejection fraction; H, heart; M, mediastinum; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.

Measurements of norepinephrine, BNP and H-FABP

A sample of venous blood was obtained from the study population on the day of ^{123}I-MIBG scintigraphy. Plasma level of norepinephrine was measured with an automated high-performance liquid chromatography analyzer (Tosoh Co., Tokyo, Japan). We also measured the plasma level of BNP by an immunoradiometric assay using a commercially available kit (SHIONORIA^{TM} BNP, SHIONOGI Co., Osaka, Japan). Serum H-FABP level was determined by a sandwich enzyme linked immunosorbent assay using two distinct murine anti-human H-FABP specific monoclonal antibodies (Markit-M H-FABP®, Dainippon Pharmaceutical Co. Ltd., Tokyo, Japan). H-FABP in the test sample was bound to a monoclonal anti-H-FABP antibody coated on microplate wells, and enzyme labeled anti-H-FABP antibody was added to the wells to form a sandwich immune complex.[20] Substrate was added to

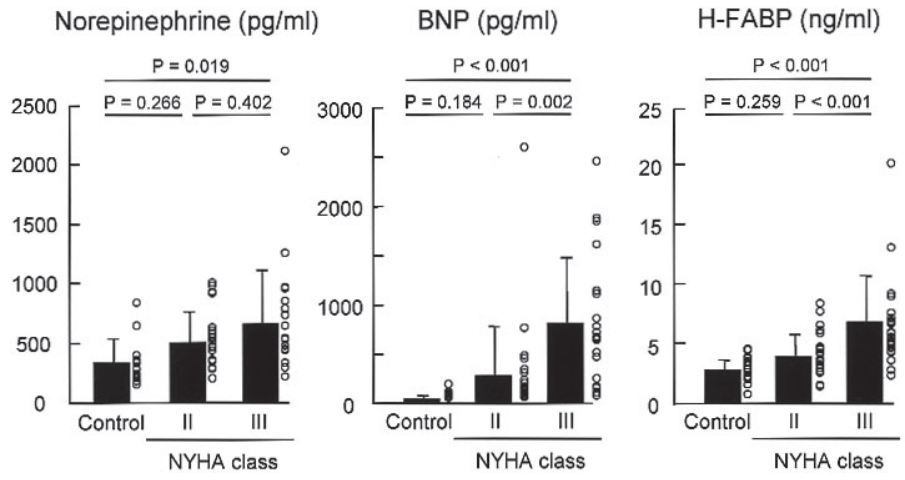

Fig. 1 Levels of norepinephrine, BNP and H-FABP in study population.

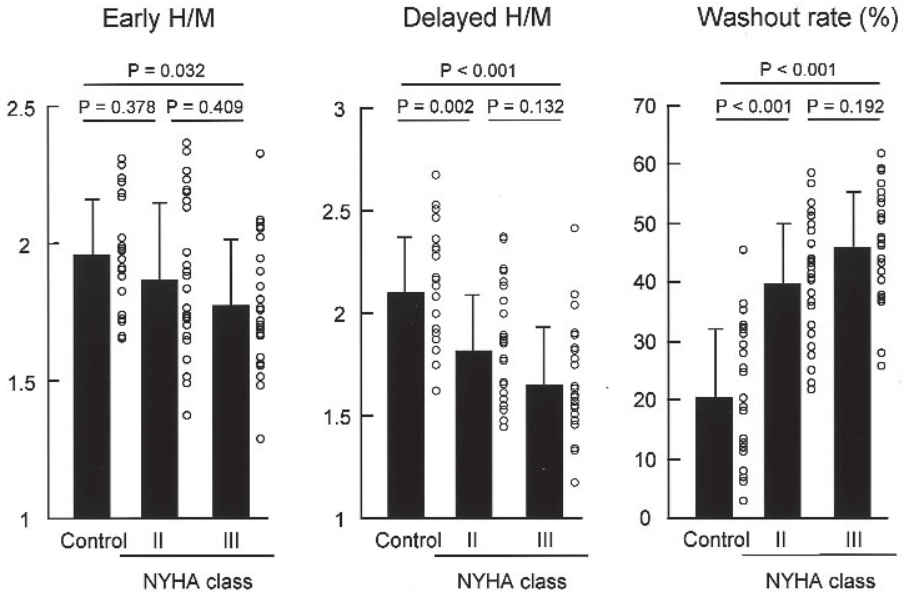

Fig. 2 Parameters of ^{123}I-MIBG imaging in study population.

start the enzymatic reaction, and absorbance was measured at 492 nm in a microplate reader.

Echocardiographic studies

Echocardiography was performed within 3 days after ^{123}I-MIBG scintigraphy using standard techniques. Left ventricular dimensions at end-diastole and end-systole were measured by two-dimensionally guided M-mode tracing, and left ventricular ejection fraction was calculated based on the Simpson's rule.

Statistics

All values were expressed as mean ± SD. Concentrations of norepinephrine, BNP and H-FABP and parameters of ^{123}I-MIBG imaging among NHYA functional classes were compared by one-way ANOVA followed by a Scheffe's test. A p value less than 0.05 was considered statistically significant.

RESULTS

Norepinephrine, BNP and H-FABP levels in the study population

Mean plasma levels of norepinephrine and BNP were 578 ± 368 pg/m*l* (median 492, range 167 to 2,078) and 504 ± 639 pg/m*l* (median 201, range 20 to 2,540) in patients with heart failure, respectively, as shown in Table 1. Mean serum level of H-FABP was 5.2 ± 3.3 ng/m*l* (median 4.5, range 1.3 to 20). The relationships between levels of these biochemical markers and the severity of heart failure were examined in Figure 1. As reported in previous studies,[14,15,20] levels of norepinephrine, BNP, and

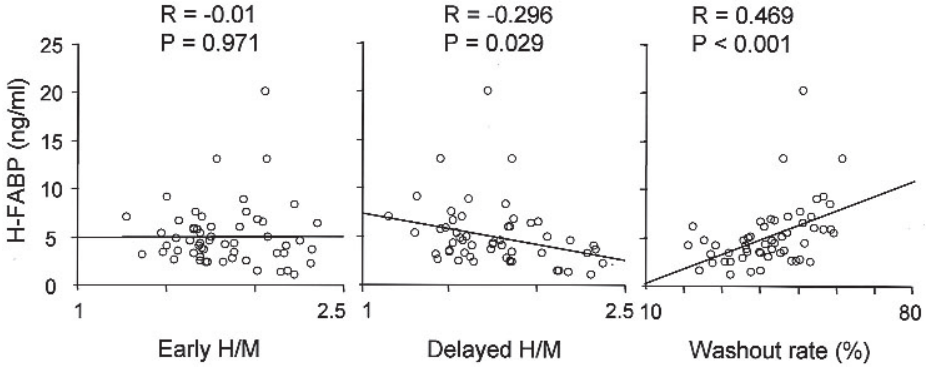

Fig. 3 Correlations between parameters of ^{123}I-MIBG imaging and serum levels of H-FABP.

H-FABP were significantly higher in heart failure patients with NYHA class III than in control subjects. As the severity of NYHA functional class advanced, norepinephrine, BNP, and H-FABP levels increased (Fig. 1). There were significant differences in BNP and H-FABP levels between patients with NYHA class II and III.

H/M ratios and washout rate of ^{123}I-MIBG in the study population

Early and delayed H/M ratios were 1.81 ± 0.26 (median 1.75, range 1.27 to 2.35) and 1.72 ± 0.28 (median 1.72, range 1.14 to 2.37), respectively, and washout rate was 42.9 ± 9.9% (median 42.8, range 21.2 to 61.1) in patients with heart failure (Table 1). Correlations between ^{123}I-MIBG parameters and NYHA functional class were examined in Figure 2. As reported in previous studies, H/M ratios of ^{123}I-MIBG at early and delayed images were lower in patients with NYHA class III than in control subjects. Washout rate of ^{123}I-MIBG was faster in patients with NYHA class II and III compared to control subjects. H/M ratios decreased, whereas washout rate increased with advancing of NYHA functional class (Fig. 2).

Correlations between biochemical markers and ^{123}I-MIBG parameters

We compared levels of biochemical markers with ^{123}I-MIBG parameters. There was a weak but statistically significant correlation between serum H-FABP levels and delayed H/M ratio of ^{123}I-MIBG ($r = -0.296$, $p = 0.029$) as shown in Figure 3. Serum H-FABP levels were also correlated significantly with the washout rate of ^{123}I-MIBG from the myocardium ($r = 0.469$, $p < 0.001$). These data indicated that high H-FABP levels were accompanied by high cardiac sympathetic nervous activity.

In accordance with previous reports,[21,22] plasma levels of norepinephrine were correlated with the washout rate of ^{123}I-MIBG from the myocardium ($r = 0.433$, $p = 0.0052$). Plasma BNP levels were also correlated with delayed H/M ratio ($r = -0.335$, $p = 0.0213$) and washout rate ($r = 0.465$, $p = 0.001$) of ^{123}I-MIBG. Early H/M ratio did not correlate with any markers in the present study.

DISCUSSION

In the present study, we demonstrated that serum levels of H-FABP, a new marker of cardiomyocyte injury, were increased in patients with heart failure. H-FABP levels were correlated significantly with H-M ratio at delayed images and washout rate of ^{123}I-MIBG, indicating that the ongoing cardiomyocyte damage related to cardiac sympathetic nervous disintegrity in patients with heart failure.

Assessing cardiac autonomic status is clinically important in the management of patients with heart failure, since sympathetic nervous activation causes excessive ventricular afterload, down-regulation of β-adrenergic receptors, tachycardiac interference with ventricular filling, heart failure progression, and increased mortality.[28] Elevated circulating norepinephrine levels, reflecting increased sympathetic nervous system activity, are an indirect marker for mortality related to severe heart failure.[14] A different approach for measuring sympathetic nervous function in the heart is to evaluate the capacity of cardiac sympathetic nerve terminals to take up catecholamines by the uptake-1 transporter. This assessment can be made non-invasively using ^{123}I-MIBG and such imaging allows the evaluation of sympathetic tone in the clinical setting.[4–6] As shown in Figures 1 and 2, neurohumoral factors and ^{123}I-MIBG parameters were correlated with the severity of heart failure in accordance with previous reports.[11–14,21,22,27]

During the development of cardiac hypertrophy and transition to heart failure, a switching of energy substrate utilization occurs with reduced fatty acid oxidation and increased glucose utilization.[29–31] H-FABP plays a critical role in the uptake and transport of long chain fatty acid in the cardiomyocyte. Both cellular uptake and lipid oxidation of long chain fatty acids are severely depressed in H-FABP knockout mice.[32] On the other hand, H-FABP is rapidly leaked into the circulation when the myocardium is injured. In this regard, H-FABP has been recently used as a biochemical marker for acute myocardial infarction[17–19] and also a clinical marker to reflect ongoing myocardial damage in patients with severe heart failure.[20]

Our study suggested that while levels vary directly with severity, H-FABP was released from the damaged myocardium at each stage of heart failure (Fig. 1).

Although several parameters of ^{123}I-MIBG imaging provide promising information to assess patients with heart failure,[7–13] the precise mechanism that underlies these findings has not yet been established. We found a correlation between serum level of H-FABP, a new marker of myocardial damage, and parameters of ^{123}I-MIBG imaging. Sustained sympathetic nervous overactivity causes excess norepinephrine release from the presynaptic nerve terminal endings, resulting in norepinephrine depletion and downregulation of β-adrenergic receptors in the myocardium.[1–3] These changes are also associated with histopathologic abnormalities, such as myocyte degeneration and necrosis in response to increased sympathetic nervous activity.[33] Indeed in the present study, serum H-FABP level was correlated significantly with H/M ratio at delayed images and washout rate of ^{123}I-MIBG, which may reflect, at least in part, enhanced norepinephrine release from the presynaptic nerve terminal endings, increased norepinephrine spillover, and decreased uptake-1 function.

Serum levels of H-FABP were augmented in some patients with high delayed H/M ratio. Although we excluded the patients with serum creatinine level >1.5 mg/d*l*, even a slight decrease in renal function might influence the serum level of H-FABP. On the other hand, low serum H-FABP levels were observed in some patients with low delayed H/M ratio of ^{123}I-MIBG. In this case, it is possible that ongoing myocardial damage might be delayed after cardiac sympathetic nervous dysfunction.

The percentage of patients who had taken β-blockers, ACE inhibitors and/or ARBs was relatively low in the present study. However, this study included mild to moderate heart failure patients with non-ischemic etiologies and patients with preserved left ventricular systolic function. We started β-blockers, ACE inhibitors and/or ARBs in almost all patients after ^{123}I-MIBG imaging.

H-FABP is released into the circulation from the damaged myocardium, whereas BNP is secreted in response to mechanical overload to the ventricles.[34,35] These differences may support the rationale of combined use of these factors for risk stratification of patients with heart failure. Kyuma et al. showed that delayed H/M ratio of ^{123}I-MIBG and plasma BNP level enable better stratification of heart failure patients at augmented risk for cardiac events.[23] Additionally, we have recently shown that combined measurements of serum H-FABP and plasma BNP levels are helpful to monitor disease outcome in patients with heart failure.[36] In future research, we need to examine whether the combined assessment of cardiac sympathetic nervous activity, myocardial cell injury and other biochemical markers would effectively risk stratify patients with heart failure.

CONCLUSIONS

We demonstrated in the present study that activation of the cardiac sympathetic nervous system was associated with ongoing cardiomyocyte damage characterized by an elevated serum level of H-FABP in heart failure patients. ^{123}I-MIBG imaging may be useful for evaluating not only cardiac sympathetic nervous activity, but also latent myocardial damage in the failing heart.

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