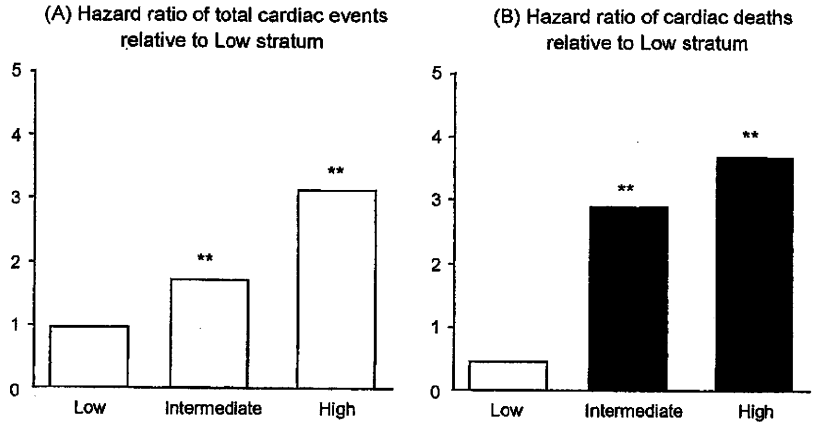

Figure 4 Hazard ratios adjusted for age and sex by univariate Cox proportional hazard analysis. The high stratum was associated with the highest risk for total cardiac events (A) and cardiac deaths (B) among the 3 strata. $^{**}p < 0.001$ vs low stratum patients.

Table 4 Univariate and multivariate analyses of predicting cardiac events.

Variable	Hazard ratio	95% confidence interval	*p*-Value
Univariate analysis			
Age (per 1 S.D. increase), (0.026, 12)	1.366	1.074–1.715	0.0111
NYHA functional class	1.305	0.810–1.117	0.0932
LVEF (per 1 S.D. increase), (0.011, 19)	0.812	0.625–1.039	0.0985
Multimarker score	1.764	1.342–2.320	<0.0001
Multivariate analysis			
Age (per 1 S.D. increase), (0.019, 12)	1.256	0.964–1.657	0.0963
NYHA functional class	1.156	0.656–1.447	0.2159
LVEF (per 1 S.D. increase), (0.0008, 19)	0.985	0.649–1.122	0.2624
Multimarker score	1.689	1.239–2.304	0.0009

Abbreviations as in Table 1.

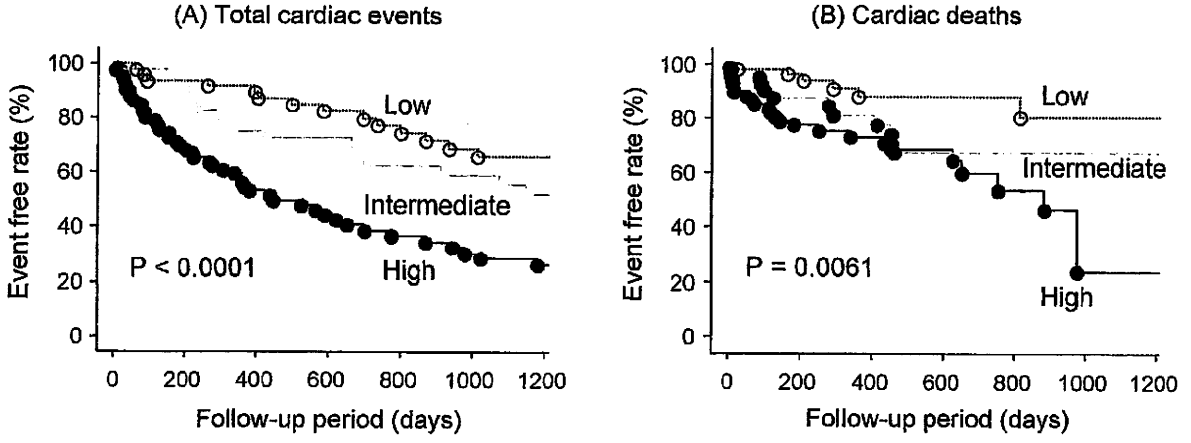

Figure 5 Kaplan–Meier analysis in chronic heart failure patients stratified into 3 strata based on multimarker score. Patients in the high stratum had significantly higher rates of total cardiac events (A) and cardiac deaths (B) compared with lower strata.

66.7% in high stratum, respectively. These results suggest that in patients with high multimarker score, prognosis is poor and intense follow-up with chest-X ray, echocardiography, and blood examination after discharge is recommended.

Discussion

In the present study, we showed that multimarker score was higher in patients with cardiac events than in those without cardiac events. The univariate Cox proportional hazard analysis demonstrated that patients in the high stratum were associated with the highest risk for cardiac events compared with lower strata. Only multimarker score was an independent predictor of cardiac events among age, NYHA functional class, and LVEF by the multivariate Cox proportional hazard regression analysis. Furthermore, cardiac events occurred most frequently in patients in the high stratum compared with lower strata. These findings suggest that the combination of multiple biomarkers could potentially improve the risk stratification of CHF patients for the prediction of cardiac events.

Our results have clinical importance; incorporating this powerful risk prediction in the management of patients with CHF may be potentially helpful to improve their dismal prognosis. The suggested multiple biomarkers reflecting different aspects of interrelated pathophysiological processes of CHF appear to be suitable to designate this high-risk group of CHF patients. The 7 biomarkers in this study are easy to measure in the routine examination, and can be used multiple times to follow up patients without interobserver variability, and are also appropriate in the emergency setting. Therefore, it seems that this approach using multiple biomarkers is useful as one of the options for risk stratification and information of tailored treatment, which includes more intense monitoring and specialist care in CHF patients.

Many clinicians have encountered problems in CHF patients. How will we identify and detect CHF patients at an earlier stage? How do we predict CHF patients with the greatest risk of cardiac events or cardiac deaths? Shortness of breath, general fatigue, and even edema do not necessarily indicate the presence of CHF in a case. Nevertheless, the clinician must have a high index of suspicion that the source of patients' problems may be CHF and must assess whether patients have volume overload and cardiac dysfunction. It seems that measurement of these 7 markers may aid in the diagnosis and assessment of CHF.

There was no difference in rate of use of ACE inhibitors, ARBs, and β-blockers at discharge among the 3 strata. Multimarker score identified CHF patients who are at increased risk of cardiac events and who may warrant more aggressive therapy. It is important that we perform therapeutic intervention in prospective clinical trials to improve prognosis of severe CHF patients in the future. In addition, patients with preserved ejection fraction were included in this study. We will analyze the difference in multimarker score between patients with preserved ejection fraction and systolic heart failure in the future. Cardiac events increased with advancing multimarker score. Because echocardiography is subject to interobserver variations in interpretation, it seems this multimarker approach is a simple and easy method to estimate severity and prognosis of CHF for many clinicians.

We selected 7 biomarkers on the basis of previous experimental and clinical studies. We acknowledge other biomarkers not tested in this study, such as troponin T or heart-type fatty acid binding protein (markers for ongoing myocardial damage) [13–15], cystatin C (a new marker for renal function) [16], and inflammatory [17] and oxidative stress markers [18]. Improvement in biomarker strategies may depend on the discovery of new biomarkers.

Conclusions

Our findings suggest that this simple multimarker approach demonstrates the potential to assist clinicians in predicting prognosis of CHF patients with low cost and wide availability. Future study is needed to show whether this multimarker approach allows clinicians to improve management and prognosis in CHF patients.

Acknowledgment

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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

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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.

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

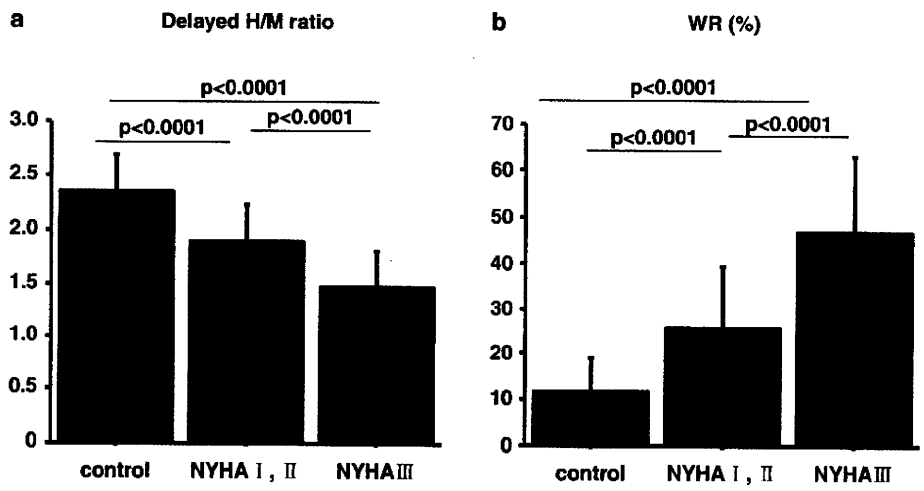

Fig. 1 Delayed *H/M* ratio of ^{123}I-MIBG (**a**) and washout rate (**b**) in the study population

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

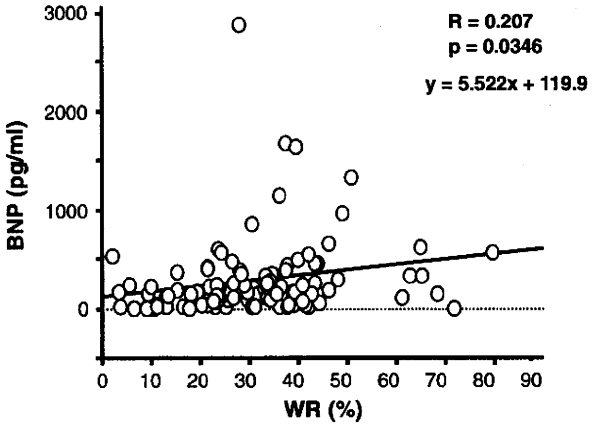

Fig. 2 Relationships between the washout rate of ^{123}I-MIBG and the plasma level of BNP

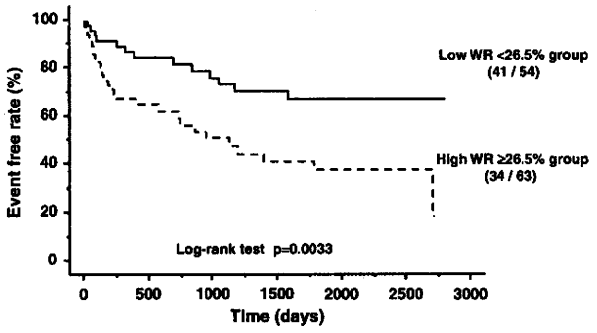

Fig. 3 Washout rate of ^{123}I-MIBG and all cardiac events of patients with heart failure with preserved ejection fraction. Survival curves were created by the Kaplan–Meier method and analyzed by the log-rank test

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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Original Article

Trends in Coronary Risk Factors Among Patients with Acute Myocardial Infarction Over the Last Decade: The Yamagata AMI Registry

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Aim: Recently, there has been an increase in the prevalence of coronary risk factors, such as diabetes and dyslipidemia, in Japan; however, it is unclear whether this has resulted in an increased incidence of acute myocardial infarction (AMI). We investigated the relationship between risk factors changes and AMI incidence in a Japanese population.

Methods: Trends in AMI incidence (per 100,000 person-years) were examined using data from the Yamagata AMI Registry from 1993 to 2007. We included 6,222 patients with a first-ever AMI (4175 men). The prevalence of coronary risk factors was investigated in three age groups of AMI patients (<65, 65-74, and ≥75 years) for the periods 1993-1997, 1998-2002, and 2003-2007. Coronary risk factors were further compared between recently registered AMI patients and 2,400 age-matched controls.

Results: The age-adjusted incidence of AMI increased significantly in men, but not in women. Younger men particularly showed a significant increase in the incidence of AMI. The prevalence of hypertension and diabetes increased in both genders; however, the prevalence of treatment for risk factors was significantly lower in men than women. Younger men showed significant increases in obesity and hypertriglyceridemia. Consequently, risk factors associated with the metabolic syndrome had accumulated among younger men. We revealed that hypertension, diabetes, hypercholesterolemia and current smoking were independent risk factors for AMI.

Conclusions: The incidence rate for AMI increased significantly in men, especially younger men. Preventive care for risk factors associated with metabolic syndrome, in addition to conventional risk factors, may be required in younger men.

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Key words; Acute myocardial infarction, Coronary risk factor, Metabolic syndrome

Introduction

Coronary heart disease (CHD) is a major cause of death in developed countries[1]. Mortality due to acute myocardial infarction (AMI) is much lower in Japan than in Western countries[2, 3], and has decreased further with advances in treatment[4, 5]. However, recently, the prevalence of AMI has increased in Japan, and AMI is therefore becoming one of the most important causes of death[6]. The Hisayama study, a community-based cohort study, previously revealed that the age-adjusted incidence of AMI had not

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changed[7]; however, a recent AMI registry study from 1990 to 2001 reported that the age-adjusted incidence of AMI had increased by 7–8% annually[8].

Previous studies indicated differences in coronary risk factors between Western and Asian countries[9-11]. A recent Japanese case-control study showed that hypercholesterolemia was an independent coronary risk factor in men, but not in women, and that obesity was not associated with AMI[12]; however, there have been marked increases in the prevalence of obesity, diabetes mellitus and hypercholesterolemia[7, 13], due to the westernization of dietary habits in Japan[14-17]. Furthermore, metabolic syndrome has gained attention as a novel cardiovascular risk factor[18-24], and its prevalence is also reported to have increased in Japan[25]. At present, there is little information on the relationship between recent changes in coronary risk factors and the incidence of AMI in Japan. In the present study, we investigated the trends in coronary risk factors among patients with a first-ever AMI who were registered between 1993 and 2007. The prevalence of risk factors was further compared between recently registered AMI patients and an age-matched general population.

Methods

Study Population

Yamagata Prefecture is located in the northern part of the main island of Japan. In the 2005 census, the population was 1,216,000 and the proportion of people ≥65 years old was higher than the average for Japan (25.5% vs. 20.1%). Since 1993, a multicenter project on the surveillance of AMI has been conducted as the Yamagata AMI Registry[5, 26, 27]. The clinical characteristics of AMI patients admitted to all hospitals belonging to the Yamagata Medical Association between 1993 and 2007 were investigated. A diagnosis of AMI required that the "definite criteria of AMI", as described in the World Health Organization MONICA Project[1], be satisfied. Of the 6,957 consecutive patients who were registered in Yamagata Prefecture from 1993 to 2007, 6,222 patients with a first-ever AMI were included in the present study. The observation period of 15 years was sub-divided into three intervals, 1993–1997 (n=1,827), 1998–2002, (n=1,999) and 2003–2007 (n=2,396). In addition, the enrolled patients were categorized into three groups by age at onset of AMI (younger, <65 years old; early elderly, 65–74 years old; late elderly, ≥75 years old).

Data Collection

Standard data were collected prospectively and entered into a computer database. These data included details of clinical presentation (age, gender, date and time of onset of AMI, time of admission to hospital), personal and family medical history, as well as coronary risk factors. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Obesity was defined as BMI ≥25 kg/m^2 for both genders. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or current use of antihypertensive drugs. Hypercholesterolemia was defined as a serum total cholesterol concentration ≥220 mg/dL and/or current use of lipid-lowering drugs. Diabetes mellitus was defined as a fasting blood glucose concentration ≥126 mg/dL, a non-fasting blood glucose concentration ≥200 mg/dL, and/or the use of antidiabetic drugs (any oral hypoglycemic agent or insulin). A family history of CHD and current cigarette smoking status were verified by a self-reported questionnaire and by interviewing the family.

Fasting blood samples were obtained during hospitalization. Low-density lipoprotein (LDL) cholesterol concentrations were calculated using the Friedwald formula when the triglyceride concentration was 400 mg/dL or less. Hypertriglyceridemia was defined as a triglyceride concentration ≥150 mg/dL and low high-density lipoprotein (HDL) cholesterol was defined as a HDL cholesterol concentration <40 mg/dL if male or <50 mg/dL if female. Metabolic syndrome was defined according to the modified National Cholesterol Education Program (NCEP) Adult Treatment Panel Ⅲ (ATP Ⅲ) guidelines and criteria[28]. Patients were deemed to have metabolic syndrome if three or more of the following five criteria were satisfied: obesity, hypertriglyceridemia, low HDL cholesterolemia, high blood pressure, and high fasting glucose, as previously reported[29]. In this study, BMI was used to define obesity because waist circumference measurements were not available.

Statistical Analysis

To calculate the incidence rates for AMI per 100,000 person-years during the three time intervals, the annual population of Yamagata Prefecture was used as the denominator. To adjust for patient age, the Japanese population, as determined by the 2005 census, was used as the standard population. In addition, a case-control study was performed, comparing coronary risk factors during 2003–2007 between AMI patients and 2,400 age-matched control subjects who were enrolled in the Takahata study in 2005. The Takahata study has been described in detail elsewhere[29, 30]. To adjust for the age of subjects, we used standardized incidence ratios.

Table 1. Clinical characteristics of the study population

	Men			p value for trend	Women			p value for trend
	1st (93'-97') n=1,202	2nd (98'-02') n=1,322	3rd (03'-07') n=1,651		1st (93'-97') n=625	2nd (98'-02') n=677	3rd (03'-07') n=745	
Age (years)	65.8±12.5	66.5±12.2	67.1±12.8*	0.0253	73.9±10.2	74.8±11.1	76.8±10.8**††	<0.0001
Number of AMI (/year)	240.4±8.5	264.4±33.8	330.2±28.1**††	0.0004	125.0±10.4	135.4±18.6	149.0±16.9	0.0902
Age-adjusted incidence rates for AMI (/10^5 person-years)	42.7±1.0	42.5±5.0	50.1±3.8*†	0.0099	20.7±2.3	19.5±2.0	18.9±1.8	0.4352
Incidence rates for AMI (/10^5 person-years)								
<64 years old	19.3±1.2	21.1±4.4	28.5±2.6**††	0.0011	3.9±0.8	4.1±0.9	3.9±0.3	0.8842
65-74 years old	125.2±7.8	127.5±9.0	132.2±15.7	0.6238	47.5±11.8	41.6±4.5	39.8±4.5	0.2965
>75 years old	172.8±18.8	157.6±27.3	189.8±28.9	0.1755	105.0±12.6	98.9±12.8	98.4±13.0	0.6736
Coronary risk factors and treatment Obesity, BMI ≥25 (%)	26.1	27.8	31.6**†	0.0124	27.4	24.6	29.2	0.2760
Hypertension (%)	51.0	54.2	58.3**†	0.0008	60.7	62.6	69.2**†	0.0037
Receiving medication (%)	85.3	84.5	85.9	0.7285	91.8	94.2	93.8	0.3933
Diabetes mellitus (%)	20.6	24.6*	30.3**††	<0.0001	24.0	32.4**	33.0**	0.0009
Receiving medication (%)	54.1	58.0	65.1**	0.0159	73.0	78.9	78.4	0.4087
Hypercholesterolemia (%)	32.2	29.1	34.6††	0.0085	35.2	35.0	39.1	0.2299
Receiving medication (%)	45.6	38.2	46.8†	0.0582	51.9	50.0	59.3	0.1555
Family history (%)	25.4	22.6	15.5**††	<0.0001	18.1	20.5	10.8**††	0.0007
Current smoker (%)	60.2	56.8	55.4*	0.0517	10.3	10.0	8.9	0.6963

$^{*}p<0.05$, $^{**}p<0.01$ compared with the 1st period; $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$ compared with the 2nd period.
AMI, acute myocardial infarction; BMI, body mass index.
Incidence rates were age-adjusted to the Japanese population using data from the 2005 census.

Categorical variables were analyzed using the chi-square test. Continuous variables are presented as the means ± SD. Differences among groups were analyzed by analysis of variance (ANOVA) with the Scheffe post hoc test. Multivariate logistic regression analysis was used to evaluate the relationship between coronary risk factors and the development of AMI. A value of $p<0.05$ was considered significant.

Results

The clinical characteristics of the 6,222 patients enrolled in the study are summarized in **Table 1**. The female patients were, on average, about 10 years older than the male patients, and the age at onset of AMI was also significantly higher in female patients. There were increases in the numbers of male patients and in the age-adjusted incidence rate of AMI among male patients. Although the incidence rate of AMI increased with advancing age, it was not increased in elderly patients during the three time periods; in contrast, there was a significant increase among younger male patients.

As shown in the lower panel of **Table 1**, significant increases in the prevalence of hypertension and diabetes mellitus were observed in both genders. In contrast, there were significant increases in the prevalence of obesity and hypercholesterolemia among males, but not among females. A decrease in the proportion of AMI patients with a family history was observed in both genders during the third period (2003-2007) (**Table 1**). While the prevalence of treatment for hypertension was relatively high in both genders, the prevalence of the control of diabetes and hypercholesterolemia was still insufficient (**Table 1**). In males, the prevalence of treatment for each risk factor was approximately 10% lower than in females. Despite decreases in the proportion of current smokers among male patients, the proportion of male smokers was about six times greater than the proportion of female smokers (**Table 1**).

To evaluate the prevalence of coronary risk factors among AMI patients, the prevalence of each risk factor was compared between AMI patients during the third period (2003-2007) and the Japanese general population. AMI patients had a higher prevalence of

Table 2. Comparison of clinical risk factors between patients with AMI in the third period (2003–2007) and age-adjusted control subjects

	Men					Women				
	3rd (03'–07') n=1,651	Takahata n=1,054	odds ratio	95% CI	p value	3rd (03'–07') n=745	Takahata n=1,346	odds ratio	95% CI	p value
Obesity, BMI ≥25 (%)	31.6	28.7	1.15	0.96–1.37	0.1235	29.2	30.9	0.92	0.73–1.15	0.4735
Hypertension (%)	58.3	47.2	1.56	1.33–1.83	<0.0001	69.2	46.0	2.63	2.17–3.19	<0.0001
Diabetes mellitus (%)	30.3	9.1	4.34	3.42–5.49	<0.0001	33.0	6.0	7.65	5.81–10.06	<0.0001
Hypercholesterolemia (%)	34.6	22.1	1.87	1.56–2.23	<0.0001	39.1	33.2	1.29	1.06–1.57	0.0091
Current smoking (%)	55.4	31.3	2.73	2.31–3.22	<0.0001	8.9	1.6	6.26	3.76–10.42	<0.0001
Multivariate analysis										
Hypertension (%)			1.32	1.10–1.60	0.0035			2.13	1.64–2.77	<0.0001
Diabetes mellitus (%)			4.02	3.06–5.29	<0.0001			6.77	4.67–9.80	<0.0001
Hypercholesterolemia (%)			1.64	1.33–2.02	<0.0001			0.95	0.73–1.24	0.7148
Current smoking (%)			3.25	2.66–3.96	<0.0001			7.57	4.33–13.24	<0.0001

Age-adjusted control subjects were enrolled in the Takahata study in 2005.
Multivariate logistic regression analysis adjusted for patient age.

hypertension, diabetes, hypercholesterolemia and current smoking than age-adjusted control subjects enrolled in the Takahata study (**Table 2**). The odds ratios for diabetes and current smoking were especially high among women. Although obesity (BMI ≥25) increased among male patients during the third period, obesity was not a significant risk factor either in males or females. In multivariate logistic regression analysis adjusted for patient age, hypertension, diabetes, and current smoking were independent risk factors for AMI in both genders. Hypercholesterolemia was an independent risk factor for AMI among men, but not among women.

Surprisingly, more than 70% of younger male patients were current smokers, and the proportion of smokers was unchanged, except among early elderly men (**Fig. 1**). Younger female patients were also more likely to be smokers than elderly female patients. Younger male patients showed increases in the prevalence of hypertension and diabetes, increases in BMI and a decrease in the proportion with a family history of MI. Younger male patients showed a greater increase in triglyceride levels, while HDL and LDL cholesterol levels were unchanged. An increase in the prevalence of diabetes was observed for most patients, except younger female patients.

As shown in **Fig. 1**, younger men showed significant increases in the prevalence of hypertension and diabetes, as well as in BMI and triglyceride levels during the third period (2003–2007). Consequently, the number of risk factors associated with metabolic syndrome increased among younger and early elderly men (**Table 3**). In contrast, there was no significant change in the number of risk factors among women.

The prevalence of risk factors associated with metabolic syndrome was compared within each age group, between AMI patients during the third period (2003–2007) and the Japanese general population. Early elderly male patients had a higher prevalence of hypertension, diabetes, and low HDL cholesterolemia than control subjects (**Table 4**); however, younger male patients had a higher prevalence of all coronary risk factors associated with metabolic syndrome than control subjects. Multivariate regression analysis revealed that hypertension, diabetes and low HDL cholesterolemia were independent risk factors for AMI among younger and early elderly men. Further, BMI was an independent risk factor for AMI among younger men, but not among early elderly men. In contrast, BMI was not an independent risk factor for AMI among younger and early elderly women (**Table 5**). Younger male patients showed a significant increase in serum triglyceride levels and the prevalence of obesity during the third period. In addition, male patients with AMI aged <40 years showed significant increases in BMI (**Fig. 2**) and the prevalence of obesity (1st, 37%; 2nd, 62%; 3rd, 68%, respectively, $p<0.05$). Consequently, there was an accumulation of risk factors associated with metabolic syndrome among younger men. Furthermore, there were differences between younger and early elderly male patients in the proportion receiving medical treatment. **Fig. 3** demonstrates that the prevalence of treatment for hypertension and diabetes was significantly lower among younger men and, in contrast to the changes observed for elderly patients, this did not improve at all during the three time periods.

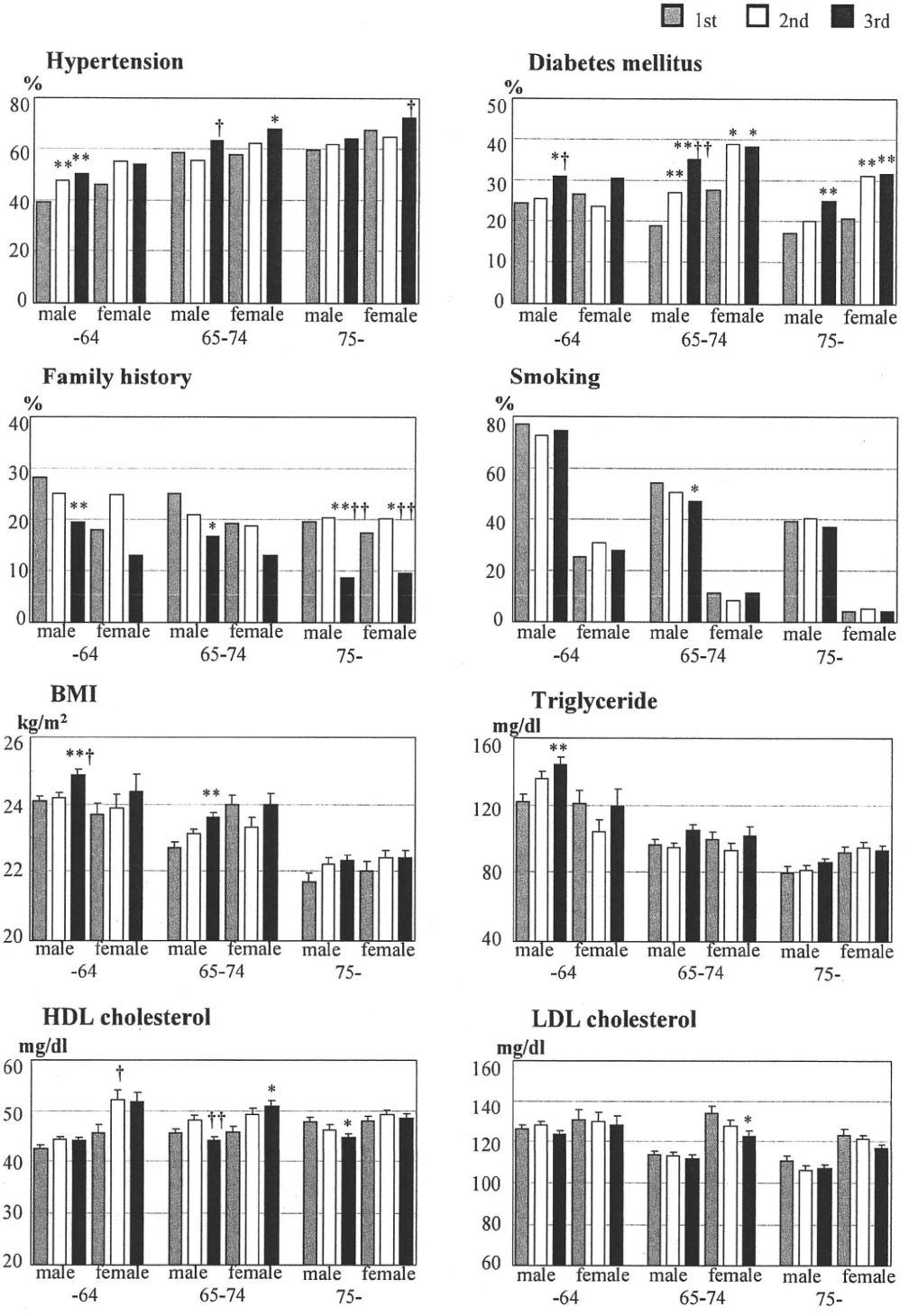

Fig. 1. Trends in coronary risk factors and lipid profiles among AMI patients.

Bars indicate the prevalence of coronary risk factors and the lipid profiles during hospitalization in the three age groups (<65, 65–74, ≥75 years old), for both genders, during the three time periods. Continuous variables are presented as the mean ± SE. $^{*}p<0.05$, $^{**}p<0.01$ compared with 1st period; $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$ compared with 2nd period.

Table 3. Trends in the number of risk factors associated with metabolic syndrome

	1st (93'-97')	2nd (98'-02')	3rd (03'-07')	*p* value for trend
Men	1.60±1.18	1.74±1.19	1.87±1.19**	<0.0001
<64 years old	1.71±1.23	1.97±1.24*	2.02±1.26**	0.0017
65-74 years old	1.54±1.17	1.57±1.14	1.94±1.13**††	<0.0001
>75 years old	1.42±1.05	1.58±1.09	1.56±1.08	0.4022
Women	2.04±1.10	2.08±1.14	2.12±1.20	0.6639
<64 years old	2.02±1.07	1.93±1.09	1.98±1.29	0.9013
65-74 years old	2.13±1.09	2.07±1.20	2.15±1.27	0.8721
>75 years old	1.96±1.13	2.14±1.13	2.14±1.15	0.3688

*$p<0.05$, **$p<0.01$ compared with 1st period; †$p<0.05$ compared with 2nd period.

Table 4. Comparison of risk factors associated with metabolic syndrome between younger and early elderly male patients with AMI during the third period (2003-2007) and control subjects

	Younger men					Early elderly men				
	3rd (03'-07') (*n*=653) 54.1±7.9y	Takahata (*n*=491) 54.9±6.4y	odds ratio	95% CI	*p* value	3rd (03'-07') (*n*=461) 69.6±2.8y	Takahata (*n*=394) 69.4±2.8y	odds ratio	95% CI	*p* value
Univariate analysis										
BMI (kg/m²)‡	24.9±3.5	23.6±3.0	1.50	1.29-1.68	<0.0001	23.6±2.9	23.5±2.9	1.06	0.92-1.22	0.4606
Hypertension (%)	50.4	40.6	1.49	1.15-1.92	0.0022	63.4	55.4	1.40	1.04-1.87	0.0244
Diabetes mellitus (%)	31.1	7.5	5.54	3.81-8.06	<0.0001	35.2	10.7	4.55	3.12-6.63	<0.0001
Hypertriglyceridemia (%)	34.8	27.1	1.44	1.10-1.87	0.0070	16.4	16.5	0.99	0.68-1.45	0.9572
Low HDL cholesterolemia (%)	36.4	11.4	4.44	3.20-6.16	<0.0001	38.4	10.4	5.37	3.65-7.90	<0.0001
Metabolic syndrome (%)	35.2	11.8	4.05	2.90-5.65	<0.0001	31.5	9.9	4.18	2.78-6.30	<0.0001
Multivariate analysis										
BMI (kg/m²)‡			1.23	1.04-1.45	0.0140					
Hypertension (%)			1.36	1.00-1.84	0.0474			1.41	1.01-1.96	0.0432
Diabetes mellitus (%)			5.27	3.37-8.24	<0.0001			4.13	2.68-6.36	<0.0001
Hypertriglyceridemia (%)			0.79	0.56-1.10	0.1646					
Low HDL cholesterolemia (%)			4.11	2.80-6.04	<0.0001			5.44	3.58-8.28	<0.0001

BMI, body mass index; HDL, high density lipoprotein
‡Data represent odds ratio corresponding to 1SD increase in BMI level

Discussion

The present study showed that the age-adjusted incidence of AMI increased in male patients. Younger men in particular showed a significant increase in the incidence of AMI during 2003-2007. In contrast, there was no increase in the incidence of AMI among females during the observation periods. There was a significant increase in the prevalence of metabolic syndrome among younger male patients compared with other age groups, as well as a greater increase in the number of risk factors associated with metabolic syndrome. These results suggested that an increase in the prevalence of risk factors associated with metabolic syndrome may be related to the increased incidence rate for AMI among younger men.

Increased Incidence of AMI Among Male Patients

An increased number of AMI was observed among male patients (**Table 1**). In contrast, the number of AMI did not increase and the age at onset increased significantly among women. There was no significant change in the age-adjusted incidence rate of AMI among women in the present study, which is consistent with the findings of the Hisayama study[7]. Another AMI registry study reported that the age-adjusted incidence rate increased by 7.6% among men and by 8.3% among women, between 1990 and 2001[8]. In contrast, the present study demonstrated that the age-adjusted incidence rate for AMI increased

Table 5. Comparison of risk factors associated with metabolic syndrome between younger and early elderly female patients with AMI during the third period (2003-2007) and control subjects

	Younger women					Early elderly women				
	3rd (03'-07') (n=87) 54.1±7.9y	Takahata (n=692) 54.9±6.4y	odds ratio	95% CI	p value	3rd (03'-07') (n=168) 69.6±2.8y	Takahata (n=479) 69.4±2.8y	odds ratio	95% CI	p value
Univariate analysis										
BMI (kg/m^2)#	24.4±4.2	23.4±3.5	1.07	1.01-1.15	0.0307	24.0±3.8	24.1±3.3	0.99	0.38-1.05	0.8321
Hypertension (%)	54.1	29.7	2.80	1.76-4.44	<0.0001	67.9	50.1	2.11	1.43-3.09	0.0001
Diabetes mellitus (%)	30.6	4.3	9.72	5.40-17.52	<0.0001	38.2	6.1	9.58	5.87-15.64	<0.0001
Hypertriglyceridemia (%)	15.3	12.3	1.29	0.65-2.55	0.4667	19.1	15.9	1.25	0.76-2.06	0.3807
Low HDL cholesterolemia (%)	50.7	18.1	4.67	2.80-7.78	<0.0001	49.2	22.3	3.37	2.24-5.07	<0.0001
Metabolic syndrome (%)	39.7	6.9	8.83	4.92-15.83	<0.0001	43.4	14.6	4.47	2.85-7.02	<0.0001
Multivariate analysis										
BMI (kg/m^2)#			1.00	0.92-1.09	0.9786					
Hypertension (%)			2.14	1.17-3.90	0.0131			1.82	1.14-2.90	0.0118
Diabetes mellitus (%)			6.92	3.14-15.28	<0.0001			7.19	4.11-12.55	<0.0001
Low HDL cholesterolemia (%)			2.35	1.23-4.49	0.0099			2.91	1.85-4.60	<0.0001

BMI, body mass index; HDL, high density lipoprotein
#Data represent odds ratio corresponding to 1SD increase in BMI level

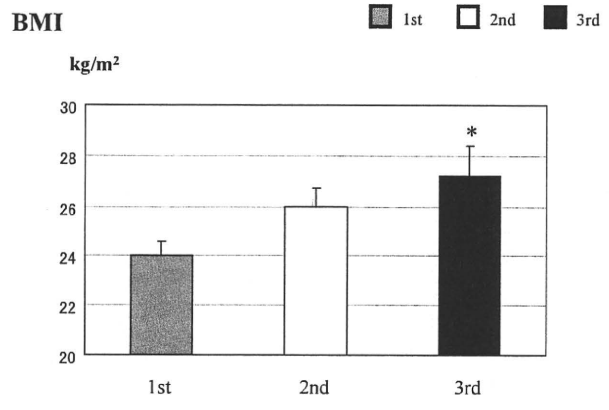

Fig. 2. Trends in BMI among male patients with AMI aged <40 years.

Bars indicate BMI during hospitalization among male AMI patients aged <40 years, during the three time periods. Continuous variables are presented as the mean±SE. *p<0.05 compared with 1st period.

only among men and was much higher than in women. Younger men in particular showed a significant increase in the incidence rate of AMI, which was seven times greater than in women during 2003-2007 (**Table 1**). These findings are not likely to be explained only by the influence of aging of the general population. We hypothesized that changes in the prevalence of risk factors, due to the westernization of dietary habits and changes in lifestyle, may have influenced the recent incidence rates of AMI.

Changes in the Prevalence of Coronary Risk Factors in AMI Patients

There were differences in the trends in coronary risk factors between men and women. Both showed a similar magnitude of increase in the prevalence of hypertension and diabetes; however, only younger men showed a significant increase in the prevalence of obesity and in serum triglyceride levels during 2003-2007 (**Fig. 1**). Consequently, the proportion of patients with metabolic syndrome increased among younger and early elderly men (**Table 3**). Several studies have demonstrated that metabolic syndrome is a significant risk factor for the development of AMI[18-24], but it had a weak or no association with CHD in the elderly[31], which is consistent with the findings of the present study.

In the present study, AMI patients of both genders showed a higher prevalence of hypertension, diabetes and hypercholesterolemia, and a higher incidence of current smoking than age-adjusted control subjects, which was consistent with the findings of the Framingham study[32]. Recently, a large Japanese case-control study demonstrated that hypertension, diabetes, current smoking, family history, and hypercholesterolemia were all independent risk factors for AMI[12]; however, only current smoking, diabetes and, hypertension were identified as independent risk factors in women in their study. Therefore, it was suggested that

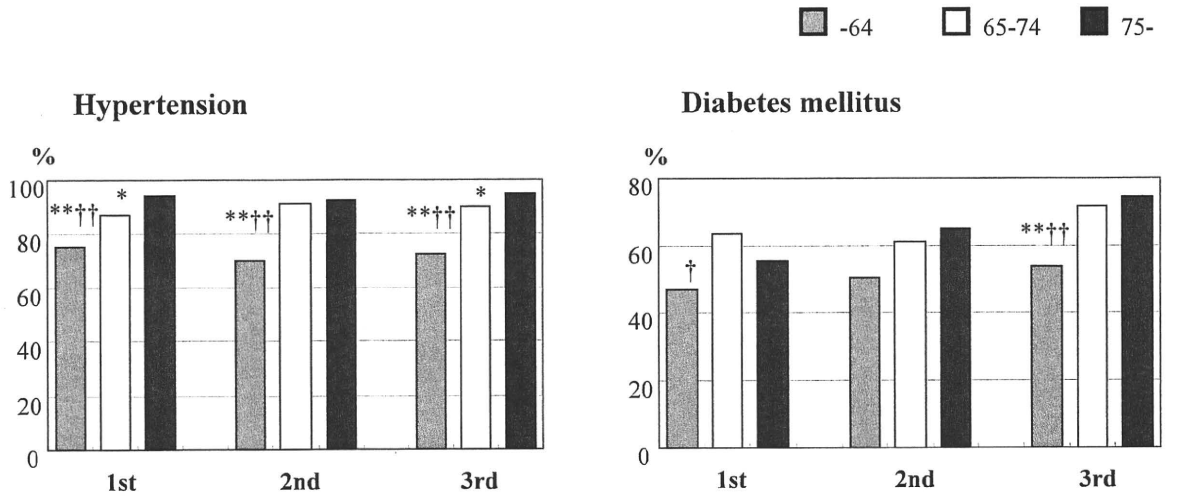

Fig. 3. Comparison of the proportions of male patients receiving medical treatment.

Bars indicate the proportions of male patients in the three age groups (<65, 65–74, ≥75 years old), receiving medical treatment for hypertension and diabetes during the three time periods. $^{*}p<0.05$, $^{**}p<0.01$ compared with late elderly patients; $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$ compared with early elderly patients.

hypercholesterolemia was an independent coronary risk factor in men, but not women, which is consistent with the results of the present study.

Previous studies reported that obesity and low HDL cholesterolemia were independent risk factors among younger male patients[33-35], which is consistent with our findings. In particular, male patients with AMI aged <40 years showed significant increases in BMI and the prevalence of obesity (**Fig. 2**).

Although the incidence of current smoking decreased during 2003–2007 in male patients (**Table 1**), it was significantly higher than in age-adjusted control subjects (**Table 2**). Surprisingly, the incidence of current smoking in female AMI patients was about six times higher than in age-adjusted control subjects, whereas it was lower than in male AMI patients. Thus, the prevalence of smoking has decreased in men, but not in women. Notably, the prevalence of smoking was significantly higher in younger women than in elderly patients. These results suggest that current smoking is an important risk factor for AMI, which is consistent with the findings from a previous study[12, 32, 36].

During 2003–2007, there was a significant decrease among both genders in the proportion of AMI patients with a family history (**Table 1**). This does not mean there was a decrease in the number of AMI patients with a family history, but rather that there was an increase in the number without a family history. In addition, the impact of lifestyle-related factors on the development of AMI may have become relatively more important in recent years[14-17, 23].

Insufficient Treatment of Coronary Risk Factors

Female AMI patients were 8–10 years older than male patients (**Table 1**). A previous study also reported that women develop CHD about 10 years later than men[37]. In general, menopause is a risk factor among females, which contributes to gender differences[38, 39]; however, it has been suggested that the difference in the age at onset is largely explained by the higher number of risk factors at younger ages in men than women[37]. The age at onset increased significantly in women in the present study. Since the number of female patients did not increase, despite an increase in the aging population, it is suggested that medical treatment may have partly contributed to suppressing the incidence of AMI in women. In fact, the proportion of patients receiving medical treatment for each risk factor was approximately 10% higher in women than men (**Table 1**). Although the proportion of patients receiving treatment for hypertension reached 94% in female patients, the proportions receiving treatment for diabetes and hypercholesterolemia remained suboptimal at 78% and 59%, respectively. In order to reduce the age-adjusted incidence of AMI in women, improved rates of treatment for diabetes and hypercholesterolemia, as well as increased rates of smoking cessation, are required.

In contrast to women, there was an accumulation of coronary risk factors and an increased incidence of AMI in male patients. Particular attention should be paid to the increased incidence of AMI among younger men, who showed a greater increase

in the prevalence of the metabolic syndrome than other age groups (**Table 4**), and also had a markedly high incidence of current smoking (**Fig. 1**), which did not decrease over the three time periods. Furthermore, the proportion of patients receiving treatment for each coronary risk factor was significantly lower in younger male patients than other age groups (**Fig. 3**). Therefore, control of the risk factors associated with metabolic syndrome, in addition to conventional risk factors, such as hypercholesterolemia, and increased rates of smoking cessation, are required to decrease the incidence of AMI among men.

In conclusion, the age-adjusted incidence of AMI increased in male patients, but not in female patients. In particular, younger men have shown a significant increase in the incidence of AMI recently. The control of conventional coronary risk factors is still thought to be insufficient, in both men and women, to contribute to a decrease in the incidence of AMI. In addition, preventive care for metabolic syndrome may be required in younger men.

Acknowledgements

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