Annals of Nuclear Medicine Vol. 21, No. 1, 57–63, 2007

Importance of renal function on prognostic value of cardiac iodine-123 metaiodobenzylguanidine scintigraphy

Tatsuhiko FURUHASHI and Masao MOROI

Division of Cardiovascular Medicine, Toho University Ohashi Medical Center

Objective: Cardiac iodine-123 metaiodobenzylguanidine (MIBG) can be used to evaluate cardiac sympathetic nerve function and is useful for assessing the prognosis of patients with heart disease. Renal impairment in heart failure patients has been recognized as an independent risk factor for morbidity and mortality, and has been observed as abnormal uptake and washout of cardiac MIBG imaging. The purpose of this study was to evaluate the prognostic value of cardiac MIBG imaging in heart disease patients with a glomerular filtration rate (GFR) either ≥60 ml/min/1.73 m^2 or <60 ml/min/1.73 m^2. ***Methods:*** Heart disease patients (n: 135, male/female: 87/48, mean age: 63 years, coronary artery disease/dilated cardiomyopathy/myocarditis: 41/62/32, mean left ventricular ejection fraction: 51%, GFR ≥60 ml/min/1.73 m^2 / GFR <60 ml/min/1.73 m^2: 103/32) underwent cardiac MIBG imaging and were followed-up for 2.7 years. GFR was calculated by the Modification of Diet in Renal Disease (MDRD) equation. Cardiac MIBG imaging was obtained 15 min and 4 h after isotope injection. The parameters analyzed for cardiac MIBG imaging were the heart-to-mediastinum ratio (H/M) on the delayed planar image and the cardiac washout rate. ***Results:*** Cardiac death was observed in 9 of 103 patients (9%) with a GFR ≥60 ml/min/1.73 m^2 and in 6 of 32 patients (19%) with a GFR <60 ml/min/1.73 m^2. The mortality ratio tended to be higher in patients with a GFR <60 ml/min/1.73 m^2 than in patients with a GFR ≥60 ml/min/1.73 m^2 ($p = 0.10$ with Kaplan-Meier survival curves). In patients with a GFR ≥60 ml/min/1.73 m^2, Cox regression analysis showed that a delayed H/M <146% was the most powerful predictor for cardiac death (Hazard ratio: 6.9, $p = 0.014$). However, in patients with a GFR <60 ml/min/1.73 m^2, the utility of cardiac MIBG imaging could not be proved. ***Conclusions:*** A delayed H/M is a powerful predictor of cardiac death if the GFR is 60 ml/min/1.73 m^2 or more.

Key words: cardiac death, cardiac sympathetic nerve function, coronary artery disease, dilated cardiomyopathy, predictors

INTRODUCTION

IN PATIENTS with heart failure, cardiac adrenergic nerve function is characterized by a reduction in norepinephrine uptake and acceleration of spillover in the myocardial adrenergic nerve terminals.[1] This abnormality of adrenergic nerve function is one of the important factors determining the prognosis of patients with heart failure.[2] Metaiodobenzylguanidine (MIBG) is an analog of the adrenergic blocking agent guanethidine; it shares the same uptake, storage, and release mechanisms as norepinephrine in adrenergic nerve terminals.[3] Cardiac iodine-123 MIBG imaging has been used extensively to assess cardiac adrenergic nerve activity.[4,5] In patients with heart failure, abnormal findings in cardiac MIBG imaging studies have been observed.[6–8] Volume and pressure overload causes increased washout and decreased uptake of MIBG in cardiac adrenergic nerve terminals, and it is related to the severity of heart failure independent of the underlying cause.[9,10] The heart and mediastinum ratio (H/M) of delayed planar images and the cardiac MIBG washout rate are useful for determining the prognosis of patients with heart failure.[11–18]

Received July 18, 2006, revision accepted November 14, 2006.

For reprint contact: Masao Moroi, M.D., Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, 2–17–6 Ohashi, Meguro-ku, Tokyo 153–8515, JAPAN.

E-mail: moroi@med.toho-u.ac.jp

In patients with heart failure, the mortality rate of patients with a creatinine clearance (Ccr) <44 ml/min is 3 times as high as that of those with a Ccr >76 ml/min.[19] Due to hyperactivity of cardiac sympathetic nerve function, abnormality of cardiac MIBG imaging has been observed in patients with chronic renal failure (CRF) especially in case of hemodialysis.[20,21] In previous studies, 60–70% of MIBG in the blood rapidly disappeared through kidneys within 24 hours.[4,22] In patients with renal failure, MIBG disappearance from blood is decreased. However, the power of cardiac MIBG imaging as a predictor of cardiac prognosis has been unclear in patients with CRF. It may be important to consider the renal function in interpreting the results of cardiac MIBG imaging. The purpose of this study was to investigate whether cardiac MIBG imaging is useful as a predictor of mortality in heart disease patients with or without CRF.

MATERIAL AND METHODS

Patient Population and Study Protocol

Patients with a previous history of heart failure (n: 135, males/females: 87/48, mean age: 62.5 ± 15.6 years) due to coronary artery disease (n = 41), dilated cardiomyopathy (n = 62), or myocarditis (n = 32) underwent cardiac MIBG imaging. We defined origin of heart diseases as follows:

Coronary artery disease; past history of coronary angioplasty at least 6 months before due to angina pectoris or myocardial infarction. No patients with coronary spasm were included in this study.

Dilated cardiomyopathy; unknown etiology of heart disease: coronary artery disease was ruled out by coronary angiography or stress myocardial perfusion imaging. Previous history of myocarditis could not be detected.

Myocarditis; acute onset of heart failure and suppressed cardiac function with previous cold symptoms with normal coronary angiography and stress myocardial perfusion imaging.

All the patients had New York Heart Association (NYHA) functional classifications of I (n = 92) to II (n = 43), and were in stable condition for at least for 2 months before cardiac MIBG imaging.

Patients were taking various medications at the time of the study (angiotensin-converting enzyme inhibitors: 53%; angiotensin receptor blocking agents: 20%; beta-blocker: 32%; calcium-channel blocker: 18%; spironolactone: 21%; digitalis: 16%); no patient was taking tricyclic antidepressants, sympathomimetic agents or other medications known to interfere with MIBG uptake. Patients were subjected to cardiac MIBG imaging once they were stabilized after receiving medical treatment.

Left ventricular end-diastolic dimension (LVDd) and left ventricular ejection fraction (LVEF) were measured by M-mode echocardiography within 1 month of MIBG imaging (mean LVDd: 55.8 ± 11.9 mm, mean LVEF: 50.7 ± 17.8%). Diabetes mellitus, hypertension, and CRF were identified in 21%, 43%, and 24% of patients respectively. We defined diabetes mellitus as a glycosylated hemoglobin (HbA_{1c}) fraction of >7.0%, or when patients were required treatment with insulin or hypoglycemic agents. We defined CRF as a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease (MDRD) equation according to Kidney Disease Outcomes Quality Initiative chronic kidney disease guidelines. The cause of CRF was hypertensive renal sclerosis in 21 patients, diabetic nephropathy in 10 patients, and unknown in 2 patients. Patients who required continuous hemodialysis were excluded from this study. All CRF patients underwent cardiac MIBG imaging at chronic and stable phase (at least for last 6 months). No CRF patients underwent kidney biopsy.

Patient follow-up was started after the assessment of cardiac function and cardiac I-123 MIBG imaging. The primary endpoint was definitive cardiac death due to pump failure and the secondary endpoint was sudden death due to sustained ventricular tachycardia or fibrillation. Patients were followed regularly for at least 2 months. Sudden cardiac death was defined as witnessed cardiac arrest or death within 1 h after the onset of acute symptoms or unexpected death (i.e., during sleep) in a patient known to have been well within the previous 24 h. Death due to deterioration of left ventricular function was classified as pump failure death. All patients gave informed consent for their participation in the study, which was approved by the Committee on Human Investigation at Toho University Ohashi Medical Center.

Quantification of Cardiac I-123 MIBG Activity

All patients underwent cardiac sympathetic nerve function imaging with I-123 MIBG (111 MBq, Daiichi Radioisotope Laboratory, Tokyo, Japan) using a three-headed gamma camera (MS-3, Siemens, Chicago, IL, USA) equipped with a low-energy high-resolution parallel-hole collimator (Siemens), and a 15% window centered at 158 keV was used. Early imaging began 15 min after the intravenous injection of 111 MBq I-123 MIBG. An anterior chest image was acquired for 300 sec in a 512 × 512 matrix, and then single photon emission computed tomography (SPECT) images were acquired. Delayed planar imaging was performed 240 min after the injection under the same acquisition conditions as used in the early imaging and then delayed SPECT imaging was performed. Two independent observers, unaware of the clinical status of the patients, assessed MIBG uptake. I-123 MIBG uptake in cardiac sympathetic nerve terminals was determined by using a manually drawn region of interest (ROI) over the whole left ventricular myocardium, and mean heart counts per pixel were calculated. Another 20 × 40 pixel ROI was placed over the upper mediastinal area, and the mean counts per pixel were calculated. The heart-to-mediastinum count ratio (H/M) was determined from the cardiac I-123 MIBG images using the following

Table 1 Baseline characteristics of the study population (n = 135)

	All patients	CRF (–)	CRF (+)	p-value
Male/Female (n)	87/48	67/36	20/12	0.83
Age (y)	62.5 ± 15.6	59.8 ± 15.2	71.3 ± 13.5	<0.001
GFR (ml/min/1.73 m^2)	73.2 ± 35.2	93.4 ± 26.8	41.3 ± 10.1	<0.001
Echocardiography				
LVDd (mm)	55.8 ± 11.9	55.8 ± 12.5	53.5 ± 9.7	0.99
LVEF (%)	50.7 ± 17.8	51.2 ± 18.1	49.1 ± 16.8	0.56
Cardiac MIBG imaging				
Delayed H/M (%)	166 ± 29	169 ± 29	155 ± 29	0.018
Washout rate (%)	45.5 ± 13.9	44.6 ± 13.9	48.4 ± 13.7	0.17
MIBG disappearance rate from blood (%)	34.3 ± 5.2	35.3 ± 4.8	31.0 ± 5.4	<0.001
Underlying disease				
Coronary artery disease	41 (30)	26 (25)	15 (47)	0.028
Dilated cardiomyopathy	62 (46)	50 (49)	12 (38)	0.54
Myocarditis	32 (24)	28 (29)	4 (13)	0.10
Diabetes mellitus	28 (21)	18 (17)	10 (31)	0.13
Hypertension	58 (43)	37 (31)	21 (66)	0.004
Hyperlipidemia	35 (26)	25 (24)	10 (31)	0.49
Medication				
ACE-I	71 (53)	51 (50)	20 (63)	0.23
Angiotensin receptor blocker	27 (20)	22 (21)	5 (16)	0.62
Beta-blocker	43 (32)	27 (26)	16 (50)	0.017
Ca channel blocker	24 (18)	16 (16)	8 (25)	0.29
Digitalis	21 (16)	18 (17)	3 (9)	0.40
Spironolactone	28 (21)	18 (17)	10 (31)	0.13
No medication	28 (21)	23 (22)	5 (16)	0.47
Cardiac deaths	15 (11)	9 (9)	6 (19)	0.19
Follow-up period (months)	33.7 ± 20.8	34.3 ± 21.2	31.9 ± 19.3	0.57

Data are presented as the mean value ± SD. CRF: chronic renal failure (glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 calculated by the modification of diet in renal disease (MDRD) equation, patients requiring hemodialysis were excluded) LV: left ventricular. LVDd: left ventricular end-diastolic dimension. EF: ejection fraction. H/M: heart and mediastinum ratio. ACE-I: Angiotensin converting enzyme inhibitor.

equation:

[H] = mean pixel counts for the heart ROI
[M] = mean pixel counts for the mediastinal ROI
H/M (%) = [H]/[M] × 100

Cardiac MIBG washout rate was defined as the percent change in activity from the immediate to delayed images within the left ventricle. The washout rate was calculated without a physical decay correction as follows:

$$\text{Washout rate (\%)} = \frac{([H]-[M])\ \text{early} - ([H]-[M])\ \text{delayed}}{([H]-[M])\ \text{early}} \times 100$$

We previously performed cardiac MIBG imaging in normal male subjects (n = 20, mean age; 52.3 ± 2.6, range 40–60). In these patients, mean delayed H/M was 220 ± 30% and mean washout rate was 27 ± 5.8%.

As shown in a previous study,[16] the disappearance of MIBG from blood is defined as the percent change in activity within the upper mediastinal area where mainly the aortic arch is present. The MIBG disappearance rate from blood was calculated as follows:

$$\text{Disappearance rate from blood (\%)} = \frac{[M]\ \text{early} - [M]\ \text{delayed}}{[M]\ \text{early}} \times 100$$

Statistical Analysis

Data are presented as the mean value ± SD. Chi-square analysis was utilized for comparison of differences in gender, underlying disease, medical treatment and number of cardiac deaths between patients with CRF and those without CRF. Student's test was utilized for comparison of age, follow-up period, echocardiograph parameters, and parameters related to cardiac MIBG imaging. Kaplan-Meier time to event curves and the log-rank test were utilized to analyze the risk of cardiac mortality in patients stratified into two groups on the basis of cardiac MIBG parameters. For parameters related to cardiac MIBG imaging and echocardiography, receiver operating characteristic (ROC) curves were adopted to determine the utility of factors as predictors of cardiac mortality, and to determine cutoff values. The Cox proportional hazards regression model was used to analyze the relationship between cardiac death and the following candidate

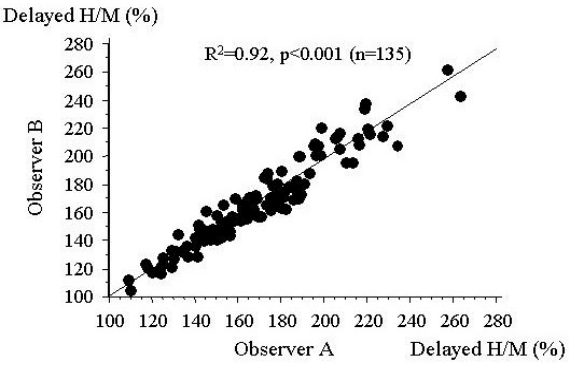

Fig. 1 Inter-observer variability in delayed H/M of cardiac MIBG imaging. There was an excellent correlation in the delayed H/M between the 2 observers.

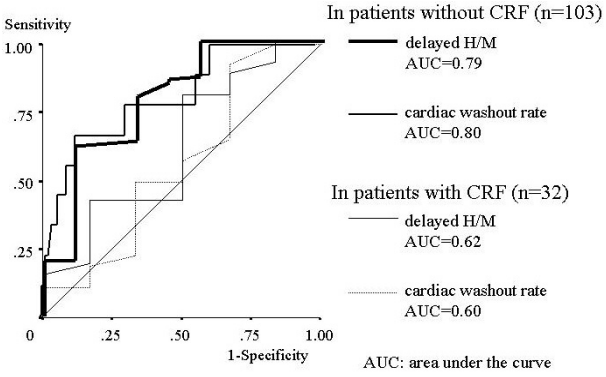

Fig. 2 Receiver operating characteristic (ROC) curves for predicting cardiac death based on parameters related to cardiac I-123 metaiodobenzylguanidine (MIBG) imaging. Parameters of cardiac MIBG imaging in patients without CRF; the ROC curves are shifted leftward compared to those in patients with CRF. Cardiac MIBG image parameters are good predictors in patients without CRF. In patients with CRF, the ROC curves could not indicate clear cut-off values for cardiac MIBG imaging.

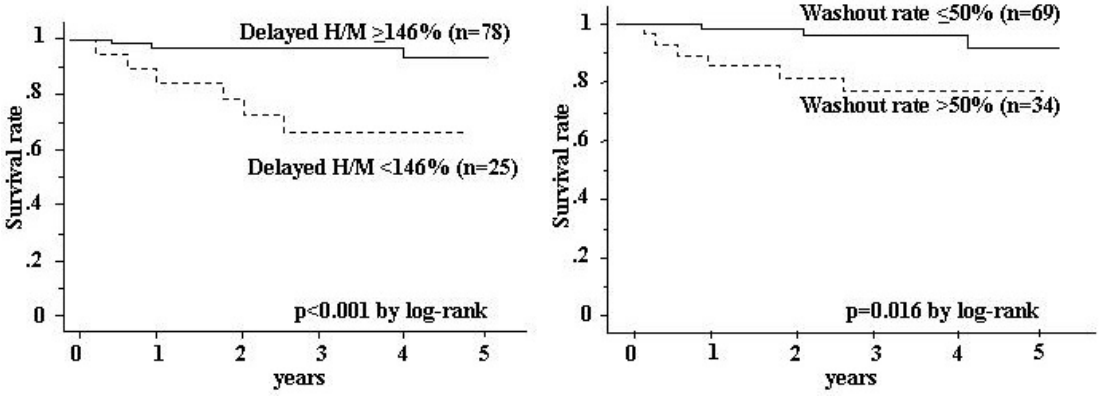

Fig. 3 Kaplan-Meier survival curves for patients without chronic renal failure (CRF) based upon cardiac I-123 metaiodobenzylguanidine (MIBG) imaging parameters. The incidence of cardiac death in patients with delayed H/M <146% was higher than in patients with delayed H/M ≥146% ($p < 0.001$ by log-rank test). The incidence of cardiac death in patients with a washout rate >50% was greater than that in patients with a washout rate ≤50% ($p = 0.016$ by log-rank test).

variables: age, gender, underlying disease, parameters related to echocardiography, and cardiac MIBG imaging. The variables entered into the multivariate analysis were selected after assessment of univariate association of all potential covariates with the endpoints. A stepwise multivariate Cox regression analysis was performed to identify variables providing the best prognostic information. A p-value < 0.05 was considered significant. These analyses were performed using the SPSS statistical program package (SPSS II; SPSS Inc. Chicago, IL, USA).

RESULTS

Patient Characteristics and Outcomes

Table 1 summarizes the baseline characteristics of the study population. During a mean follow-up period of 33.7 (range: 2 to 65) months, 15 cardiac deaths were observed: 11 patients died from pump failure and 4 patients died from sudden cardiac death. In 15 patients with cardiac death, cardiac death occurred in 9 patients (9%) without CRF and 6 patients (19%) with CRF. During the follow-up period, no acute coronary syndrome occurred and no patients were subjected to coronary revascularization. Mean age, presence of coronary artery disease, and hypertension were significantly higher in patients with CRF than in those without CRF. There were 28 patients without any medications for heart failure, such as ACE-I, angiotensin receptor blockers, beta blockers or spironolactone. In these patients, 5 patients had CRF and 23 patients had no CRF. There was no significant difference between

Table 2 Univariate proportional hazard model in patients without CRF (n = 103)

	Hazard ratio	95% CI	Wald chi-squared	p-value
Age (y)	1.0	0.97 to 1.1	0.65	0.42
Gender (Female)	0.48	0.10 to 2.3	0.83	0.36
Underlying disease				
Coronary artery disease	2.8	0.61 to 12	1.8	0.19
Diabetes mellitus	0.8	0.092 to 6.3	0.064	0.80
Hypertension	0.27	0.032 to 2.2	1.4	0.22
Hyperlipidemia	0.52	0.063 to 4.3	0.36	0.55
Echocardiography				
LVDd	1.1	1.0 to 1.1	4.7	0.030
LVEF	0.91	0.85 to 0.98	6.4	0.011
Cardiac MIBG imaging				
Delayed H/M	0.94	0.90 to 0.98	9.5	0.002
Washout rate	1.1	1.0 to 1.2	11	<0.001

Data are presented as the mean value ± SD. Abbreviations as in Table 1.

Table 3 Multivariate proportional hazard model in patients without CRF

	Hazard ratio	95% CI	Wald chi-squared	p-value
Echocardiography (LVEF < 47%)	1.3	0.27 to 5.9	0.09	0.77
Cardiac MIBG imaging (delayed H/M < 146%)	6.9	1.5 to 32	6.0	0.014

Data are presented as the mean value ± SD. Abbreviations as in Table 1.

patients with and without CRF in no medication patients (p = 0.47). The delayed H/M of cardiac MIBG images tended to be lower in patients with CRF than those without CRF. The MIBG disappearance rate from blood was significantly lower in patients with CRF than in patients without CRF. As shown in Figure 1, Pearson's analysis revealed that there was an excellent correlation in the delayed H/M between the 2 observers (observer A: range 107–261%, mean 166 ± 29.4%; observer B: range 105–262%, mean 165 ± 29.8%, $R^2 = 0.92$, $p < 0.001$).

Prognostic Analysis

In Kaplan-Meier survival curves, the mortality ratio tended to be higher in patients with CRF than in patients without CRF. For the parameters related to cardiac MIBG imaging (delayed H/M and cardiac washout rate), the ROC curves showed greater areas under the curve for patients without CRF than for patients with CRF, confirming the better prognostic value for predicting cardiac death in patients without CRF. Based on the ROC curves, the utility of cardiac MIBG imaging as a predictor for cardiac death was unclear in patients with CRF (Fig. 2). We also performed power analysis between patients without CRF and with CRF. The power was only 33%; therefore, we could not confirm the predictive value of cardiac MIBG imaging in patients with CRF. On the other hand, in patients without CRF the power was 74%.

In patients without CRF, the Kaplan-Meier survival curves using a threshold value of 146% for delayed H/M and 50% for washout rate are shown in Figure 3. These thresholds were adopted based on the ROC curves. The survival rate in patients with a delayed H/M <146% or washout rate >50% were significantly lower than those with a delayed H/M ≥146% ($p < 0.001$ by log-rank) or a washout rate ≤50% ($p = 0.016$ by log-rank).

The variables used for the univariate analysis are presented in Table 2. There were no significant associations between cardiac death and age, gender, or underlying disease. For parameters related to echocardiography, LVDd and LVEF predicted cardiac mortality. For the variables related to cardiac MIBG imaging, a delayed H/M or cardiac washout rate also predicted cardiac death.

In patients with CRF, parameters of cardiac MIBG imaging (delayed H/M and cardiac washout rate) and GFR were adopted for univariate analysis. These parameters were not predictive of cardiac deaths in CRF patients (delayed H/M; hazard ratio = 0.26, p = 0.45. cardiac washout rate; hazard ratio = 1.02, p = 0.57. GFR; hazard ratio = 0.97, p = 0.54).

As shown in Table 3, multivariate analysis was applied to parameters related to cardiac MIBG images and echocardiography. The best predictor of cardiac death was a delayed H/M for cardiac MIBG imaging <146% (hazard ratio: 6.9, p = 0.014).

DISCUSSION

Advanced renal dysfunction itself can be an independent risk factor for cardiac death.[19] In a Kaplan-Meier survival analysis, there was a trend toward greater cardiac death in patients with CRF than in those without CRF. However, this trend was not significant (p = 0.10). In this study, the

mean GFR of patients with CRF was relatively high (41.3 ± 10.1 m*l*/min/1.73 m^2). It might be the reason that the mortality ratio tended to be higher but not significantly so in patients with CRF than in patients without CRF.

In all patients, GFR could be a predictor for cardiac death in all patients in univariate hazard analysis (hazard ratio = 0.98, p = 0.028). In multivariate hazard analysis between cardiac MIBG imaging (delayed H/M) and GFR, cardiac MIBG imaging was a stronger predictor (hazard ratio = 0.95, p = 0.011) than GFR (hazard ratio = 0.98, p = 0.30).

In patients without CRF, the H/M for the delayed cardiac MIBG image was the most predictive parameter for cardiac death. However in patients with CRF, the utility of cardiac MIBG imaging in predicting cardiac death was unclear.

Electrolyte (sodium and potassium) imbalances, impaired volume control, and anemia might be dominant factors affecting prognosis in patients with CRF.[23,24] These factors make it difficult to predict long-term cardiac death. Previous studies showed that MIBG is excreted mainly from the kidneys.[4,22] And MIBG excretion rate from blood correlated with GFR.[22] On the other hand, a study concluded that disappearance rate of MIBG is 53% per 24 hours, and only partially related to GFR.[25] Therefore, we hypothesized that renal dysfunction affects disappearance of MIBG from the blood, and we calculated disappearance of MIBG from the blood. In this study, the disappearance rate of MIBG was significantly lower in patients with CRF than in patients without CRF (31.4 ± 5.4% vs. 35.3 ± 4.8%, p < 0.001). Within 4 hours after injection of MIBG for cardiac imaging, urinary excretion of MIBG may be a small factor for cardiac MIBG imaging in heart disease patients with CRF.

One study showed that MIBG imaging is very useful in predicting cardiac death in patients with both coronary artery disease and cardiomyopathy.[10] In this study, based on multivariate analysis, cardiac MIBG imaging was a stronger predictor than a history of coronary artery disease in patients without CRF.

Limitations of This Study

In this study, GFR was calculated using the MDRD equation, which approximates the actual value. We did not calculate GFR based on urinary collections. Because of the small number and varied causes of heart diseases in CRF patients, we can not conclude that cardiac MIBG imaging is useless for prediction of cardiac death in CRF patients. The number of patients with diabetes mellitus was small in this study; therefore we cannot assess the impact of diabetes mellitus on cardiac MIBG imaging. In addition, we performed echocardiography to evaluate left-ventricular volume and left-ventricular systolic function, instead of left-sided and right-sided catheterization, which might be more exact methods for this evaluation. In this study, 28 (21%) patients were receiving no medication for heart failure. In patients with no medication, 24 patients had preserved left-ventricular systolic function (LVEF ≥ 50% calculated by echocardiography). In no medication patients, 3 of 5 (60%) CRF patients and 21 of 23 (91%) non-CRF patients had preserved left-ventricular systolic function. That is why patients had no medication for heart failure. In CRF patients, one of 5 (20%) patients with no medication and 5 of 27 (19%) patients with medication patients experienced cardiac deaths (p > 0.99). We can not conclude the effectiveness of the medication of ACE-I and angiotensin receptor blocker due to the small number. We also did not consider the influence of medications during follow-up on cardiac death. Use of diuretics, renin-angiotensin system inhibitors, and beta-blockers and changes in the dosages of these medications after the assessment might bias the outcome of the follow-up study. One study suggested that the underlying etiology of cardiac dysfunction may affect the threshold of cardiac MIBG activity for the differentiation of high-risk patients.[10] In this study, the frequency of coronary artery disease was significantly higher in patients with CRF. This may explain, in part, the loss of utility for cardiac MIBG imaging to predict cardiac death in patients with CRF.

Serum B-type natriuretic peptides (BNP) levels were measured within 1 month from cardiac MIBG imaging. However, only 58 were measured (17 CRF patients; 387 ± 452 pg/m*l*. 41 non-CRF patients; 277 ± 297 pg/m*l*. p = 0.28). Cardiac deaths were observed in 6 of the 58 patients. In this study, due to the small number of patients whose serum BNP levels were measured, we can not assess the utility as a predictor of cardiac death as compared with cardiac MIBG imaging.

Left ventricular diastolic function (E/A ratio) was measured by echocardiography only in 26 patients (6 patients with CRF: E/A = 1.0 ± 0.2, 20 patients without CRF: E/A = 1.2 ± 0.1, p = 0.43). Among these patients whose E/A ratio was calculated, no cardiac death was observed. We can not assess the prognosis of cardiac death from this parameter.

CONCLUSION

In heart disease patients with normal renal function, cardiac iodine-123 MIBG imaging is very useful in evaluating prognosis with respect to cardiac death. Heart disease patients with CRF should be distinguished from heart disease patients with normal renal function because the usefulness of cardiac MIBG imaging in this group of patients is unclear.

ACKNOWLEDGMENT

We thank Chihiro Hamazaki for assistance with the MIBG imaging.

REFERENCES

1. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in congestive heart failure: evidence of increased cardiorenal and total sympathetic nerve activity. *Circulation* 1986; 73: 615–621.
2. Cohn JN, Levine BT, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984; 311: 819–823.
3. Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu JL, Clinthome NH, et al. Myocardial imaging with radioiodinated norepinephrine storage analog. *J Nucl Med* 1981; 22: 22–31.
4. Kline RC, Swanson DP, Wieland DM, Thrall JH, Gross MD, Pitt B, et al. Myocardial imaging in man with I-123 meta-iodobenzylguanidine. *J Nucl Med* 1981; 22: 129–132.
5. Sisson JC, Shapiro B, Meyers L, Mallette S, Mangner TJ, Wieland DM, et al. Metaiodobenzylguanidine to map scintigraphically the adrenergic nervous system in man. *J Nucl Med* 1987; 28: 1625–1636.
6. Schofer J, Spielmann R, Schuchert A, Weber K, Schuluter M. Iodine-123 meta-iodobenzylguanidine scintigraphy: a noninvasive method to demonstrate myocardial adrenergic nervous system disintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1988; 12: 1252–1258.
7. Henderson EB, Kahn JK, Corbett JR, Jansen DE, Pippin JJ, Kulkarni P, et al. Abnormal I-123 metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive cardiomyopathy. *Circulation* 1988; 78: 1192–1199.
8. Glowniak JV, Turner FE, Gray LL, Palac RT, Lagunas-Solar MC, Woodward WR. Iodine-123 metaiodobenzylguanidine imaging of the heart in idiopathic congestive cardiomyopathy and cardiac transplants. *J Nucl Med* 1989; 30: 1182–1191.
9. Imamura Y, Ando H, Mitsuoka W, Egashira S, Masaki H, Ashihara T, et al. Iodine-123 metaiodobenzylguanidine images reflect intense myocardial adrenergic nervous activity in congestive heart failure independent of underlying cause. *J Am Coll Cardiol* 1995; 26: 1594–1599.
10. Wakabayashi T, Nakata T, Hashimoto A, Yuda S, Tsuchihashi K, Travin MI, et al. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac death. *J Nucl Med* 2001; 42: 1757–1767.
11. Merlet P, Valette H, Dubois-Rande JL, Moyse D, Duboc D, Dore P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med* 1992; 33: 471–477.
12. Merlet P, Benvenuti C, Moyse D, Pouillant F, Dubois-Rande JL, Dural AM, et al. Prognostic value of MIBG imaging in idiopathic dilated cardiomyopathy. *J Nucl Med* 1999; 40: 917–923.
13. Momose M, Kobayashi H, Iguchi N, Matsuda N, Sakomura Y, Kasanuki H, et al. Comparison of parameters of ^{123}I-MIBG scintigraphy for predicting prognosis in patients with dilated cardiomyopathy. *Nucl Med Commun* 1999; 20: 529–535.
14. Ogita H, Shimonagata T, Fukunami M, Kumagai K, Yamada T, Asano Y, et al. Prognostic significance of cardiac ^{123}I metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: a prospective study. *Heart* 2001; 86: 656–660.
15. Imamura Y, Fukuyama T, Mochizuki T, Miyagawa M, Watanabe K; Ehime MIBG Heart Failure Study Investigators. Prognostic value of iodine-123-metaiodobenzylguanidine imaging and cardiac natriuretic peptide levels in patients with left ventricular dysfunction resulting from cardiomyopathy. *Jpn Circ J* 2001; 65: 155–160.
16. Imamura Y, Fukuyama T. Prognostic value of myocardial MIBG scintigraphy findings in patients with cardiomyopathy—importance of background correction for quantification of MIBG activity. *Ann Nucl Med* 2002; 16: 387–393.
17. Nakata T, Miyamoto K, Doi A, Sasao H, Wakabayashi T, Kobayashi H, et al. Cardiac death prediction and impaired cardiac sympathetic innervation assessed by MIBG in patients with failing and non-failing hearts. *J Nucl Cardiol* 1998; 5: 579–590.
18. Cohen-Solal A, Esanu Y, Logeart D, Pessione F, Dubois C, Dreyful G, et al. Cardiac metaiodobenzylguanidine uptake in patients with moderate chronic heart failure: relationship with peak oxygen uptake and prognosis. *J Am Coll Cardiol* 1999; 33: 759–766.
19. Hillege HL, Girbes ARJ, de Kam PJ, Boomsta F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000; 102: 203–210.
20. Kurata C, Wakabayashi Y, Shouda S, Okayama K, Yamamoto T, Ishikawa A, et al. Enhanced cardiac clearance of iodine-123-MIBG in chronic renal failure. *J Nucl Med* 1995; 36: 2037–2043.
21. Kurata C, Uehara A, Sugi T, Ishikawa A, Fujita K, Yonemura K, et al. Cardiac autonomic neuropathy in patients with chronic renal failure on hemodialysis. *Nephron* 2000; 84: 312–319.
22. Blake GM, Lewington VJ, Zivanovic MA, Ackery DM. Glomerular filtration rate and kinetics of I-123-metaiodobenzylguanidine. *Eur J Nucl Med* 1989; 15: 618–623.
23. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Lerey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001; 38: 955–962.
24. Braunwald E, Colucci WS, Grossman W. Clinical aspects of heart failure: high-output heart failure-pulmonary edema. In: Braunwald E, ed. *Heart disease: A Textbook of Cardiovascular Medicine*. Philadelphia, PA; WB Saunders, 1997: 445–470.
25. Wafelman AR, Nortier YL, Rosing H, Maessen HJ, Taal BG, Hoefnagel CA, et al. Renal excretion of metaiodobenzylguanidine after therapeutic doses in cancer patients and its relation to dose and creatinine clearance. *Nucl Med Commun* 1995; 16: 767–772.