Cardiac Sympathetic Denervation and Ongoing Myocardial Damage for Prognosis in Early Stages of Heart Failure

TAKANORI ARIMOTO, MD, PhD, YASUCHIKA TAKEISHI, MD, PhD, TAKESHI NIIZEKI, MD, NAOKI NOZAKI, MD, PhD, OSAMU HIRONO, MD, PhD, TETSU WATANABE, MD, PhD, JOJI NITOBE, MD, PhD, YUICHI TSUNODA, MD, PhD, SATOSHI SUZUKI, MD, YO KOYAMA, MD, TATSURO KITAHARA, MD, AKIO OKADA KAZUEI TAKAHASHI AND ISAO KUBOTA, MD, PhD

Yamagata, Japan

ABSTRACT

Background: Iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) can assess cardiac sympathetic nervous function. Heart-type fatty acid binding protein (H-FABP) has been used as a marker of ongoing myocardial damage. The prognostic value of combination ^{123}I-MIBG imaging and H-FABP in heart failure is unknown.

Methods and Results: We prospectively enrolled consecutive 104 patients with heart failure in whom we quantified ^{123}I-MIBG scintigraphy, simultaneously measured serum H-FABP and plasma brain natriuretic peptide (BNP) levels, and analyzed clinical outcomes. The multivariate Cox regression analysis revealed that augmented H-FABP level and decreased heart to mediastinum ratio of ^{123}I-MIBG at 240 minutes (delayed H/M ratio), but not BNP, were the independent predictors for cardiac events. The cutoff values for H-FABP and delayed H/M ratio were determined from the receiver operating characteristic curves as 5.2 ng/mL for H-FABP and 1.73 for delayed H/M ratio. The cardiac event rate was markedly higher in patients with both H-FABP and delayed H/M ratio of ^{123}I-MIBG was abnormal. Conversely, no cardiac events occurred in patients with both H-FABP level and delayed H/M ratio were normal.

Conclusion: H-FABP adds independent prognostic information to delayed H/M ratio of ^{123}I-MIBG imaging, and the combination of these approaches may improve the accuracy of prognostic determination in heart failure. (*J Cardiac Fail 2007;13:34−41*)

Key Words: ^{123}I-MIBG imaging, H-FABP, Heart failure.

Several noninvasive examinations for cardiac status have emerged as strong predictors of risk among patients presenting heart failure and are now routinely available to clinicians. Activation of sympathetic nervous system plays an important role in the progression of 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.[7−11]

On the other hand, heart-type fatty acid binding protein (H-FABP), a biomarker of ongoing myocardial damage, is small cytosolic protein that binds long chain fatty acid and functions as the principle transporter of long chain fatty acid in the cardiomyocyte.[12−19] H-FABP is present abundantly in the myocardium and is released into the circulation when the myocardium is injured. We and others have recently demonstrated that serum H-FABP level is closely related to the severity of heart failure and predicts subsequent cardiac events independently of established prognostic variables in heart failure.[15−18] Little is known, however, about the combination of these examinations, ^{123}I-MIBG and H-FABP, in heart failure. We hypothesized that simultaneous assessment of these 2 tests would provide

From the First Department of Internal Medicine, Yamagata University School of Medicine, Yamagata, Japan.

Manuscript received February 14, 2006; revised manuscript received July 17, 2006; revised manuscript accepted September 22, 2006.

Reprint requests: Yasuchika Takeishi, MD, First Department of Internal Medicine, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata, 990-9585 Japan.

Supported in part by a grant-in-aid for Scientific Research (No. 17590702) from the Ministry of Education, Science, Sports and Culture, Japan; a grant-in-aid from the 21st Century Center of Excellence (COE) program of the Japan Society for the Promotion of Science; and grants from Takeda Science Foundation and Fukuda Foundation for Medical Technology.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2006.09.002

complementary information and enable clinicians to stratify risk more effectively in patients with heart failure. Therefore, we prospectively enrolled patients with heart failure, performed ^{123}I-MIBG imaging, measured H-FABP levels simultaneously, and analyzed their clinical outcomes under medical managements.

Methods

Study Subjects

We performed ^{123}I-MIBG scintigraphy and measured serum levels of H-FABP and plasma levels of brain natriuretic peptide (BNP) in consecutive 104 patients (67 men and 37 women, mean age of 66 ± 14 years) who admitted to the Yamagata University Hospital for the treatment of worsening chronic heart failure, or for the diagnosis and pathophysiologic investigations, or therapeutic evaluations of heart failure. Written informed consent was obtained from all patients, and the Institutional Review Board on human research approved the study protocol. Hypertension was defined as elevated systolic blood pressure of >140 mm Hg, diastolic blood pressure >90 mm Hg, or when patients had taken antihypertensive drugs. Diabetes mellitus was defined as an increased fasting plasma glucose concentration of >126 mg/dL, glycosylated hemoglobin of >6.4%, or when patients undergo treatment with insulin or hypoglycemic agents.

Hyperlipidemia was defined as augmented total cholesterol level of >220 mg/dL, triglyceride >150 mg/dL, decreased high-density lipoprotein level of <40 mg/dL, or when patients had taken drugs of antihyperlipidemia.[20] We performed conventional 2-dimensional echocardiographic studies using standard techniques within 3 days after ^{123}I-MIBG scintigraphy. Left ventricular ejection fraction was calculated based on Simpson's rule.[19,20] No patients had clinical symptoms or signs suggestive acute myocardial infarction, unstable angina, or acute myocarditis in the 1 year preceding admission. Patients with renal insufficiency characterized by a serum creatinine level >1.8 mg/dL were excluded from the present study. Coronary arteriography was performed to diagnose ischemic heart failure.

^{123}I-MIBG Imaging

We performed ^{123}I-MIBG imaging before discharge in stable condition. A dose of 111 MBq of ^{123}I-MIBG (Daiichi Radioisotope Laboratories, Tokyo, Japan) was administered with 20 mL saline under resting supine condition after an overnight fast. All images were acquired using a 3-head rotating gamma camera equipped with a low-energy, high-resolution collimator (Multispect 3, Siemens Medical Systems, Chicago, IL) as previously reported.[19,21–23] Five mid-anterior planar imaging was carried out at 30 minutes and 240 minutes 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 as previously reported.[19,21–23] Washout rate from the myocardium was calculated as [(H − M) at 30 minutes − (H − M) at 240 minutes] × 100/(H − M) at 30 minutes (%) (H: mean counts/pixel in the left ventricular myocardium, M: mean counts/pixel in the upper mediastinum).

H-FABP and BNP Assay

A sample of venous blood was obtained from study subjects on the day of ^{123}I-MIBG scintigraphy. Serum H-FABP level was determined by a sandwich enzyme-linked immunosorbent assay using 2 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[16–19] Substrate was added to start the enzymatic reaction, and absorbance was measured at 492 nm in a microplate reader. 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 374 days. The endpoints were (1) cardiac death, defined as death from progressive heart failure or sudden cardiac death, and (2) progressive heart failure requiring rehospitalization. Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was established by the attending physician.

Statistics

All values were expressed as mean ± SD. Significance between 2 groups, with or without cardiac event and New York Heart Association (NYHA) class II versus class III, was determined by unpaired Student's *t*-test for continuous variables and by chi-square test for discrete variables. Values of $P < .05$ were considered significant. The Cox proportional hazard regression model was used to determine which variables were related significantly to cardiac events. Only variables with *P* value less than .05 in the univariate Cox regression analysis were entered into the stepwise multivariate Cox regression analysis. The receiver operating characteristic (ROC) curves were constructed to illustrate various cutoff values at 1 year and to determine optimal sensitivity and specificity. The areas under the curves were calculated by the trapezoidal rule. Kaplan-Meier survival curves determined the time-dependent cumulative cardiac event free rates in patients stratified into 2 or 4 groups based on the values for H-FABP and delayed H/M ratio of ^{123}I-MIBG, and were analyzed by a log-rank test.

Results

Clinical Characteristics of Study Subjects

Clinical characteristics including biochemical, ^{123}I-MIBG scintigraphic, and echocardiographic findings of the 104 patients enrolled in the study are shown in Table 1. There were 64 patients with NYHA functional Class II and 40 patients with Class III. The etiologies of heart failure were identified as ischemic heart failure in 20 (19%) patients, idiopathic dilated cardiomyopathy in 45 (43%) patients, valvular heart disease in 18 (17%) patients, hypertensive heart disease in 9 (9%) patients, and others in the remaining 12 (12%) patients. Hypertension, diabetes mellitus, and hyperlipidemia were identified in 44 (42%), 22 (21%), and 20 (19%) patients, respectively.

Early and delayed H/M ratios were 1.86 ± 0.29 (median 1.83, range 1.24–2.58) and 1.74 ± 0.31 (median 1.73, range 1.07–2.46), respectively, and washout rate was 44 ± 12% (median 43.5, range 6.1–80.4) in patients with heart failure (Table 1). As reported in previous studies, early