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Persistent Abnormal Value of Late Potential in Brugada Syndrome Associated with Hypokalemia

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Hypokalemia accentuates the electrocardiographic (ECG) pattern of Brugada syndrome. We report two patients with Brugada syndrome and hypokalemia-induced lethal events. Despite concealing the typical ECG pattern with normalization of serum potassium levels, late potentials were persistently detected by signal-averaged ECG, even at the 18-month follow-up. An implantable cardioverter defibrillator was inserted to prevent sudden cardiac death.

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Brugada syndrome; hypokalemia; late potential

Low potassium levels are associated with Brugada syndrome and the occurrence of ventricular arrhythmia.[1,2] However, no studies have shown late potentials (LPs) detected by signal-averaged electrocardiography (ECG) after restoring serum potassium levels in patients with Brugada syndrome.

CASE 1

A 50-year-old man was being transported following syncope. In the ambulance, he experienced ventricular fibrillation (VF), which was successfully treated with direct current shock. His body temperature was 37.0°C and chest x-ray and echocardiogram were normal. Blood chemistry showed hypokalemia (2.6 mEq/L). The 12-lead ECG on admission showed an ECG aspect compatible with pattern of Brugada in precordial leads (Fig. 1A). The Brugada ECG was normalized with restoration of serum potassium (3.6 mEq/L, Fig. 1B). No further arrhythmic events occurred during hospitalization. Cardiac catheterization revealed no significant stenosis in the coronary arteries. During the electrophysiological study, VF was reproducibly induced by programmed stimuli from the right ventricle. An intravenous pilsicainide (50 mg) test exaggerated the ECG pattern of Brugada syndrome (Fig. 1C). An implantable cardioverter defibrillator (ICD) was implanted to prevent sudden cardiac death.

CASE 2

A 53-year-old man who suffered sudden cardiopulmonary arrest was referred to our hospital for cardiopulmonary resuscitation. His body temperature was 39.2°C. Laboratory evaluation revealed leukocytosis (16,400 mm^3), elevated C-reactive protein (8.85 mg/dL), and hypokalemia (3.0 mEq/L). Echocardiography showed normal wall motion of the left ventricle. Chest x-ray and computed tomography (CT) scan confirmed pneumonia. The 12-lead ECG revealed complete right bundle branch block with a coved-type ST-segment elevation in precordial leads (Fig. 1D). An intravenous infusion of potassium and intravenous administration of antibiotics were initiated. Serum potassium was 3.9 mEq/L on day 2, with normalization of coved ST elevation, irrespective of marked febrile state (Fig. 1E). No significant stenosis was observed in the coronary arteries. VF was reproducibly induced by programmed stimuli from the right ventricle. An ICD was inserted to prevent sudden death.

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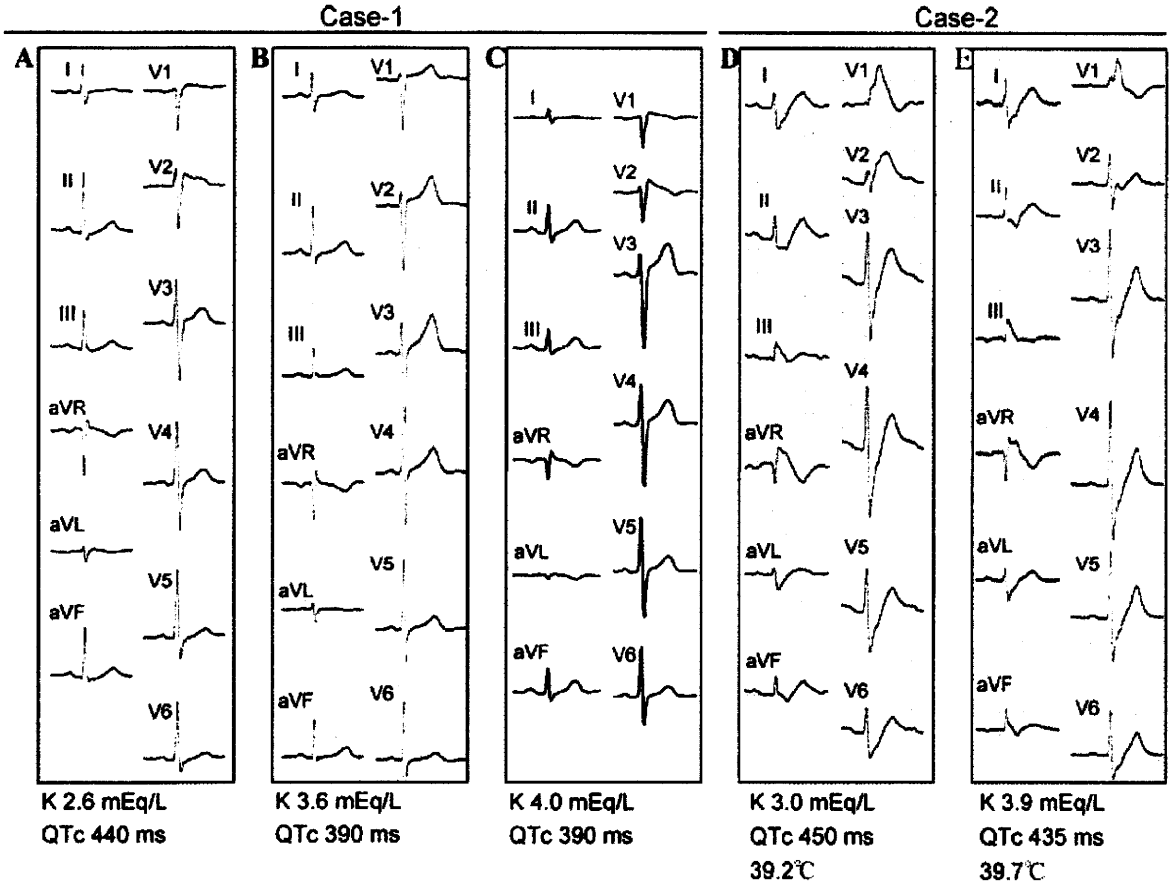

Figure 1. ECG patterns of two patients with Brugada syndrome and hypokalemia-induced lethal events. (A) A 12-lead ECG of Case-1 on admission showed an ECG aspect compatible with pattern of Brugada. (B) Normalization of the ECG upon restoration of serum potassium levels. (C) An intravenous pilsicainide (50 mg) test reproduced the ECG pattern of Brugada syndrome. (D) A 12-lead ECG of Case-2 at Emergency Room revealed complete right bundle branch block with a coved-type ST-segment elevation in precordial leads. (E) Normalization of the ST-segment elevation upon restoration of serum potassium, even in the presence of high fever.

LPs BY SIGNAL-AVERAGED ECG

The LPs were analyzed using a signal-averaged ECG System (FCP7541, Fukuda Denshi Co., Tokyo, Japan). Three parameters were assessed via a computer algorithm: (1) the filtered QRS duration; (2) the root mean square voltage of the terminal 40 ms in the filtered QRS complex (RMS_{40}); and (3) the duration of low-amplitude signals <40 μV in the terminal filtered QRS complex (LAS_{40}). LPs were considered abnormal when two criteria (RMS_{40} < 20 μV and LAS_{40} > 38 ms) were met.[3] Despite the normalization of serum potassium level, LPs were persistently abnormal in both patients before discharge and even at the 18-month follow-up (Table 1).

DISCUSSION

In both cases, hypokalemia was clearly associated with Brugada syndrome and the occurrence of lethal events. We implanted an ICD because latent conduction delay was evident even when typical ECG patterns were masked. Abnormal LP values were persistently observed at the 18-month follow-up, irrespective of serum potassium levels.

The ECG features of Brugada syndrome are often concealed but can be unmasked or modulated by many factors.[4-7] Hypokalemia is also known to be associated with Brugada syndrome and occurrence of the polymorphic ventricular tachyarrhythmia.[1,2] In consistence with previous case reports, the Brugada ECG pattern was observed when the serum

Table 1. Serum Potassium Levels and LPs (by Signal-Averaged Electrocardiogram) of Two Cases Presenting with Brugada Syndrome and Hypokalemia-Induced Lethal Events

	Case-1		Case-2	
	Before Discharge	**After 18 Months**	**Before Discharge**	**After 18 Months**
Serum potassium level (mEq/L)	4.0	4.4	4.2	3.9
fQRS (ms)	117	119	194	175
RMS_{40} (μV)	13.3	13.8	2.4	5.5
LAS_{40} (ms)	41	40	136	116

fQRS = the filtered QRS duration; LAS_{40} = the duration of low-amplitude signals <40 μV in the terminal filtered QRS complex; RMS_{40} = the root mean square voltage of the terminal 40 ms in the filtered QRS complex.

potassium levels were 2.6 mEq/L (Case 1) and 3.0 mEq/L (Case 2), respectively. A febrile state also accentuates the Brugada ECG pattern and precipitates VF.[6] Case 2 exhibited a coved-type Brugada ECG pattern with hypokalemia and high body temperature. The characteristic ST-segment elevation was normalized with intravenous potassium infusion, even in the presence of high fever. In both cases, hypokalemia was mainly related to a Brugada ECG pattern. The cause of hypokalemia was not known and these patients had no prior drug use, and urinary potassium excretion levels and blood endocrine activity were also within the normal range.

A majority of spontaneous type 1 Brugada syndrome with a history of life-threatening events have demonstrated LPs.[3,8] Multivariate analyses revealed that the presence of LPs is an independent predictor of sudden death. LPs have also been observed in a high percentage of Brugada syndrome patients with induced VF.[9] Conduction delays, especially at the right ventricular outflow track, produce LPs in Brugada syndrome.[9] Despite the restoration of serum potassium level, LPs were persistently abnormal even at the long-term follow-up. Ventricular tissue abnormality may exist irrespective of serum potassium levels in both patients.

CONCLUSION

Although the role of hypokalemia in Brugada syndrome is not so clear and has been rarely described, in the cases presented here, LPs were obvious even at the 18-month follow-up. These cases provided further evidence of risk for the future in Brugada syndrome associated with hypokalemia. ICD implantation should be considered to prevent sudden cardiac death in these patients.

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ORIGINAL ARTICLE

Iodine-123-metaiodobenzylguanidine imaging can predict future cardiac events in heart failure patients with preserved ejection fraction

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Abstract
Objective Iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) has been used to assess the function of the cardiac sympathetic nervous system in patients with chronic heart failure (HF). The usefulness of ^{123}I-MIBG imaging for evaluating patients with heart failure with preserved ejection fraction (HFPEF) has not been established.
Methods We performed ^{123}I-MIBG scintigraphy and echocardiography and measured the plasma brain natriuretic peptide (BNP) levels of 117 consecutive HF patients (64 men, mean age 66 ± 14 years) with a left ventricular ejection fraction (LVEF) of ≥50% who were admitted to our hospital. Patients were divided into 2 groups according to the New York Heart Association (NYHA) functional class.
Results The ^{123}I-MIBG delayed heart-to-mediastinum (*H/M*) ratio was significantly lower, and the washout rate (WR) was higher in patients with HFPEF with advanced NYHA functional class (NYHA functional class I and II vs. III: 1.90 ± 0.34 vs. 1.49 ± 0.32, $p < 0.0001$; 25.9 ± 13.4 vs. 46.9 ± 16.3%, $p < 0.0001$, respectively). On the other hand, the ^{123}I-MIBG WR was not correlated with LVEF and had a weak correlation with plasma BNP levels ($R = 0.207$, $p = 0.0346$). Moreover, patients with a high ^{123}I-MIBG WR showed a poor clinical outcome ($p = 0.0033$).
Conclusions ^{123}I-MIBG imaging provides independent prognostic information in patients with HFPEF.

Keywords Cardiac imaging · Sympathetic nervous system · Washout rate · Preserved ejection fraction

Introduction

Activation of the 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, 5]. Cardiac imaging with iodine-123-metaiodobenzylguanidine (^{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 reported that ^{123}I-MIBG imaging provides powerful diagnostic and prognostic information especially in HF patients with reduced left ventricular (LV) systolic function [6–8].

Congestive HF without reduced LV systolic function is commonly referred to as HF with preserved ejection fraction (HFPEF) [9–11], and HFPEF is increasingly recognized as a common problem and has been observed in 30–50% of congestive HF patients in recent times. Although morbidity and mortality rates in patients with HFPEF are high [9, 10, 12], most of the previous studies have focused on systolic HF. The clinical usefulness of ^{123}I-MIBG scintigraphy to predict an adverse outcome has not been established yet for HFPEF. Therefore, the aim of the present study was to examine whether ^{123}I-MIBG imaging could reliably identify patients with HFPEF who are at risk for future cardiac events.

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Methods

Study subjects

We performed ^{123}I-MIBG scintigraphy and measured plasma levels of brain natriuretic peptide (BNP) in 368 consecutive patients who were admitted to our hospital for the treatment of worsening HF, the diagnosis and pathophysiologic investigations of HF, and the therapeutic evaluations of HF from April 2002 to December 2009. In addition, 117 HF patients with an LV ejection fraction (LVEF) of ≥50% [12, 13] (64 men, 53 women, mean age 66 ± 14 years) were enrolled in this study. The diagnosis of HF was made by two senior cardiologists using the generally accepted Framingham criteria and patient information, including a history of dyspnea and symptomatic exercise intolerance with signs of pulmonary congestion, peripheral edema, presence of moist rales on auscultation, or documentation of LV dysfunction by chest X-ray or echocardiography. In the present study, patients were divided according to the New York Heart Association (NYHA) functional class when ^{123}I-MIBG scintigraphy was performed. Twenty-five subjects without HF, who underwent ^{123}I-MIBG scintigraphy, served as controls. Those subjects were diagnosed as normal by physical examinations, electrocardiography, chest X-ray, and echocardiography. A written informed consent was given by all patients, and the institutional review board of our institute approved the study protocol [14–16].

No patient had clinical symptoms or signs suggestive of 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 [14, 15, 17]. Patients with renal insufficiency characterized by a serum creatinine level of >2.0 mg/dL and ischemic HF patients were excluded from the present study. Coronary arteriography was performed to diagnose ischemic HF.

^{123}I-MIBG imaging

We performed ^{123}I-MIBG imaging just before discharge (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 the patients were resting in the supine position 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, USA) as previously reported [15]. Five-minute anterior planar imaging was carried out at 30 and 240 min following ^{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- and 240-min images. The heart-to-mediastinum (*H/M*) ratios of ^{123}I-MIBG uptake at 30 min (early *H/M*) and at 240 min (delayed *H/M*) were calculated as previously reported. The washout rate (WR) from the myocardium was calculated as [(H − M) at 30 min–(H − M) at 240 min] × 100/(H − M) at 30 min (%) [8].

Echocardiography and blood examination

We performed conventional M-mode and two-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 the study subjects within 3 days of the day when ^{123}I-MIBG scintigraphy was performed. The glomerular filtration rate (GFR) was estimated from the modification of diet in renal disease formula [18].

End-points and follow-up

Patients were prospectively followed up for a mean period of 1025 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 the 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 range. Significance between the 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 of <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, NC, USA).

Results

Clinical characteristics of study subjects

Clinical characteristics, including ^{123}I-MIBG scintigraphic, biochemical, and echocardiographic findings, acquired when the patients were in a stable condition before discharge and medications of the 117 HFPEF patients and 25 control subjects enrolled in the study are shown in Table 1. There were 27 patients with NYHA functional class I; 73 patients with NYHA functional class II; and 17 patients with NYHA functional class III when ^{123}I-MIBG imaging was performed. Hypertension, hyperlipidemia, and diabetes mellitus were identified in 71 (61%), 32 (27%), and 25 (21%) patients, respectively; 27 patients (23%) were current smokers. The etiologies of HF were identified as idiopathic dilated cardiomyopathy (DCM) in 11 patients (9%), hypertensive heart disease (HHD) in 44 (38%) patients, hypertrophic cardiomyopathy (HCM) in 15 (13%) patients, arrhythmia-induced HF in 21 (18%) patients, and others in the remaining 26 patients (22%). The median plasma level of BNP was 165 pg/mL (range 61.8–344 pg/mL) in patients with HFPEF in a stable condition. Early and delayed *H/M* ratios were significantly lower and the WR was significantly higher in patients with HFPEF than in control subjects (Table 1). There were no significant differences in WR and *H/M* ratio among these cardiomyopathies; however, LVEF was significantly lower in the DCM group (54.7 ± 5.2%) and higher in the HCM group (74.5 ± 7.2%). In the HHD group, the number of patients with hypertension and diabetes mellitus was significantly larger than in the other groups.

Relationships between ^{123}I-MIBG imaging parameters and NYHA functional class

As shown in Fig. 1a, b, the delayed *H/M* ratio was significantly lower and the WR was higher in patients with HFPEF and advanced NYHA functional class (NYHA functional class I and II vs. III: 1.90 ± 0.34 vs. 1.49 ± 0.32, $p < 0.0001$; 25.9 ± 13.4 vs. 46.9 ± 16.3%, $p < 0.0001$, respectively).

Comparison of clinical characteristics of HFPEF patients between the low WR group and the high WR group

We divided the patients with HFPEF into 2 groups on the basis of the cut-off value of ^{123}I-MIBG WR (26.5%), which was calculated from the receiver-operator characteristic (ROC) curve: low WR group (<26.5%, $n = 54$) and high WR group (≥26.5%, $n = 63$). The clinical characteristics were compared between patients in the low and high ^{123}I-MIBG WR groups (Table 2). The complication of diabetes mellitus was more prevalent in the high WR group than in the low WR group. The NYHA functional class was more severe in the high WR group than in the low WR group. BNP was significantly higher and the 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 the WR was significantly higher in the patients in the high WR group than in the patients in the low WR group. Regarding the echocardiographic LVEF, there was no significant difference between the 2 groups (Table 2).

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

The ^{123}I-MIBG WR was weakly correlated with BNP ($R = 0.207$, $p = 0.0346$) by a simple linear regression analysis (Fig. 2). The 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 (0.6621 vs. 0.4946 or 0.6201), suggesting that ^{123}I-MIBG WR was superior to BNP or delayed *H/M* ratio in predicting adverse cardiac events. The sensitivity and specificity to detect future cardiac events were 69.0 and 59.2% by ^{123}I-MIBG WR, 63.6 and 63.8% by BNP, and 78.3 and 50.0% by delayed *H/M* ratio, respectively.

Prognosis of subjects and ^{123}I-MIBG WR value

There were 42 cardiac events (3 cardiac deaths and 39 rehospitalizations) during the follow-up period in all patients with HFPEF. Cumulative event-free survival curves were calculated by the Kaplan–Meier method and compared by a log-rank test (Fig. 3). The cardiac event-free rate was significantly lower in the high WR group than in the low WR group (54.0 vs. 75.9%, log-rank test $p = 0.0033$).

In the present study, if the patients with HFPEF were divided into 2 groups by the cut-off level of plasma BNP (165.3 pg/mL, from ROC curve), the cardiac event-free rate would be also significantly lower in the high plasma BNP group than in the low plasma BNP group (Kaplan–Meier analysis; log-rank test $p = 0.0188$) (data not shown).

The univariate Cox proportional hazards analysis to predict cardiac events for ^{123}I-MIBG WR and other variables is shown in Table 3. An increase of 1 SD (15.8%) in the ^{123}I-MIBG WR value was a significant variable [hazard ratio 1.881, 95% confidence interval (CI) 1.41–2.51, $p < 0.0001$]. Furthermore, for the NYHA functional class, an increase of 1 SD in the uric acid concentration, $\log_{10}$BNP, echocardiographic left atrial dimension (LAD), left ventricle end-diastolic dimension (LVEDD), and left

Table 1 Clinical characteristics of control subjects and 117 patients with heart failure

	Control $n = 25$	HFPEF $n = 117$	p value
Age (years)	57 ± 15	66 ± 14	0.0055
Gender (male/female)	12/13	64/53	NS
NYHA functional class (I/II/III)	–	27/73/17	–
Hypertension	7 (28%)	71 (61%)	0.0029
Hyperlipidemia	7 (28%)	32 (27%)	NS
Diabetes mellitus	4 (16%)	25 (21%)	NS
Current smoker	4 (16%)	27 (23%)	NS
Etiology			
Dilated cardiomyopathy	–	11 (9%)	–
Hypertensive heart disease	–	44 (38%)	–
Hypertrophic cardiomyopathy	–	15 (13%)	–
Arrhythmogenic	–	21 (18%)	–
Others	–	26 (22%)	–
Blood examination			
Sodium (mEq/L)	142 ± 2.0	141 ± 2.7	NS
Uric acid (mg/dL)	4.6 ± 1.1	6.2 ± 1.9	0.0001
Estimated GFR (mL/min/1.73 m^2)	82.6 ± 24.6	64.0 ± 22.8	0.0004
BNP (pg/mL)	22.0 (6.5–60.8)	165 (61.8–344)	<0.0001
Echocardiography			
IVSD (mm)	11.0 ± 3.6	12.3 ± 3.6	NS
LVPWD (mm)	10.4 ± 2.0	11.9 ± 2.7	0.0207
LVEDD (mm)	47 ± 5.9	48 ± 8.9	NS
LVEF (%)	69 ± 10	65 ± 9.8	NS
LAD (mm)	35 ± 6.2	44 ± 9.7	0.0003
E/A ratio	1.10 ± 0.5	1.00 ± 0.5	NS
E-wave DCT (ms)	206 ± 55	217 ± 81	NS
E/E' ratio	5.3 ± 1.4	10.4 ± 4.0	0.0200
^{123}I-MIBG imaging			
Early *H/M* ratio	2.19 ± 0.3	1.93 ± 0.3	0.0006
Delayed *H/M* ratio	2.36 ± 0.3	1.84 ± 0.4	<0.0001
WR (%)	11.8 ± 7.1	29.1 ± 15.8	<0.0001

HFPEF heart failure with preserved ejection fraction, *NYHA* New York Heart Association, *GFR* glomerular filtration rate, *BNP* brain natriuretic peptide, *IVSD* intraventricular septal dimension, *LVPWD* left ventricular posterior dimension, *LVEDD* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction, *LAD* left atrial dimension, *DCT* deceleration time, *^{123}I-MIBG* iodine-123 metaiodobenzylguanidine, *H/M* heart to mediastinum, *WR* washout rate, *NS* no significance

ventricular posterior dimension (LVPWD) 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 <0.05 were entered into the multivariate Cox proportional hazard regression analysis. The ^{123}I-MIBG WR was an independent predictor of cardiac events among those variables (Table 4).

Discussion

In the present study, by using ^{123}I-MIBG scintigraphy, we found several new factors that could predict prognosis in HFPEF patients. The ^{123}I-MIBG WR and delayed *H/M* ratio could classify patients with HFPEF by the NYHA functional class. (1) The ^{123}I-MIBG WR was significantly higher and the delayed *H/M* ratio was lower in patients with HFPEF in increased with advancing NYHA functional class. (2) In patients with HFPEF, the 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, although multivariate analysis showed that $\log_{10}$BNP and LVEF were not independent predictors, ^{123}I-MIBG WR was an independent predictor for subsequent cardiac events. Furthermore, ^{123}I-MIBG WR was not correlated with LVEF (data not shown) and showed an extremely weak correlation with the 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 [6–8]. However, the clinical usefulness of ^{123}I-MIBG scintigraphy to evaluate a severity of the patient with HFPEF has not been established yet. In the present study, we found that

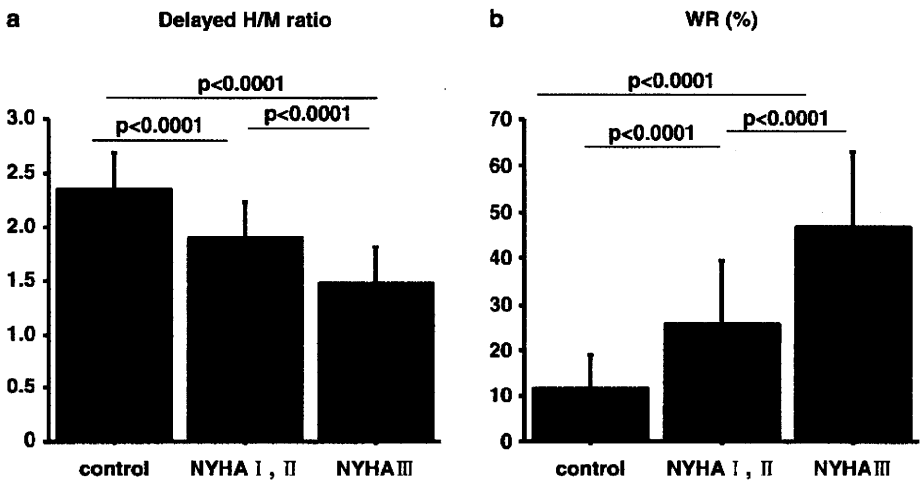

Fig. 1 Delayed *H/M* ratio of ^{123}I-MIBG (**a**) and washout rate (**b**) in the study population

delayed *H/M* ratio was decreased and ^{123}I-MIBG WR was increased as NYHA functional class was increased. These findings implicated an important relationship between cardiac sympathetic activation and the pathogenesis of HFPEF. Grassi et al. [19] have reported that the marked sympathetic activation in patients with hypertension depended on an impairment of the arterial baroreflex. It was reported that the serum NE level was similar in patients with diastolic HF and systolic HF and was markedly increased as compared to normal subjects [20]. Moreover, there are several studies using animal models, which implied the importance of NE in the development of diastolic dysfunction [21–23].

It is suggested that the renin–angiotensin system (RAS) is associated with cardiac sympathetic activation. In humans, inhibition of RAS controls hypertension and regresses LV hypertrophy. In animal models of LV hypertrophy, RAS activity is upregulated and the increased activity of angiotensin-converting enzyme in the myocardium impairs its diastolic function [20, 24]. It was reported that activation of RAS was associated with NE release from cardiac sympathetic nerve endings in HF [25]. Therefore, there is a possibility that the ^{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 well as in those with reduced LV systolic function. From the results of the present study, we expect that the ^{123}I-MIBG findings may be an indication for the treatment of HFPEF. Several studies have reported on the relationships between the cardiac nervous system and HFPEF [26–28]. One of these studies, however, was conducted in a smaller population, one of them was a report of patients with HCM, and one of them was a report on the improvement in ^{123}I-MIBG findings at 6 months after candesartan treatment. There are no reports in which investigators followed future cardiac events by ^{123}I-MIBG scintigraphy in more than 100 patients with HFPEF.

It is of special clinical significance that ^{123}I-MIBG WR was an independent predictor for future cardiac events in the absence of a correlation with LVEF in patients with HFPEF in the present study. It has been recognized that LVEF is one of the acceptable indicators of the prognosis in HF patients with reduced LV systolic function. However, because LVEF is preserved in patients with HFPEF, it is possible that LVEF could not be a useful predictor for future cardiac events in HFPEF patients.

Grewal et al. [29] 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. In the present study, the cardiac event-free rate was also significantly lower in the high plasma BNP group than in the low plasma BNP group (Kaplan–Meier analysis, data not shown). However, in the multivariate Cox proportional hazards analysis, $\log_{10}$BNP was not an independent predictor for future cardiac events (Table 4). One possible explanation is that the impaired relaxation and/or compliance per se is not sufficient to trigger cardiac BNP secretion and BNP might be a suboptimal marker of diastolic dysfunction [30]. As for the extremely weak relationship between plasma BNP level and ^{123}I-MIBG WR, the plasma BNP level is known to be secondarily increased because of the LV overload as is the case in congestive HF [31]. At the same time, the ^{123}I-MIBG scintigraphic findings directly reflect cardiac sympathetic nerve activity and ongoing myocardial damage [1, 2, 6, 7]. In the above-mentioned conditions, it appeared that ^{123}I-MIBG WR—but not plasma levels of BNP—was an independent predictor for future cardiac events in the multivariate analysis.

On the basis of these findings, we propose that the reduction of rising cardiac sympathetic nerve activity by using β-blockers is a beneficial therapy in patients with HFPEF. Further randomized trials with or without

Table 2 Comparisons of clinical characteristics between patients with low and high values of ^{123}I-MIBG washout rate

	Low WR (<26.5%) group $n = 54$	High WR (≥26.5%) group $n = 63$	p value
Age (years)	61 ± 14	70 ± 13	0.0004
Gender (male/female)	30/24	34/29	NS
NYHA functional class (I/II/III)	23/30/1	4/43/16	0.0003
Hypertension	30 (56%)	41 (65%)	NS
Hyperlipidemia	14 (26%)	18 (29%)	NS
Diabetes mellitus	5 (9%)	20 (32%)	0.0031
Current smoker	12 (22%)	15 (24%)	NS
Etiology			
Dilated cardiomyopathy	5 (11%)	6 (8%)	NS
Hypertensive heart disease	16 (30%)	28 (44%)	NS
Hypertrophic cardiomyopathy	10 (19%)	5 (8%)	NS
Arrhythmogenic	12 (22%)	9 (14%)	NS
Others	10 (19%)	16 (25%)	NS
Blood examination			
Sodium (mEq/L)	141 ± 2.4	141 ± 3.0	NS
Uric acid (mg/dL)	6.1 ± 1.7	6.4 ± 2.1	NS
Estimated GFR (mL/min/1.73 m^2)	69.4 ± 24.9	59.5 ± 20.0	0.0182
BNP (pg/mL)	92.0 (41.7–183)	229 (118–440)	0.0003
Echocardiography			
IVSD (mm)	11.7 ± 3.3	12.8 ± 3.9	NS
LVPWD (mm)	11.3 ± 2.4	12.5 ± 2.9	0.0229
LVEDD (mm)	48 ± 8.9	49 ± 9.0	NS
LVEF (%)	65 ± 9.3	66 ± 10	NS
LAD (mm)	43 ± 8.1	44 ± 11	NS
E/A ratio	1.17 ± 0.7	0.88 ± 0.4	0.0178
E-wave DCT (ms)	215 ± 73	219 ± 89	NS
E/E' ratio	10.6 ± 3.0	10.3 ± 4.4	NS
^{123}I-MIBG imaging			
Early *H/M* ratio	2.01 ± 0.3	1.87 ± 0.4	0.0222
Delayed *H/M* ratio	2.04 ± 0.3	1.67 ± 0.3	<0.0001
WR (%)	16.3 ± 8.3	40.1 ± 11.8	<0.0001
Medications			
ACE inhibitors and/or ARBs	28 (52%)	47 (75%)	0.0105
β-Blockers	24 (44%)	32 (51%)	NS
Ca-channel blockers	15 (28%)	22 (35%)	NS
Loop diuretics	23 (43%)	35 (56%)	NS
Spironolactone	5 (9%)	16 (25%)	0.0234
Statins	8 (15%)	15 (24%)	NS
Digoxin	9 (17%)	13 (21%)	NS

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker

Other abbreviations see in Table 1

β-blockers and with a follow-up that evaluates future cardiac events in HFPEF patients are required.

Study limitations

Several potential limitations should be considered with respect to our findings. We defined that study subjects were HF patients with an LVEF of ≥50%. Therefore, a number of them could have been diastolic HF patients, but we did not get sufficient diastolic parameters by echocardiography, for instance, the early diastolic transmitral velocity-to-early diastolic tissue velocity ratio (*E/E'* ratio) was measured in only 28 HFPEF patients in the present study. We measured the early-to-late diastolic transmitral velocity

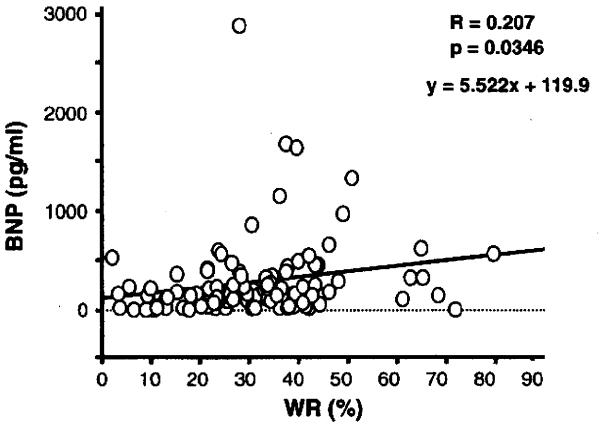

Fig. 2 Relationships between the washout rate of ^{123}I-MIBG and the plasma level of BNP

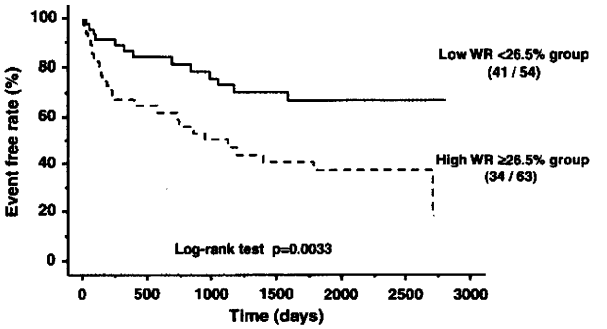

Fig. 3 Washout rate of ^{123}I-MIBG and all cardiac events of patients with heart failure with preserved ejection fraction. Survival curves were created by the Kaplan–Meier method and analyzed by the log-rank test

ratio (*E/A* ratio) and the E-wave deceleration time by echocardiography, which might require some variation in the treatments for congestive HF and therefore could not be powerful indicators of diastolic HF [9, 32].

In the present study, there were some variations in the etiologies of HFPEF as compared to other studies. Tsuchihashi-Makaya et al. [12] recently showed the etiologies of 429 Japanese patients with HFPEF in their report. They reported that the prevalence of HFPEF was 26% and the etiologies of HFPEF were identified as idiopathic DCM in 5%, ischemic HF in 25%, hypertensive HF in 44%, HCM in 10%, and others in 36%. In the present study, the number of patients with DCM was slightly larger and that of hypertensive HF was slightly smaller than in their study. One possible explanation is that our study was conducted at a single university hospital and the number of patients with pure HHD was small. It was, however, important and interesting that we assessed future cardiac events in patients with HFPEF for approximately 3 years.

Table 3 Results of the univariate Cox proportional hazard analysis

Variables	HR	95% CI of HR	*p* value
Age (per 1 year increase)	1.022	0.997–1.048	NS
Gender	1.245	0.679–2.283	NS
NYHA functional class I, II versus III	3.414	1.724–6.760	0.0004
Diabetes mellitus	0.771	0.387–1.535	NS
Hypertensive heart disease	1.255	0.652–2.416	NS
Arrhythmogenic	2.474	0.967–6.329	NS
Sodium[a]	0.860	0.615–1.203	NS
Uric acid[a]	1.440	1.040–1.991	0.0278
Estimated GFR[a]	0.778	0.575–1.100	NS
Log_{10}BNP[a]	1.593	1.155–2.200	0.0045
LAD[a]	1.825	1.383–2.412	<0.0001
LVEDD[a]	1.365	1.018–1.826	0.0398
LVEF[a]	1.030	0.757–1.414	NS
IVSD[a]	1.130	0.857–1.485	NS
LVPWD[a]	1.328	1.014–1.734	0.0391
E/E' ratio[a]	1.927	0.941–3.930	NS
WR[a]	1.881	1.410–2.511	<0.0001

HR hazard ratio, *CI* confidence interval. Other abbreviations see in Table 1

[a] Per 1 SD increase

Table 4 Results of the multivariate Cox proportional hazards analysis

Variables	HR	95% CI of HR	*p* value
NYHA functional class I, II versus III	1.692	0.552–5.184	NS
Uric acid[a]	1.191	0.822–1.629	NS
Log_{10}BNP[a]	1.010	0.638–1.599	NS
LVPWD[a]	1.409	0.995–2.001	NS
LAD[a]	1.287	0.953–1.760	NS
LVEDD[a]	1.415	0.982–2.017	NS
WR[a]	1.581	1.016–2.474	0.0435

Other abbreviations see in Tables 1 and 3

[a] Per 1 SD increase

Conclusions

The ^{123}I-MIBG WR was increased and the 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.

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Serum YKL-40 Predicts Adverse Clinical Outcomes in Patients With Chronic Heart Failure

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ABSTRACT

Background: Human cartilage glycoprotein-39 (YKL-40), a novel inflammatory marker, is secreted into circulation by macrophages, neutrophils, chondrocytes, vascular smooth muscle cells and cancer cells. Circulating levels of YKL-40 are related to the degree of inflammation, tissue remodeling, fibrosis, and cancer progression.

Methods and Results: We examined serum YKL-40 levels in 121 patients with chronic heart failure (CHF) and 39 control subjects. The patients were followed up to register cardiac events for a mean of 720 days. Serum YKL-40 levels were measured by sandwich enzyme-linked immunoassay. Serum YKL-40 was significantly higher in New York Heart Association (NYHA) Class III/IV patients than control subjects and NYHA Class I/II patients ($P < .0001$). Serum YKL-40 was also higher in patients with cardiac events than in event-free patients ($P = .0023$). Cutoff value of YKL-40 was determined by receiver operating characteristic curve analysis. Kaplan-Meier analysis demonstrated that high level of YKL-40 was associated with higher rates of cardiac events than low levels of YKL-40 ($P = .003$). The multivariate Cox hazard analysis demonstrated that serum YKL-40 level was an independent prognostic factor of cardiac events (hazard ratio 2.085, 95% confidence interval 1.233-3.499, $P < .0048$).

Conclusions: Serum YKL-40, a new marker of inflammation, was increased in CHF, and YKL-40 detected high risk patients for adverse outcomes in CHF. (*J Cardiac Fail 2010;16:873–879*)

Key Words: Human cartilage glycoprotein 39, inflammation, prognosis.

Chronic heart failure (CHF) is characterized by a complex syndrome of hemodynamic, neurohormonal, and metabolic abnormalities with high mortality.[1,2] In the CHF state, activation of the inflammatory system occurs, resulting in the production and release of proinflammatory cytokines, activation of the complement system, and production of autoantibodies and other substances into the bloodstream.[1,3] Besides immune cells, fibroblasts, endothelial cells, vascular smooth muscle cells, and cardiac myocytes are capable of producing various cytokines and chemokines under hypoxic conditions and mechanical stresses. Several studies have reported that the increased plasma or serum levels of inflammatory cytokines and chemokines are significantly correlated with deterioration of functional cardiac performance.[4–6] Moreover, these inflammatory mediators provide important prognostic information in CHF patients.[4,5,7]

YKL-40, also named as human cartilage glycoprotein 39, is a member of the mammalian chitinase-like proteins, 40 kDa plasma protein without chitinase activity.[8,9] YKL-40 is secreted by activated macrophages and macrophages during late stage of differentiation,[9,10] neutrophils,[11] chondrocytes,[12] vascular smooth muscle cells,[13] and cancer cells.[14] Circulating levels of YKL-40 are found to be related to the degree of inflammation, pathological tissue remodeling, and ongoing fibrosis. High serum YKL-40 level is associated with poor prognosis in patients with purulent meningitis[15] and *Streptococcus pneumoniae* bacteremia[16] as well as in patients with alcoholic liver fibrosis.[17] Several studies have demonstrated the association of YKL-40 with atherosclerosis.[18,19] Boot et al have shown a strong induction of YKL-40 mRNA expression in subpopulations of macrophages associated with

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human atherogenesis.[20] Kucur et al have revealed a significant association between the levels of YKL-40 and the extent of coronary artery disease defined by the numbers of stenosed vessels.[21] In addition, elevated levels of plasma YKL-40 have been reported in patients with type II diabetes mellitus and related with insulin resistance.[22]

However, the relationship between serum YKL-40 levels and severity and prognosis of CHF has not been previously examined. Therefore, the aims of this study were to examine serum levels of YKL-40 in CHF patients and evaluate the predictive capability of serum YKL-40 for future clinical outcomes in patients with CHF.

Methods

Study Subjects

We examined 121 consecutive patients who admitted to the Yamagata University Hospital for evaluation or treatment of CHF between 2004 and 2007. The clinical diagnosis of heart failure was based on the medical history, physical examination, documentation of left ventricular enlargement or dysfunction by chest x-ray, echocardiography, or left ventriculography. Exclusion criteria were acute coronary syndrome within 3 months preceding admission, inflammatory diseases, renal failure (defined as a serum creatinine level > 2.0 mg/dL), and malignant diseases. There were 68 males and 53 females, mean age 69 ± 13 years. Baseline clinical characteristics of study subjects are shown in Table 1. The etiologies of CHF were recognized as dilated cardiomyopathy in 36 (30%), ischemic heart disease in 18 (15%), valvular heart disease in 25 (21%), hypertensive heart disease in 10 (8%), and others in the remaining 32 (26%) patients. There were 62 patients (51%) in New York Heart Association (NYHA) Class I/II and 59 patients (49%) in Class III/IV. Hypertension, diabetes mellitus, and hyperlipidemia were identified in 56 (46%), 31 (26%), and 21 (17%) patients, respectively. Hypertension was defined as a diastolic blood pressure of at least 90 mm Hg or a systolic blood pressure of at least 140 mm Hg, or by the current use of antihypertensive drugs. Diabetes mellitus was defined by medical records. Hyperlipidemia was defined as plasma total cholesterol level of >220 mg/dL, plasma triglyceride level of >150 mg/dL, a decreased high-density lipoprotein level of ≤40 mg/dL, or current use of lipid-lowering drugs. Concurrent medications in CHF, either alone or in combination, included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n = 84), aldosterone receptor blockers (n = 37), β-blockers (n = 32), calcium channel blockers (n = 24), and loop diuretics (n = 73).

The study group was compared with a control group of 39 age-matched subjects (mean age 67 ± 9 years, 21 males and 18 females). Those subjects were hospitalized during the same period with the suspicion of coronary artery disease. Coronary arteriography revealed no coronary artery stenoses in the control group.

All procedures were in accordance with ethical standards as formulated in the Helsinki Declaration of 1975 (revised 1983). The research protocol was approved by the institution's ethical committee, and a written informed consent was obtained from all subjects.

End Points and Follow-up

Patients were followed (median follow-up period of 755 days, range 17-1452 days) after discharge until the occurrence of cardiac events. There were no patients lost in follow-up period.

Table 1. Clinical Characteristics of Control Subjects and Patients with CHF

	Control n = 39	CHF n = 121	*P* Value
Age (y)	67 ± 9	69 ± 13	.4205
Sex (male/female)	21/18	68/53	.7971
NYHA functional class			
I/II		62 (51%)	
III/IV		59 (49%)	
Hypertension	24 (62%)	56 (46%)	.1165
Diabetes mellitus	5 (13%)	31 (26%)	.0874
Hyperlipidemia	22 (56%)	21 (17%)	<.0001
Etiology of chronic heart failure			
Dilated cardiomyopathy		36 (30%)	
Ischemic heart disease		18 (15%)	
Valvular heart disease		25 (21%)	
Hypertensive heart disease		10 (8%)	
Others		32 (26%)	
Echocardiography			
LAD (mm)	37.2 ± 6.7	45.2 ± 10.0	<.0001
LVEDD (mm)	46.5 ± 6.1	55.1 ± 10.0	<.0001
LVEF (%)	69.5 ± 8.0	46.6 ± 17.4	<.0001
Blood examination			
BNP (pg/mL)	65.7 ± 95.0	613.4 ± 658.6	<.0001
Serum creatinine (mg/dL)	0.74 ± 0.20	0.97 ± 0.51	.0014
Estimated GFR (mL/min per 1.73m^2)	77.8 ± 19.3	64 ± 23.8	.0012
Uric acid (mg/dL)	5.5 ± 1.7	6.9 ± 5.8	.0493
Na (mEq/L)	142.3 ± 2.4	140.6 ± 3.1	.0908
hs-CRP (mg/dL)	0.13 ± 0.19	1.32 ± 2.45	<.0001
YKL-40 (ng/mL)	163 ± 77	205 ± 105	.0216
Pharmacotherapy			
ACE inhibitors/ARBs	18 (46%)	84 (69%)	.0086
β-blockers	4 (10%)	32 (27%)	.0352
Calcium channel blockers	22 (56%)	24 (20%)	<.0001
Loop diuretics		73 (60%)	<.0001
Spironolactone		37 (30%)	<.0001
Digitalis		38 (31%)	<.0001

CHF, chronic heart failure; NYHA, New York Heart Association; LAD, left atrial dimension; LVEDD, left ventricular dimension at end diastole; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; GFR, glomerular filtration rate; hs-CRP, high sensitive C-reactive protein, ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Events were adjudicated using medical records, autopsy reports, death certificates, and witness statements. The study end points were cardiac death, included sudden cardiac death and death from worsening CHF, and rehospitalization from progressive heart failure.[7] Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was established by the attending physician.

YKL-40 Assay

Venous blood samples were obtained at admission and were immediately centrifuged at 2500*g* for 15 minutes at 4°C. All serum samples were frozen and stored at −80°C until assay. Serum YKL-40 concentrations were determined by a commercial 2-site sandwich type enzyme-linked immunosorbent assay (Quidel Corporation, Santa Clara, CA) according to the manufacturer's instruction.

Statistical Analysis

Results are presented as means ± SD for continuous variables and as numbers and percentages for categorical variables. Student's t test was used to compare continuous variables. If data were not distributed normally, the Mann-Whitney U test was

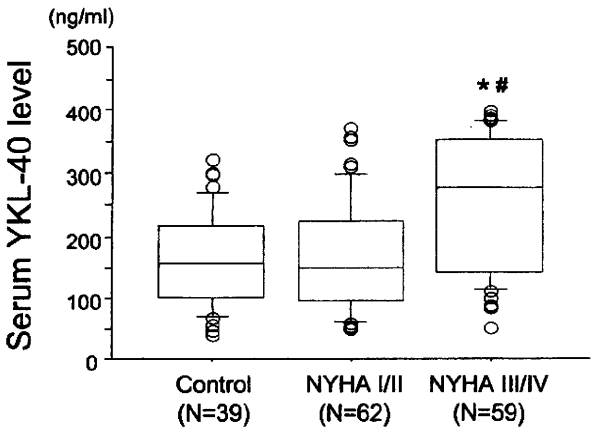

Fig. 1. Association between serum levels of YKL-40 and severity of NYHA functional class. *P < .0001 vs. control and #P < .0001 vs. NYHA Class I/II.

used. Chi-square test was used to compare categorical variables. A P value less than .05 was considered statistically significant. The Cox proportional hazard regression model was used to determine which variables were associated with cardiac events. Significant variables selected in the univariate analysis were entered into the multivariate analysis. The cardiac-event-free rates were calculated using the Kaplan-Meier method, and the log-rank test was used to compare the results. The receiver operating characteristic (ROC) curve was constructed to evaluate the cutoff value and area under the ROC curve. All analyses were performed using a standard statistical program package (Stat View, version 5.0, SAS Institute Inc, Cary, NC).

Results

Serum YKL-40 Levels in Patients with CHF

Baseline characteristics of all study subjects are listed in Table 1. Serum YKL-40 levels were significantly higher in patients with CHF than in control subjects (P = .0216). Moreover, as shown in Fig. 1, the concentration of serum YKL-40 level increased with advancing NYHA functional class and was significantly higher in severe CHF patients with NYHA Class III/IV than in control subjects (P < .0001) and mild CHF patients with NYHA Class I/II (P < .0001).

In CHF patients, serum YKL-40 levels were higher in hypertensive patients than in nonhypertensive patients (226 ± 110 ng/mL vs. 183±95 ng/mL, P = .0248). Serum YKL-40 level was not different between diabetic and nondiabetic patients and between patients with and without hyperlipidemia. A simple linear regression analysis showed that serum YKL-40 levels were positively correlated with plasma B-type natriuretic peptide (BNP) levels (P = .0045, r = 0.258), but not with left ventricular ejection fraction, left ventricular end-diastolic dimension, or high sensitive C-reactive protein (hs-CRP).

Serum YKL-40 and Cardiac Event Rates

There were 45 cardiac events including 17 cardiac deaths and 28 rehospitalizations from progressive heart failure during follow-up periods among all CHF patients. We compared clinical characteristics between patients with and without cardiac events in Table 2. Patients with cardiac events were older (P = .0471) and had significantly higher levels of YKL-40 (P = .0023), BNP (P < .0001), serum creatinine (P = .0307), uric acid (P = .0067), hs-CRP (P = .012), and left atrial dimension (P < .0001) than event-free patients. Patients with cardiac events had significantly lower levels of Na (P = .0076) and estimated glomerular filtration rate (GFR) (P = .013) than event-free patients.

We divided all CHF patients into 4 groups according to serum YKL-40 levels: 1st quartile (<123 ng/mL, n = 31), 2nd quartile (124-180 ng/mL, n = 30), 3rd quartile (181-293 ng/mL, n = 30), and 4th quartile (>293 ng/mL, n = 30). As shown in Fig. 2, the highest 4th quartile of YKL-40 was associated with the highest risk of all cardiac events (3.38-fold compared with the 1st quartile, P < .01).

ROC curve for serum YKL-40 concentrations in prediction of cardiac events is shown in Fig. 3. At the 292 ng/mL cutoff for serum YKL-40, sensitivity was 74%, and specificity was 59% to predict cardiac events.

CHF patients were divided into 2 groups based on this cutoff level (high YKL-40 group ≥292 ng/mL, n = 89; low YKL-40 group <292 ng/mL, n = 32), and clinical characteristics were compared between the 2 groups as shown in Table 3. In the high YKL-40 group, the patients were older (P = .0024) and had more severe NYHA functional class (P = .0001), higher levels of plasma BNP (P = .0006), serum creatinine (P = .0253), and

Table 2. Comparisons of Clinical Characteristics between Patients with Cardiac Events and Event-free

	Events (−) N=76	Events (+) N=45	P value
Age (Y)	67 ± 14	72 ± 13	0.0471
Sex (male/female)	40/36	28/17	0.3041
NYHA functional class			
NYHA I/II	49 (65%)	13 (29%)	
NYHA III/IV	27 (35%)	32 (71%)	0.0002
Hypertension	38 (50%)	18 (40%)	0.3033
Diabetes mellitus	20 (27%)	11 (24%)	0.8415
Hyperlipidemia	14 (18%)	7 (16%)	0.7033
Etiology of chronic heart failure			
Dilated cardiomyopathy	21 (28%)	15 (33%)	
Ischemic heart disease	13 (17%)	5 (11%)	
Valvular heart disease	16 (21%)	9 (20%)	
Hypertensive heart disease	5 (6%)	5 (11%)	
Others	21 (28%)	11 (25%)	0.7692
Echocardiography			
LAD (mm)	42.3 ± 7.6	50.7 ± 11.6	<0.0001
LVEDD (mm)	54.0 ± 8.7	57.4 ± 12.0	0.0905
LVEF (%)	44 ± 18	48 ± 17	0.3390
Blood examination			
BNP (pg/mL)	453 ± 605	890 ± 662	<0.0001
Serum creatinine (mg/dL)	0.91 ± 0.51	1.06 ± 0.50	0.0307
Estimated GFR (mL/min per 1.73m^2)	71 ± 23	61 ± 23	0.0130
Uric acid (mg/dL)	6.7 ± 7.2	7.2 ± 2.5	0.0067
Na (mEq/l)	141.1 ± 2.5	139.6 ± 3.7	0.0076
hs-CRP (mg/dL)	1.1 ± 2.2	1.8 ± 2.7	0.0120
YKL-40 (ng/mL)	183 ± 95	243 ± 110	0.0023

Abbreviations as in Table 1.

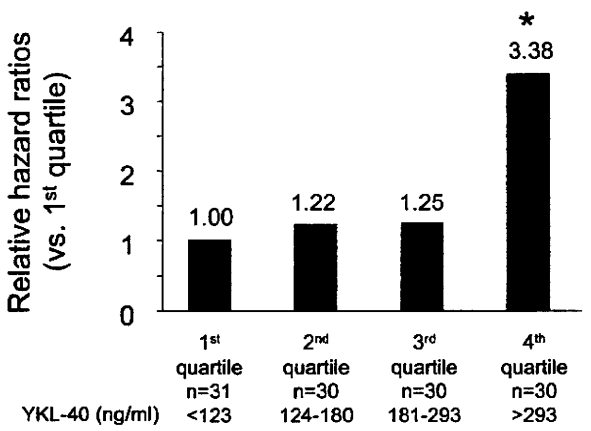

Fig. 2. Comparisons of hazard ratios relative to the 1st quartile for cardiac events. *$P < .01$ vs. 1st quartile.

hs-CRP ($P = .0015$). Cardiac events were more frequently occurred in high YKL-40 group than in low YKL-40 group (59% vs. 29%, $P = .0025$). As shown in Fig. 4, Kaplan-Meier survival curves demonstrated that event free rate was significantly lower in high YKL-40 group than low YKL-40 group ($P = .0003$ by a log-rank test).

The Prognostic Value of Serum YKL-40 for Future Cardiac Events

The ability of variables to predict cardiac events was examined by the univariate and multivariate Cox proportional hazard analysis. In the univariate analysis, serum YKL-40 levels were associated with cardiac death and rehospitalization (per 1 SD increase, hazard ratio 1.695, 95% confidence interval 1.260-2.280, $P = .0005$), as shown in Table 4. Furthermore, the univariate analysis revealed significant association of age, NYHA functional class, left atrial dimension, BNP, serum creatinine, Na, and estimated GFR with cardiac events. Those variables with P value less than .05 by the univariate analysis were entered into the multivariate Cox hazard regression model. As shown in Table 5, left atrial dimension, BNP, estimated GFR, Na, and YKL-40 were independent predictors for cardiac events in patients with CHF.

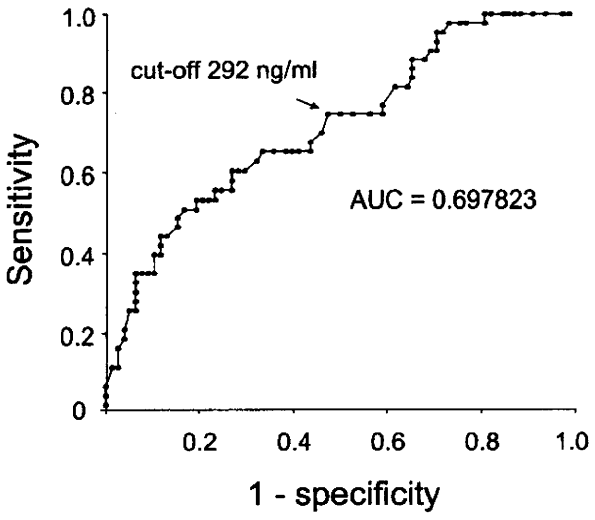

Fig. 3. Receiver operated characteristic (ROC) curve for YKL-40. AUC, area under the ROC curve.

Table 3. Comparisons of Clinical Characteristics between Patients with Low and High YKL-40 Levels

	Low YKL-40 < 292ng/ml N=89	High YKL-40 ≥ 292ng/ml N=32	*P* value
Cardiac events	26 (29%)	19 (59%)	0.0025
Cardiac death	12 (14%)	5 (17%)	0.7649
Age (Y)	67 ± 14	75 ± 10	0.9945
Sex (male/female)	50/39	18/14	0.9945
NYHA functional class			
NYHA I/II	55 (62%)	7 (22%)	
NYHA III/IV	34 (38%)	25 (78%)	0.0001
Hypertension	37 (42%)	19 (59%)	0.6491
Diabetes mellitus	26 (29%)	5 (16%)	0.1433
Hyperlipidemia	17 (19%)	4 (13%)	0.4204
Etiology of chronic heart failure			
Dilated cardiomyopathy	26 (29%)	10 (31%)	
Ischemic heart disease	14 (16%)	4 (12%)	
Valvular heart disease	18 (20%)	7 (22%)	
Hypertensive heart disease	5 (6%)	5 (16%)	
Others	26 (29%)	6 (19%)	0.3986
Echocardiography			
LAD (mm)	44.8 ± 9.9	46.2 ± 10.2	0.5514
LVEDD (mm)	55.7 ± 10.2	53.7 ± 9.6	0.3997
LVEF (%)	46.8 ± 17.8	46 ± 17	0.8210
Blood examination			
BNP (pg/mL)	494 ± 580	942 ± 753	0.0006
Serum creatinine (mg/dL)	0.95 ± 0.56	1.02 ± 0.34	0.0253
Estimated GFR (mL/min per 1.73m^2)	65 ± 24	63 ± 22	0.7474
Uric acid(mg/dL)	6.2 ± 2.1	8.7 ± 10.5	0.1657
Na (mEq/l)	141 ± 3	140 ± 3	0.3057
hs-CRP (mg/dL)	0.98 ± 1.7	2.18 ± 3.6	0.0015

Abbreviations as in Table 1.

Discussion

In this study, we demonstrated that serum YKL-40 levels were elevated in severe CHF patients with NYHA functional Class III/IV. The patients with adverse events had significantly higher serum YKL-40 levels than event-free ones, and higher levels of YKL-40 were associated with a higher incidence of cardiac events. Moreover, YKL-40 was an independent prognostic factor for cardiac events by the multivariate Cox proportional hazard analysis.

CHF is considered as a condition characterized not only by hemodynamic and metabolic disorders, but also in part by immune activation and inflammation.[1,23–25] Patients with CHF exhibit elevated levels of inflammatory and anti-inflammatory cytokines.[4,5,26] The mechanism by which serum YKL-40 is increased in patients with CHF is not fully understood. YKL-40 has been regarded as an acute phase protein, because its serum concentration increases by more than 25% after an inflammatory stimulus in patients with *Streptococcus pneumoniae* pneumonia,[16] active rheumatoid arthritis,[10] and osteoarthritis.[27] In human endotoxemia, which is accompanied by increased tumor

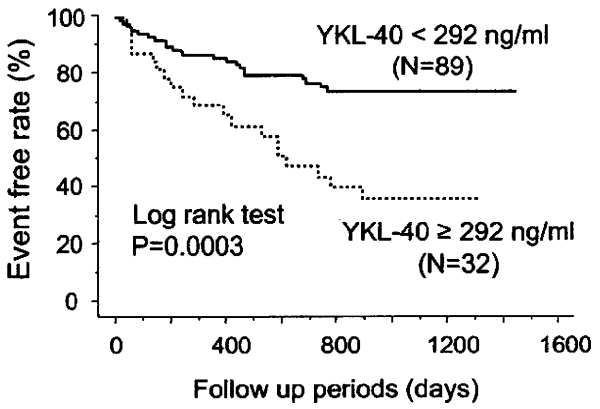

Fig. 4. Kaplan-Meier survival analysis between high and low serum levels of YKL-40 in patients with CHF. Event free rate was significantly lower in high YKL-40 group.

necrosis factor-α and interleukin-6 levels, plasma YKL-40 level is increased.[28] Interleukin-6 is the regulator of acute phase protein synthesis including CRP in response to inflammatory signals, and has been implicated in the pathogenesis and clinical course of atherosclerotic vascular disease and heart failure. Relationships between serum YKL-40 and CRP levels and disease activity in patients with rheumatoid arthritis, inflammatory bowel disease, and giant cells arteritis have been found.[27] In the present study, we demonstrated elevated hs-CRP levels in patients with CHF (Table 1). Although hs-CRP levels were significantly higher in high YKL-40 group than in low YKL-40 group (Table 3) and in patients with cardiac events than in event-free patients (Table 2), there was no correlation between levels of YKL-40 and hs-CRP. Furthermore, hs-CRP was not an independent prognostic factor for cardiac events in CHF patients in this study. Although YKL-40 has been connected to inflammation, its role in inflammation *per se* has not been clearly elucidated. YKL-40 is secreted by inflammatory cells and exerts its role as a growth factor for several cell types including fibroblasts resulting in cell

Table 4. Univariate Cox Proportional Hazard Analysis

Variables	Hazard ratio	95% CI	*P* value
Age	1.028	1.001–1.056	0.0434
Male	1.493	0.790–2.820	0.2172
NYHA class	1.279	1.798–7.179	0.0003
Hypertension	1.578	0.837–2.973	0.1584
Diabetes mellitus	1.144	0.559–2.343	0.7127
Hyperlipidemia	1.050	0.464–2.373	0.9075
LAD (per 1 SD increase)	1.954	1.438–2.641	<0.0001
LVEDD (per 1 SD increase)	1.391	0.980–1.967	0.0631
LVEF (per 1 SD increase)	1.254	0.569–1.149	0.2252
BNP (per 1 SD increase)	1.932	1.000–1.931	<0.0001
Creatinine (per 1 SD increase)	1.228	1.004–1.502	0.0457
Estimated GFR (per 1 SD increase)	1.572	1.153–2.166	0.0216
Uric acid (per 1 SD increase)	1.047	0.848–1.298	0.6566
Na (per 1 SD decrease)	1.774	0.403–0.777	0.0005
hs-CRP (per 1 SD increase)	1.161	0.882–1.528	0.2889
YKL-40 (per 1 SD increase)	1.695	1.260–2.280	0.0005

Abbreviations as in Table 1.

Table 5. Multivariate Cox Proportional Hazard Analysis

Variables	Hazard ratio	95% CI	*P*
Age	0.988	0.959–1.018	0.4968
NYHA class	1.074	0.375–3.081	0.5567
LAD (per 1 SD increase)	2.034	1.397–2.970	0.0002
BNP (per 1 SD increase)	1.932	1.000–1.931	0.0002
Creatinine (per 1 SD increase)	1.051	0.711–1.274	0.7398
Estimated GFR (per 1 SD increase)	1.857	1.209–2.787	0.0050
Na (per 1 SD decrease)	1.774	0.363–0.815	0.0032
YKL-40 (per 1 SD increase)	2.085	1.233–3.499	0.0048

Abbreviations as in Table 1.

proliferation, differentiation and tissue remodeling.[29,30] Moreover, YKL-40 is also involved in endothelial dysfunction which aggravates vascular heart disease.

Serum concentrations of YKL-40 have recently been found to be elevated in patients with coronary artery disease. Kucur et al demonstrated connection between serum YKL-40 levels and degree of coronary artery disease defined by the numbers of diseased vessels.[21] Nojgaard et al reported transient increase of serum YKL-40 levels in patients with acute myocardial infarction.[31] In the present study, patients with acute coronary syndrome within 3 months were excluded, and ischemic heart disease was recognized as etiology of CHF in only 15% of patients and there were no differences in serum YKL-40 levels between patients with and without ischemic heart disease.

YKL-40 has been recently shown to be correlated with insulin resistance and is elevated in patients with type 2 diabetes.[18,22] In our study, 31 (26%) patients had diabetes mellitus, but there were no differences in YKL-40 levels in patients with and without diabetes mellitus. The discrepancy with the previous report by Rathcke at al[18,22] can be explained by the fact that in that study all anti-hyperglycemic medications were withdrawn 2 weeks prior to the study, presumably resulting in higher blood glucose levels and subclinical diabetic decompensation.

Interestingly, serum YKL-40 levels were significantly higher in CHF patients with hypertension than normotensive CHF patients. In all subjects including both control and CHF patients, this differences was not significant (P = .0525). In the present study, hypertensive heart disease as etiology of CHF was detected in 8%, and hypertension were identified in 46% of patients. The Framingham heart study confirmed that arterial hypertension is a major attributable risk factor for CHF. Moreover, hypertension is a leading contributor to the growing burden of CHF.[32] In addition, hypertension is known to be one of the most important risk factors for atherosclerosis and may contribute to the development and progression of atherosclerotic lesions in arterial blood vessels,[19,21] which also may be connected with elevating of YKL-40 levels.

Serum YKL-40 levels were positively correlated with BNP (P = .0045, r = 0.258). BNP is a useful marker for diagnosis of impaired ventricular function, assessing risk and predicting the outcome in patients with CHF.[33] Our study suggests that YKL-40 may be a novel marker in addition

to a prognostic model including BNP, renal dysfunction with estimated GFR, and severity of heart failure symptoms.

Functional role of YKL-40 in CHF is not clear. Also, the biological function of YKL-40 is not yet known in detail. YKL-40 protein expression has been detected by immunohistochemistry in developing rat hearts.[34] It has been reported that YKL-40 can counteract the inflammatory response to tumor necrosis factor-α and interleukin-1 by phosphorylation of Akt, thus attenuating apoptosis.[35] Besides binding to collagen types I, II, and III,[36] YKL-40 may play a role in tissue remodeling through protecting extracellular matrix in inflammatory milieu.

YKL-40 might be a potential target for therapy of CHF. Because serum levels of YKL-40 in healthy subjects is very low, YKL-40 inhibition does not seem to bear any major threat to patients. To our knowledge, no YKL-40 inhibitors are available. Theoretically, there are several approaches to design such substances. Small molecule inhibitors targeting YKL-40 itself or its receptors (if discovered) are most promising in the light of modern technology and future clinical implications. Monoclonal antibodies can also be used for this purpose, although they are costly and may result in higher adverse effect rate in patients. Strategies to inhibit YKL-40 in cancer patients are discussed by Johansen et al.[14]

Conclusions

Concentration of serum YKL-40 levels was increased in patients with heart failure and was related to the severity of disease. The present study for the first time reported the prognostic role of YKL-40 as an independent risk factor to predict adverse clinical outcomes in patients with CHF.

Disclosures

None.

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Silent Myocardial Ischemia in Adult Bland–White–Garland Syndrome

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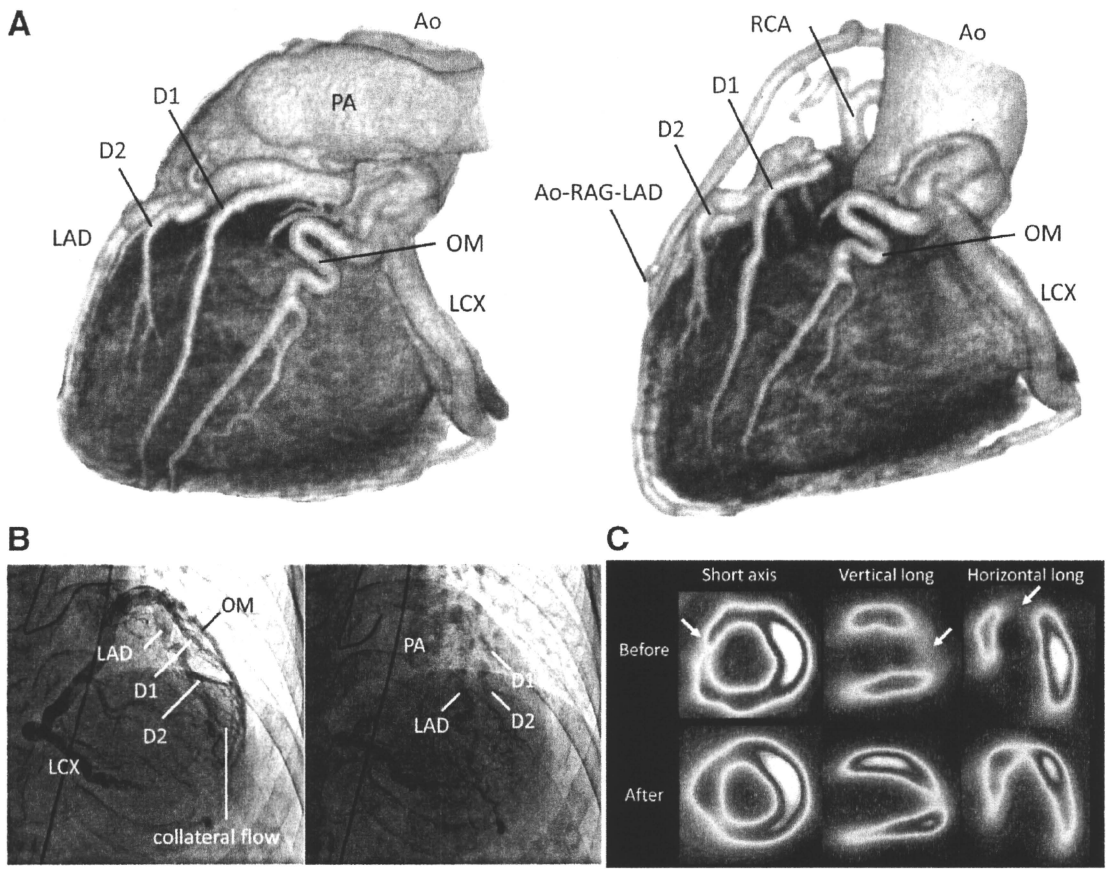

Figure. (**A**) Coronary multislice computed tomography (CT) showing the left anterior descending artery (LAD) arising from pulmonary artery (PA), and the left circumflex artery (LCX) arising from the normal sinus of Valsalva (**Left**). Post-operative CT showing radial artery bypass graft (RAG) from the ascending aorta (Ao) to the LAD, with ligation of the anomalous origin, and the right coronary artery (RCA) arising from the normal sinus of Valsalva (**Right**). D1, first diagonal branch; D2, second diagonal branch; OM, obtuse marginal branch. (**B**) Left coronary artery angiography showing the retrograde blood flow in the LAD, D1 and D2 via collaterals from the LCX and OM (**Left**). Retrograde LAD flow draining into the PA (**Right**). (**C**) Pre-operative resting myocardial perfusion scintigraphy (**Upper**) with 99mTc-sestamibi showing decreased uptake from the anterior-septal wall to the apex of the left ventricle (arrow). Improvement of myocardial perfusion after surgical correction (**Lower**).

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