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Risk Stratification of Sudden Cardiac Death by Evaluating Myocardial Sympathetic Nerve Activity Using Iodine-123 Metaiodobenzylguanidine Scintigraphy in Patients with Chronic Heart Failure and Dilated Cardiomyopathy

Yoshikazu Yazaki, Toshimasa Seki, Atsushi Izawa, Minoru Hongo and Uichi Ikeda

Additional information is available at the end of the chapter

1. Introduction

A Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) has proven the efficacy of prophylactic implantable cardioverter defibrillator (ICD) use for chronic heart failure patients without sustained ventricular tachycardia (SVT) and a history of ventricular fibrillation, not restricted in those with myocardial infarction [1]. Since ICD is an expensive device, risk stratification is required to identify heart failure patients at high risk for sudden death without SVT.

Iodine-123 Metaiodobenzylguanidine (^{123}I-MIBG) is an analogue that metabolizes in a manner similar to that of norepinephrine (NE) [2]. ^{123}I-MIBG is used to assess myocardial sympathetic nervous activity, and a decrease in myocardial ^{123}I-MIBG uptake and an increase in spillover have been observed in patients with heart failure and are related to disease severity [3-5]. An increase in sympathetic tone is associated with ventricular tachyarrhythmia and sudden cardiac death [6, 7].

Therefore, the purpose of this study was to test our hypothesis that ^{123}I-MIBG scintigraphy may be useful in the prediction of future sudden death in heart failure patients without SVT and a history of ventricular fibrillation.

2. Methods

2.1. Patients

We retrospectively examined 120 consecutive heart failure patients with a left ventricular ejection fraction (LVEF) of less than 50 % who underwent ^{123}I-MIBG scintigraphy between April 1998 and December 2004. There were 84 men and 36 women with a mean age of 57±14 years ranging from 22 to 95 years. New York Heart Association (NYHA) functional class assessment at the time of the scintigraphy showed 23 patients in class I, 66 in class II and 31 in class III. All patients underwent cross sectional and M-mode echocardiography as well as coronary angiography. The study population included non-ischemic dilated cardiomyopathy in 73 patients, ischemic cardiomyopathy in 21 and others in 26 which systolic dysfunction might be caused by valvular diseases, hypertension and/or congenital heart disease. All patients showed stable clinical condition for at least 3 months on conventional medications with angiotensin-converting enzyme inhibitor and diuretics. Fifty-nine patients were on β–blocker drugs.
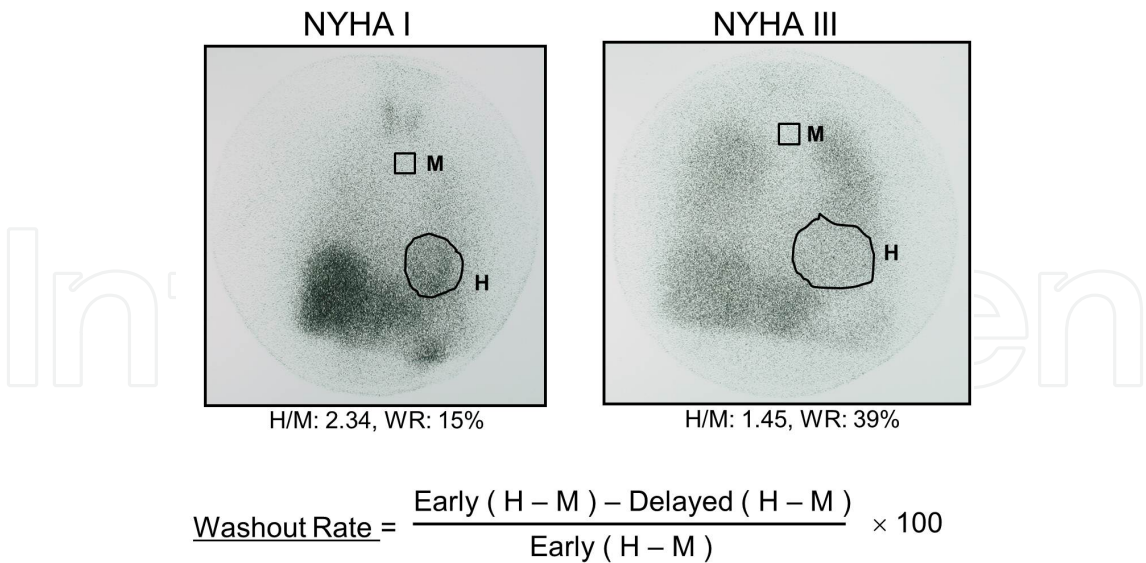
2.2. ^{123}I-MIBG data acquisition

^{123}I-MIBG is an analogue of guanethidine that is metabolized in a qualitatively similar manner to norepinephrine at the synaptic nerve terminal. After ^{123}I-MIBG uptakes through the uptake-1 mechanism and storages in the synaptic nerve ending, it releases according to the sympathetic activity. Since the myocardium of patients with chronic heart failure is characterized by a significant reduction of pre-synaptic norepinephrine uptake and post-synaptic beta-adrenoreceptor density, uptake-1 function and beta–receptor downregulation can be evaluated by ^{123}I-MIBG imaging [8]. Under resting and fasting condition, patients were injected intravenously with 111MBq of commercially available ^{123}I-MIBG (Daiichi Radioisotopes Labs, Tokyo, Japan). Anterior planar images were acquired 15 minutes and 3 hours after the injection and stored in a 64 x 64 matrix by means of a scintillation camera (model ZLC 7500; Siemens, Solana, Sweden) equipped with a long-energy, general purpose collimator interfaced to a minicomputer (SCINTIPAC 7000; Shimazu, Kyoto, Japan), with a 20% window centered on the 159keV photopeak of Iodine-123. Regions of interest (ROI) were manually drawn over the heart and upper mediastinum by a nuclear cardiologist without knowledge of the patient's data (Figure 1). The total number of counts of each ROI was determined, and a geometric mean was calculated as counts per pixel. We determined the heart to mediastinum activity ratio (H/M) for all early and delayed images. ^{123}I-MIBG washout rate from the heart was calculated from the difference between early and delayed images according to the formula shown in figure 1.

Demonstrable two cases are shown in figure 1. A case with NYHA class III shows lower H/M ratio and higher washout rate as compared to a case with NYHA class I.
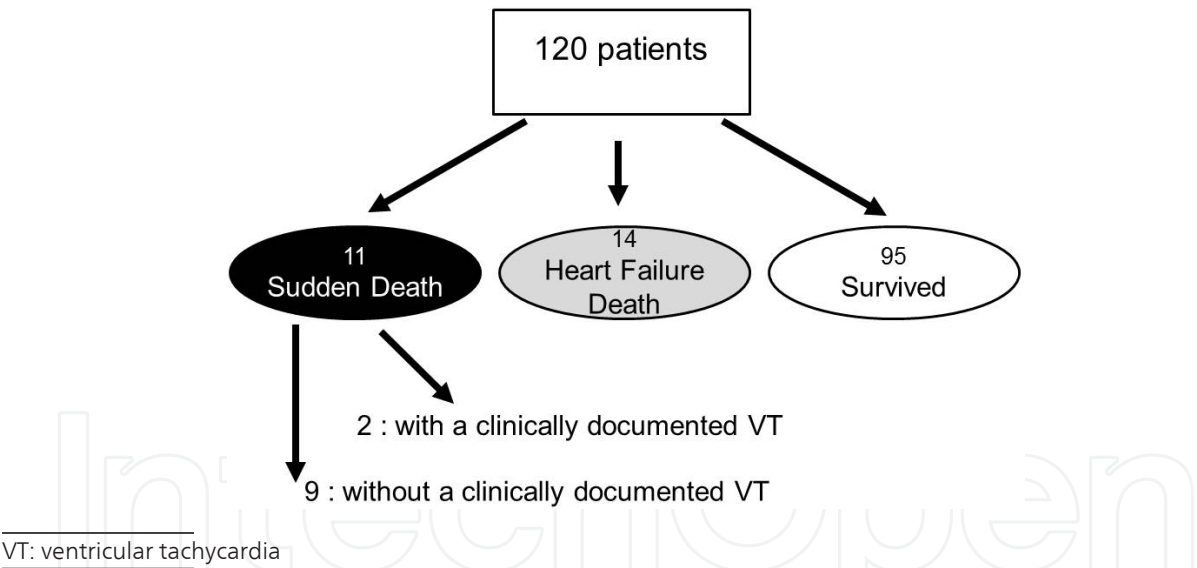
2.3. Follow-up information and end-point

Medical records of all patients were carefully reviewed. The primary end-point of this study was the occurrence of cardiac death including death due to congestive heart failure and sudden

NYHA I   NYHA III

H/M: 2.34, WR: 15%   H/M: 1.45, WR: 39%

$$\text{Washout Rate} = \frac{\text{Early}\,(\,H - M\,) - \text{Delayed}\,(\,H - M\,)}{\text{Early}\,(\,H - M\,)} \times 100$$

H: heart; M:mediastinum; H/M: heart to mediastinum activity ratio; 123I-MIBG: Iodine-123 Metaiodobenzylguanidine; NYHA: New York Heart Association.

Figure 1. ^{123}I-MIBG imaging. (A) A case of NYHA functional class I status. (B) A case of NYHA functional class III status.

120 patients

11 Sudden Death   14 Heart Failure Death   95 Survived

2 : with a clinically documented VT

9 : without a clinically documented VT

VT: ventricular tachycardia

Figure 2. Clinical course of all patients.

cardiac death. Sudden cardiac death was defined as death within 1 hour after the acute onset of symptom, death during sleep or unwitnessed death. Clinical course of the 120 patients are summarized in figure 2. During a mean follow-up of 57±24 months, 14 patients died of refractory heart failure and 11 died suddenly including 9 without clinical VT. Echocardia-graphic and hemodynamic variables ware compared among the three groups. Plasma norepinephrin concentration of 40 patients and brain natriuretic polypeptide (BNP) of 64 patients were measured close to the time of scintigraphic examination.

2.4. Statistical analysis

Student's *t*-test was used to compare all continuous variables expressed as mean ± SD of the two groups. Incidence was compared by means of χ^2 tests. Receiver operating characteristic analysis was used to select the most appropriate indicator of ^{123}I-MIBG. Survival rates were estimated with the Kaplan-Meier method, and differences in survival assessed with the log-rank test. Univariate and multivariate analyses of the event risks associated with selected clinical variables used the Cox proportional hazard model (SPSS v 9.0, Chicago, IL). A *p* value of < 0.05 was considered statistically significant.

3. Results

3.1. Comparisons of clinical variables among patients stratified by cause of death (table 1)

Patients who died of congestive heart failure were significantly older than those who survived, or died suddenly without SVT. The patients with congestive heart failure death also showed the most deteriorated echocardiographic and hemodynamic conditions among the 3 groups. There were no statistically significant differences in any variables between surviving patients and patients who died suddenly without SVT.
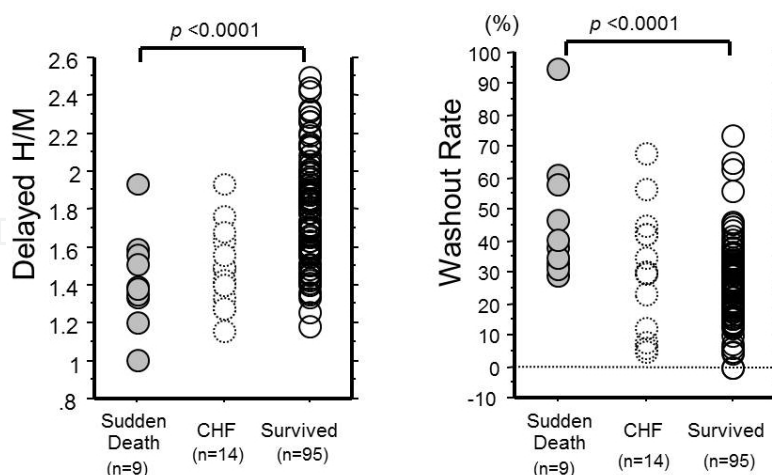
	Sudden death without s-VT	CHF	Survived
	(N=9)	(N=14)	(N=95)
Age (yrs.)	56.0±5.8	64.0±8.5*	55.3±14.2
Gender: Female	1 (10)	3 (21)	32(33)
β-blockers	4 (40)	5 (36)	59(63)
LVEDd (mm)	62.5±15.0	67.6±12.1†	62.8±9.8
LVEF (%)	30.8±11.2	22.6±10.3†	36.1±13.2
PCWP (mmHg)	13.1±6.3	21.0±8.7*	11.0±6.1
mPAP (mmHg)	22.8±7.4	30.9±9.0*	18.5±7.2
CI (l/min/mm²)	2.51±0.73	2.21±0.47	2.61±1.25
BNP (pg/ml)	**219±255**	**697±516†**	**107±110**

* p < 0.05 (for sudden death and survived patients); † p <0.05 (for survived patients)

BNP:brain natreuretic peptide; CI:cardiac index; LVDd:left ventricular end-diastolic diameter; LVEF: left

ventricular ejection fraction; PCWP:pulmonary capillary wedge pressure; mPAP:mean pulmonary wedge pressure

Table 1. Clinical Variables among the Patients Stratified by Cause of Death

CHF: congestive heart failure; H/M: heart to mediastinum activity ratio; 123I-MIBG: Iodine-123 Metaiodobenzylguanidine

Figure 3. Comparisons of delayed H/M (left panel) and washout rate (right panel) of 123I-MIBG among the patients stratified by cause of death

3.2. Comparisons of ^{123}I-MIBG parameters among patients stratified by cause of death (figure 3)

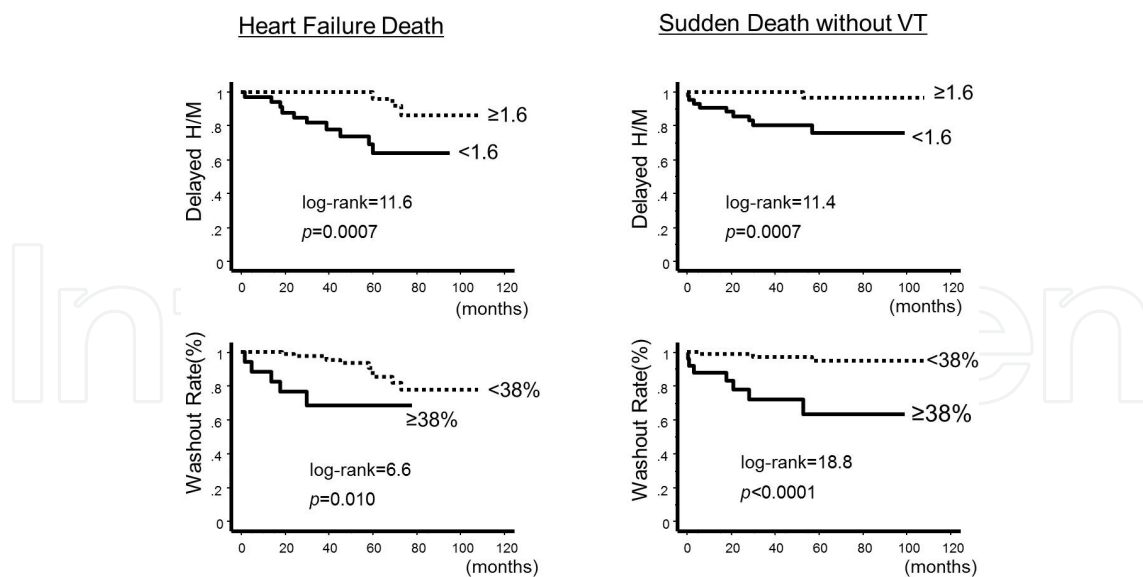^{123}I-MIBG parameters were better in surviving patients compared to those in patients with death due to congestive heart failure and with sudden death. There were significant differences in delayed H/M and washout rate of ^{123}I-MIBG between surviving patients and patients who died suddenly, although clinical variables were similar between the two groups.

3.3. Survival

Comparison of Kaplan-Meier survival curve was depicted in figure 4. Receiver operating characteristic analysis indicated that the optimal cut-off point of the delayed heart to mediastinum ratio for all cause of cardiac death was 1.6. Survival of the patients with delayed H/M ratio greater than 1.6 was significantly worse than that less than 1.6. Receiver operating characteristic analysis indicated that the optimal cut-off point of heart ^{123}I-MIBG washout rate for all cause of cardiac death was 38%. Survival of the patients with washout rate greater than 38% was significantly worse than that less than 38%. In the analysis of washout rate, a log-rank statistics of sudden cardiac death in heart failure patients without SVT was greater than that of death due to heart failure, whereas similar in the analysis of the delayed H/M ratio.

3.4. Univariate predictors for heart failure death and sudden death

Univariate predictors for heart failure death are summarized in Table 2. Age, left ventricular end-diastolic diameter, left ventricular ejection fraction (LVEF), pulmonary capillary wedge pressure, mean pulmonary artery pressure, delayed H/M ratio, and heart ^{123}I-MIBG washout

H/M: heart to mediastinum activity ratio; 123I-MIBG: Iodine-123 Metaiodobenzylguanidine; VT: ventricular tachycardia

Figure 4. Comparison of Kaplan-Meier survival curves. Heart failure death (left panel) abd sudden cardiac death (right panel).

rate were associated with death due to heart failure. Univariate predictors for sudden cardiac death are summarized in Table 3. Delayed H/M ratio and heart ^{123}I-MIBG washout rate were associated with sudden cardiac death in heart failure patients without SVT.

	X^2	HR	95%CI	*p value*
Age (yrs.)*	4.39	1.07	1.004–1.141	.036
Gender :Male	0.72	0.57	0.153–2.104	.397
on β-blockade	2.25	0.40	0.119–1.327	.134
LVDd (mm)*	2.31	1.04	0.988–1.105	.129
PCWP (mmHg)*	21.3	1.24	1.131–1.357	.0000
mPAP (mmHg)*	20.8	1.19	1.105–1.283	.0000
CI (l/min/mm²)†	5.17	0.19	0.045–0.795	.023
LVEF (%)*	8.90	0.91	0.861–0.969	.003
Delayed H/M*	11.9	0.01	0.001–0.124	.0006
Washout rate (%)*	2.17	1.03	0.991–1.064	.141

Hazard ratio reflects risk with an increase of 1* and 0.1†.

CI:cardiac index; H/M:heart to mediastinum activity ratio; LVDd:left ventricular end-diastolic diameter; LVEF:

left ventricular ejection fraction; PCWP:pulmonary capillary wedge pressure; mPAP:mean pulmonary wedge pressure

Table 2. Univariate Predictors for Heart Failure Death

	X²	HR	95%CI	*p value*
Age (yrs.)*	0.27	0.99	0.953–1.028	.605
Gender :Male	2.96	0.17	0.022–1.282	.085
on β-blockade	1.71	0.47	0.154–1.452	.191
LVDd (mm)*	0.41	1.02	0.965–1.073	.521
PCWP (mmHg)*	0.18	1.02	0.937–1.107	.671
mPAP (mmHg)*	0.87	1.03	0.966–1.104	.350
CI (l/min/mm²)†	0.02	0.94	0.425–2.086	.881
LVEF (%)*	1.00	0.98	0.934–1.023	.318
Delayed H/M*	12.8	0.01	0.001–0.116	.0004
Washout rate (%)*	14.8	1.06	1.027–1.086	.0001

Hazard ratio reflects risk with an increase of 1* and 0.1†.

CI:cardiac index; H/M:heart to mediastinum activity ratio; LVDd:left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; PCWP:pulmonary capillary wedge pressure; mPAP:mean pulmonary wedge pressure; VT:ventricular tachycardia

Table 3. Univariate Predictors for Sudden Death without Sustained VT

3.5. Multivariate analysis

Cox multiple variable logistic regression model with a backward stepwise approach including 10 clinical variables (age, gender, on beta-blockers, left ventricular end-diastolic diameter, pulmonary capillary wedge pressure, mean pulmonary artery pressure, cardiac index, LVEF, delayed H/M ratio, heart ^{123}I-MIBG washout rate) identified pulmonary capillary wedge pressure and delayed H/M ratio as independent predictors of death due to heart failure, and delayed H/M ratio and heart ^{123}I-MIBG washout rate as independent predictors of sudden cardiac death in heart failure patients without SVT (Table 4).

	X²	HR	95%CI	*p* value
PCWP*	15.3	1.28	1.078–1.409	.0000
Delayed H/M*	6.25	0.01	0.001–0.124	.012
(a) For Heart Failure Death				
	X²	HR	95%CI	*p* value
Washout rate*	5.12	1.05	1.007–1.126	.024
Delayed H/M*	4.29	0.02	0.023–0.346	038
(b) For Sudden Death without Sustained VT				

(a) Hazard ratio (HR) reflects risk with an increase of 1*. H/M:heart to mediastinum activity ratio; PCWP:pulmonary capillary wedge pressure

(b) Hazard ratio (HR) reflects risk with an increase of 1*. H/M:heart to mediastinum activity ratio; VT: ventricular tachycardia

Table 4. Multiivariate analysis

4. Discussion

The principal finding of this study is that ^{123}I-MIBG parameters, especially washout rate is useful for the risk stratification of sudden cardiac death in chronic heart failure patients without SVT. To the best of our knowledge, this is the first report to show a relation between sudden cardiac death and cardiac sympathetic nervous function using ^{123}I-MIBG in heart failure patients without documented VT.

4.1. MIBG parameters and heart failure

Reduced pre-synaptic norepinephrine uptake and post-synaptic beta-adrenoreceptor density might contribute to the remodeling process of the left ventricle in the diseased heart [9]. Increased washout and decreased uptake of ^{123}I-MIBG in the myocardium are related to the severity and prognosis of heart failure [10]. A recent meta-analysis including 18 studies with a total of 1755 patients reconfirmed that decreased uptake and increased washout of ^{123}I-MIBG showed a poor prognosis in patients with heart failure. ^{123}I-MIBG also has been used to assess the functioning of the pulmonary capillary endothelium under a variety of experimental or clinical conditions [11, 12]. Mu et al. speculated the increased lung uptake of ^{123}I-MIBG in heart failure patients might be due to the enhanced permeability of the pulmonary endothelial cells [13]. We have demonstrated that the combined assessment of lung and heart ^{123}I-MIBG uptake may help to predict future clinical outcome in patients with idiopathic dilated cardiomyopathy more accurately than myocardial evaluation alone [14].

4.2. Autoantibody against the beta1 adrenoreceptor and heart failure

We previously investigated the relationship between ^{123}I-MIBG parameters and the anti-beta1-adrenoreceptor autoantibody level in chronic heart failure patients [15]. The autoantibodies stimulate the second extracellular domain of the beta1-adrenoreceptor like norepinephrine, and are associated with reduced cardiac function in patients with heart failure [16]. We have demonstrated that the anti-beta1-adrenoreceptor autoantibodies are closely associated with cardiac sympathetic nervous activity assessed by ^{123}I-MIBG and cardiac event in patients with chronic heart failure [15]. Iwata et al. has reported that the autoantibodies predict VT and sudden death in patients with idiopathic dilated cardiomyopathy [17]. These results suggest that sudden cardiac death associated with ventricular tachyarrhythmias might be related to sympathetic nervous activity evaluated by ^{123}I-MIBG scintigraphy.

4.3. Cardiac sympathetic nervous function and sudden cardiac death associated with ventricular tachyarrhythmias

Several electrocardiographic markers such as heart rate variability, single-averaged electrocardiogram, and QT dispersion have been proposed for the prediction of cardiac event in patients with heart failure [18-20]. Heart rate variability is a noninvasive tool for the condition of autonomic nervous activity and has been shown to predict future sudden cardiac death. Tamaki et al. reported a comparison of cardiac ^{123}I-MIBG imaging with other electrocardiographic markers, and concluded that washout rate of ^{123}I-MIBG was

the most powerful predictor for sudden cardiac death in patients with mild-to-moderate heart failure [21].

Using ^{123}I-MIBG, the role of impaired cardiac sympathetic innervations has been reported in patients with ventricular tachyarrhythmias. Akutsu et al. reported that impairment of cardiac sympathetic nervous system predicted recurrent ventricular tachyarrhythmic events in patients with a history of VT or fibrillation [22]. A prospective multicenter pilot study demonstrated that only defect severity of ^{123}I-MIBG single photon emission computed tomography (SPECT) was predictive of inducibility of VT or fibrillation, whereas the conventional index such as H/M was not [23].

4.4. ^{123}I-MIBG kinetics and indication for implantable cardioverter defibrillator (ICD)

A recent Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [1] has proven the efficacy of prophylactic ICD use for chronic heart failure patients without sustained VT and a history of ventricular fibrillation, not restricted in those with myocardial infarction. Since ICD is an expensive device, risk stratification is required to identify heart failure patients at high risk for sudden death without sustained VT. Based on the several guidelines, prophylactic use of an ICD is recommended in patients with ventricular tachycardia who have severe systolic dysfunction. Nagahara et al. demonstrated that when combined with plasma BNP or cardiac function, impairment of cardiac sympathetic innervations would predict an ICD shock associated with lethal arrhythmias, contributing to identify suitable candidates for prophylactic ICD implantation [24]. Severely reduced left ventricular systolic function is a powerful predictor of sudden cardiac death. They concluded that ^{123}I-MIBG scintigraphic evaluation for cardiac sympathetic innervations may be an option for screening patients at high risk for sudden cardiac death. Furthermore, such abnormality had incremental and additive prognostic power when combined with left ventricular dysfunction.

Those recent reports mentioned above support our present results. Increased neuronal release of norepinephrine and decreased efficiency in the reuptake of norepinephrine through the uptake-1 mechanism contribute to the increased cardiac adrenergic drive, and lead to life threatening ventricular tachyarrhythmias in patients with heart failure.

4.5. Study limitations

There are several limitations in this study. First, because of the retrospective study design, definite conclusions could not be drawn from our present data. BNP which is one of the important prognostic factors should be excluded in our multivariate analysis for prognostic determinants because of imperfect data. Second, the number of cardiac death was relatively small because the follow-up period was not long enough, so that more extensive case studies and longer follow-ups are required to validate the results reported here.

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5. Conclusions

We investigated the relationship between ^{123}I-MIBG findings and mode of death in patients with chronic heart failure. Sudden cardiac death in heart failure patients is closely associated with cardiac sympathetic nervous activity assessed by ^{123}I-MIBG scintigraphy. Our data, thus, confirm that increased sympathetic tone in the myocardium play a harmful role on the progression of life-threatening ventricular tachyarrhythmias. Assessment of cardiac sympathetic nervous activity using ^{123}I-MIBG may be helpful for the candidate selection of ICD in heart failure patients without sustained ventricular tachycardia.

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