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Prognostic value of myocardial MIBG scintigraphy findings in patients with cardiomyopathy—importance of background correction for quantification of MIBG activity

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Objective: To assess the prognostic value of I-123 metaiodobenzylguanidine (MIBG) scintigraphy findings, and establish the most appropriate method for calculating myocardial MIBG activity in patients with left ventricular dysfunction due to cardiomyopathy (CM). ***Methods:*** Predictors of cardiac death related to progressive heart failure (HF) were examined in 150 patients with CM (80 patients with idiopathic CM and 70 patients with ischemic CM). All patients underwent MIBG scintigraphy at rest and other hemodynamic studies when their clinical status was stable. MIBG scintigrams were obtained 15 minutes and 4 hours after the injection of the isotope. The parameters for quantification of myocardial MIBG activity were heart/mediastinal activity ratio (H/M) and myocardial washout rate (WR). The WR was calculated with and without background (BG) correction. ***Results:*** The WR showed better correlation with plasma norepinephrine and left ventricular ejection fraction after BG correction. During a mean follow-up period of 33 ± 9 (7 to 54) months, 12 patients died due to HF; 7 patients due to progressive HF and 5 patients due to sudden cardiac death. Cox regression analysis indicated, the H/M and the WR with and without BG correction, were significant predictors of cardiac death (Wald chi-squared value: H/M [15 min] = 9.7, H/M [4 hr] = 19.5, WR with BG correction = 29.9, WR without BG correction = 12.6). WR prognostic value was better after BG correction, and a high WR with BG correction was the only independent predictor of cardiac death (relative risk [RR] = 1.174, $p < 0.0001$). ***Conclusions:*** Accelerated WR is a powerful predictor of the patient's prognosis and BG correction is essential for calculating WR.

Key words: prognosis, cardiomyopathy, MIBG imaging, background correction

INTRODUCTION

IN PATIENTS with congestive heart failure (HF), activation of the adrenergic nerve system is one of the important physiologic responses elicited to compensate for depressed myocardial function. But an inverse relationship between the circulating norepinephrine level and prognosis has been demonstrated and sustained activation of the adrenergic nerve system is thought to be associated with increased mortality rates.[1] Iodine-123-metaiodobenzylguanidine (MIBG) shares many cellular transport properties with norepinephrine and MIBG, at the low concentrations used in clinical practice, and it is mainly taken up by adrenergic nerves at the presynaptic site.[2,3] Myocardial MIBG imaging plays a role in detecting adrenergic nerve activity, specifically, in the heart. It has been suggested that the initial uptake of MIBG reflects the ability of presynaptic adrenergic neurons to uptake norepinephrine and a myocardial washout of MIBG would therefore reflect myocardial adrenergic nerve activity.[4]

Myocardial MIBG scintigraphy is useful to estimate the severity of heart failure and also useful to predict the prognosis of patients with HF, but there is still controversy regarding the appropriate parameter of myocardial MIBG activity.[5–8] A high myocardial MIBG washout has been reported to be a useful predictor of future cardiac events in patients with cardiomyopathy,[9] but it has also been reported that myocardial MIBG activity, as assessed

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by heart/mediastinal activity ratio, is the only useful indicator of prognosis, and that MIBG washout cannot be used as an index of prognosis.[10] But since the method for calculating myocardial MIBG washout differed in these studies, this difference can be the reason for the discrepancies concerning the prognostic impact of myocardial MIBG washout. The goal of this study was to assess the prognostic value of MIBG scintigraphy findings and to clarify the most appropriate indices derived from MIBG scintigraphy for predicting the prognosis of patients with cardiomyopathy.

MATERIALS AND METHODS

Study Population

The subjects of this study were patients with left ventricular dysfunction resulting from cardiomyopathy. Patients were entered into this study consecutively from Feb. 1997 to Feb. 1999. Informed consent was obtained from all the patients. Since it has been reported that myocardial MIBG activity is affected by some medications, such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers, patients were subjected to myocardial MIBG scintigraphy once they were stabilized after receiving medical treatment.[11,12] All clinical and laboratory data were obtained within two weeks. We studied 150 patients whose left ventricular ejection fraction was less than 40% as measured by radionuclide angiography. All patients underwent coronary angiography. Eighty patients with normal coronary arteries and no other recognized etiology were considered to have idiopathic cardiomyopathy. Seventy patients with coronary stenosis and a clinical history thereof were considered to have ischemic cardiomyopathy.

There were 111 men and 39 women aged 63 ± 11 years. 110 patients had sinus rhythm and 40 patients had atrial fibrillation. Thirty-eight patients were in functional class I of the New York Heart Association [NYHA] functional classification, 75 patients were in NYHA class II, 32 patients were in NYHA class III and 5 patients were in NYHA class IV. Patients were taking various medications at the time of the study, but none of the patients was taking tricyclic antidepressants, sympathomimetics or other drugs known to interfere with MIBG uptake.

Protocol and Imaging

Hemodynamic examination, including neuroendocrine measurement and MIBG imaging, were performed within two weeks after the patients became clinically stable.

Blood samples were drawn to determine plasma norepinephrine (NE) after the patients had rested in the supine position for at least one hour in the morning on the day of MIBG imaging. Treatment with drugs which included digitalis preparations, diuretics, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors and calcium channel antagonists, was continued. Patients were asked to rest in the supine position and an i.v. catheter was placed in an antecubital vein. Iodine-123-MIBG was obtained commercially (Daiichi Radioisotope Laboratory, Tokyo, Japan). 111 MBq of ^{123}I-MIBG was injected and flushed with normal saline. Myocardial images were acquired with a standard-field gamma camera and a 20% window centered at 159 keV was used. Planar imaging was performed in the anterior view of the chest. The first acquisition began 15 minutes after the tracer was injected and the second one began 4 hours after the tracer was injected.

Image Analysis

Left ventricular ^{123}I-MIBG activity was measured with a manually drawn region of interest (ROI) around the left ventricular myocardium. A 20×20 pixel ROI was placed over the upper mediastinum area. Background correction was performed with the upper mediastinum ROI. To evaluate the myocardial uptake of MIBG, the heart/mediastinal activity ratio was calculated from scintigrams obtained 15 minutes (immediate image) and 4 hours (delayed image) after the isotope was injected by the following formula:

$$\text{heart/mediastinal activity ratio: } H/M = [H]/[M],$$

where [H] = mean counts/pixel in the left ventricle; and [M] = mean counts/pixel in the upper mediastinum.

Myocardial MIBG washout was defined as the percent change in activity from the immediate and delayed images within the left ventricle. The myocardial MIBG washout rate (WR) was calculated both with and without background (BG) correction as follows:

$$\text{WR with BG correction} = \frac{([H]-[M])\ \text{immediate} - ([H]-[M])\ \text{delayed}}{([H]-[M])\ \text{immediate}} \times 100\ (\%).$$

$$\text{WR without BG correction} = \frac{[H]\ \text{immediate} - [H]\ \text{delayed}}{[H]\ \text{immediate}} \times 100\ (\%).$$

Disappearance of MIBG from blood was defined as the percent change in activity within the upper mediastinum area where only the aortic arch exists, and we named this index the aortic disappearance rate. The aortic MIBG disappearance rate was calculated as follows:

$$\text{Aortic disappearance rate} = \frac{[M]\ \text{immediate} - [M]\ \text{delayed}}{[M]\ \text{immediate}} \times 100\ (\%).$$

Noninvasive Hemodynamic Examination

The X-ray cardiothoracic ratio was calculated with the maximal cardiac diameter and the intrathoracic diameter at the level of the right costocardiac border. Equilibrium radionuclide angiocardiography was performed with 740

Table 1 Baseline characteristics of the study population as a whole and in patients distributed according to outcome

	All patients (n = 150)	Event-free (n = 138)	Cardiac death (n = 12)
Age (yr)	63 ± 11	64 ± 10	60 ± 15
Gender, M/F	111/39	102/36	8/4
Causes of heart failure (Idiopathic/Ischemic)	83/67	78/60	7/5
Medical treatment (%)			
Diuretics	111 (74)	105 (76)	10 (91)
Digitals	108 (72)	101 (73)	8 (73)
ACE inhibitors	120 (80)	109 (79)	9 (82)
β-blockers	84 (56)	81 (59)	6 (55)
Ca-antagonists	52 (35)	50 (36)	6 (55)
Hemodynamic data			
CTR (%)	55 ± 7	55 ± 7	65 ± 10*
LV end-diastolic diameter (mm)	59 ± 9	58 ± 9	67 ± 9*
LV end-systolic diameter (mm)	48 ± 11	47 ± 10	59 ± 10*
LVEF (%)	27 ± 10	28 ± 9	17 ± 7*
Neurohumoral data			
NE (pg/m*l*)	0.62 ± 0.38	0.59 ± 0.35	1.05 ± 0.492*
MIBG data			
H/M-I	1.78 ± 0.27	1.80 ± 0.26	1.54 ± 0.21*
H/M-D	1.64 ± 0.26	1.67 ± 0.25	1.28 ± 0.18*
WR-BGC	46 ± 12	44 ± 12	66 ± 9*
WR-BGU	39 ± 7	38 ± 7	46 ± 2*

ACE-inhibitor = angiotensin-converting enzyme inhibitor; β-blocker = beta-adrenergic blocking agent; Ca-antagonist = calcium channel antagonist; CTR = cardiothoracic ratio (%); LV end-diastolic diameter and LV end-systolic diameter = left ventricular end-diastolic and end-systolic diameters measured by echocardiography (mm); LVEF = left ventricular ejection fraction measured by routine radionuclide angiography; NE = plasma norepinephrine (pg/m*l*); H/M-I = heart/mediastinal activity ratio in immediate image; H/M-D = heart/mediastinal activity ratio in delayed image; WR-BGC = myocardial MIBG washout rate background corrected (%) and WR-BGU = myocardial MIBG washout rate background uncorrected (%).

* p < 0.01 versus Event-free subgroup (One way analysis of variance).

MBq of technetium-99m and the left ventricular ejection fraction (LVEF) was calculated with a standard software program. Left ventricular end-diastolic and end-systolic diameters were measured in the parasternal long-axis view by two-dimensional-guided M-mode echocardiography. NE was determined by Biomedical Laboratories (Tokyo) by means of high-performance liquid chromatography (HPLC) with electrochemical detection.

Follow-up Data

Patients were followed-up for at least twelve months, the mean (± SD) follow-up period was 33 ± 9 (7 to 54) months. The prospectively defined outcome measures was cardiac death, defined as death from progressive HF or sudden cardiac death.

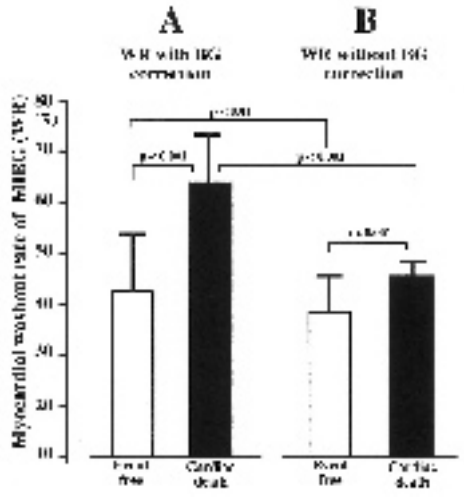

Fig. 1 Myocardial washout of MIBG (WR) in patients who died due to heart failure and in patients without heart failure events. Myocardial washout of MIBG was calculated with and without background (BG) correction (A: with background correction and B: without background correction).

Statistical Analysis

All statistical calculations were performed with Statistical Analysis System computer programs (SAS: Abacus Concepts, Inc., USA). Data were presented as the mean value ± SD. More than two groups were compared by analysis of variance (ANOVA) followed by the multiple comparison test (modified t-test according to Bonferroni). Differences were considered statistically significant when the p value was <0.05.

The Cox proportional hazards regression model was used to assess the relative prognostic values of different variables considered likely to have a clinically important association with the outcome during follow-up. Variables included in this analysis were age, gender, underlying causes (idiopathic or ischemic), NYHA functional class, non-invasive hemodynamic studies, neurohumoral measurements and MIBG imaging data. The chi-squared value was calculated from the log of the ratio of maximal partial likelihood functions. Variables for which the p value of the univariate chi-squared test was <0.05 were considered significant predictors of prognosis. 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.

RESULTS

Patient's characteristics and clinical outcome

Table 1 shows the baseline characteristics of the study

population as a whole and those in patients distributed by the clinical outcome. During a mean (± S.D.) follow-up period of 33 ± 9 (7 to 54) months, 12 patients died from HF (7 patients died from progressive HF and 5 died of sudden cardiac death) whose etiology of LV dysfunction was idiopathic in 7 patients and ischemic in 5. Two patients had non-fatal myocardial infarction. Four patients had experienced worsening of angina and underwent angioplasty or bypass surgery. The X-ray cardiothoracic ratio, LV end-diastolic and end-systolic diameters and plasma norepinephrine levels were higher, whereas the left ventricular ejection fraction was lower in patients who died. The heart/mediastinal activity ratios in both immediate and delayed images were lower in patients who died. Although the myocardial washout rates, both with and without background correction, were higher in patients who died, the difference in the myocardial washout rate between patients who died and event-free patients was lower without BG correction (Fig. 1).

Cox regression analysis

The variables used for the univariate analysis are pre-

Table 2 Estimated relative risk for significant univariate predictors of death from heart failure

	Cardiac Death		
	RR (95% CI)	Wald chi-squared	p value
Clincal data			
Age	1.019 (0.943–1.089)	0.42	NS
Gender	1.822 (0.399–9.223)	0.53	NS
Cause of HF	1.225 (0.341–4.372)	0.17	NS
NYHA class	3.832 (1.912–7.684)	14.3	0.0002
Hemodynamic data			
CTR	1.149 (1.087–1.214)	18.0	<0.0001
LVEF	0.847 (0.774–0.927)	12.9	0.0003
LV end-diastolic diameter	1.109 (1.046–1.177)	12.0	0.0005
LV end-systolic diameter	1.112 (1.057–1.170)	16.7	<0.0001
Neurohumoral data			
NE	13.07 (3.885–43.98)	17.2	<0.0001
MIBG data			
H/M-I	0.011 (0.001–0.242)	9.7	0.0034
H/M-D	0.034 (0.008–0.152)	19.5	<0.0001
WR-BGC	1.159 (1.099–1.222)	29.9	<0.0001
WR-BGU	1.185 (1.083–1.297)	12.6	0.0003

p values were calculated on the basis of Cox proportional hazard analysis.
RR = relative risk; CI = confidence interval.
Gender means male vs. female and cause of HF means idiopathic vs. ischemic.
Abbreviations are given in Table 1.

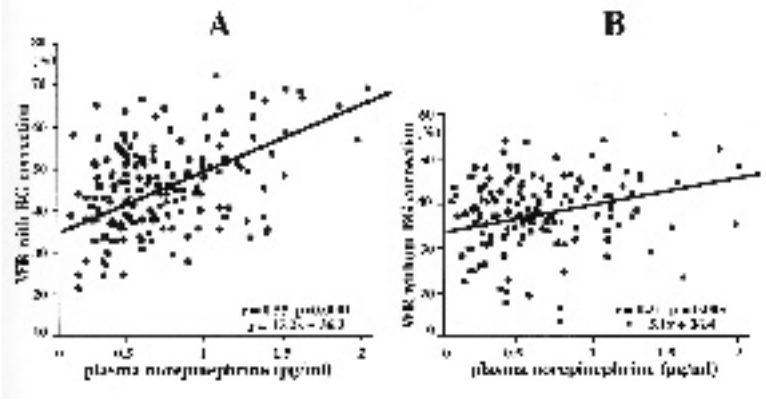

Fig. 2 Correlation between plasma norepinephrine levels (pg/m*l*) and myocardial washout of MIBG (WR). Myocardial washout of MIBG was calculated with and without background (BG) correction (A: with background correction and B: without background correction).

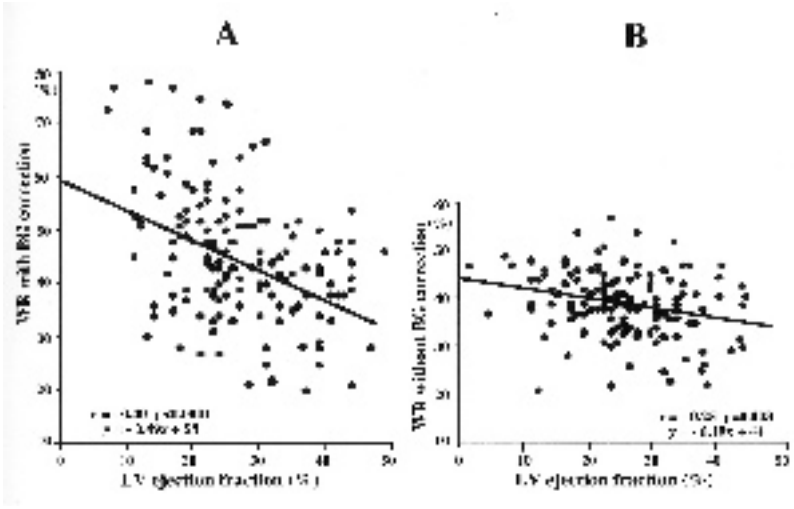

Fig. 3 Correlation between left ventricular (LV) ejection fraction and myocardial washout of MIBG (WR). Myocardial washout of MIBG was calculated with and without background (BG) correction (A: with background correction and B: without background correction).

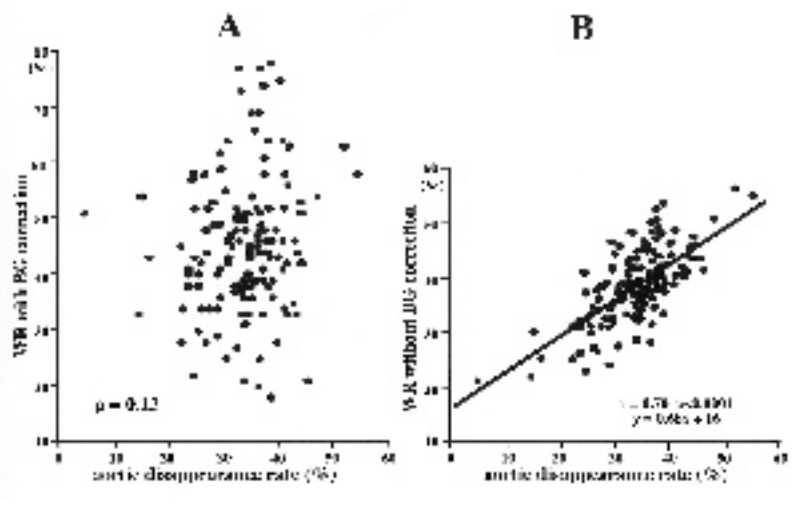

Fig. 4 Correlation between aortic disappearance rate and myocardial washout of MIBG (WR). Myocardial washout of MIBG was calculated with and without background (BG) correction (A: with background correction and B: without background correction). Note that the WR correlated well with aortic disappearance rate when BG was not corrected (Fig. 4B), whereas this correlation disappeared when BG was corrected properly (Fig. 4A).

sented in Table 2. Among all clinical, hemodynamic and neurohumoral data, the NYHA functional classification, the X-ray cardiothoracic ratio, the left ventricular ejection fraction, LV end-diastolic and end-systolic diameters, and plasma norepinephrine levels were predictors of mortality due to HF. As for the variables examined by MIBG imaging, the heart/mediastinal activity ratios in both immediate and delayed images and myocardial washout rates with and without BG correction were also significant predictors of mortality.

When the Cox regression analysis was applied to MIBG imaging findings and all other hemodynamic and neurohumoral variables, the best independent predictor of mortality from HF was the myocardial washout rate with BG correction (relative risk [RR] = 1.174, $p < 0.0001$).

Relationship between myocardial washout rate of MIBG and neurohumoral and hemodynamic data

The myocardial washout rate correlated positively with plasma norepinephrine levels, but the correlation was weak without BG correction ($r = 0.55$, $p < 0.0001$ for WR with BG correction: Figure 2A and $r = 0.31$, $p = 0.005$ for WR without BG correction: Figure 2B). Myocardial washout rate correlated inversely with left ventricular ejection

fraction, but its correlation was also weak without BG correction ($r = -0.40$, $p < 0.0001$ for WR with BG correction: Figure 3A and $r = -0.25$, $p = 0.003$ for WR without BG correction: Figure 3B). The myocardial washout rate without BG correction correlated positively with aortic disappearance rate, but the myocardial washout with BG correction did not ($p = 0.13$ for WR with BG correction: Figure 4A and $r = 0.70$, $p < 0.0001$ for WR without BG correction: Figure 4B).

DISCUSSION

The major finding of this study was that the myocardial MIBG washout rate with BG correction was high in patients who died of HF, and that the myocardial washout rate provided independent prognostic information. In addition, the myocardial washout rate with BG correction correlated well with plasma norepinephrine levels, whereas the myocardial washout rate without BG correction correlated well with aortic MIBG disappearance rate. These lines of evidence suggest that in patients with cardiomyopathy the adrenergic nervous system was activated, as assessed by the myocardial washout rates with BG correction, and therefore, the washout rate provides independent prognostic information with regard to subsequent cardiovascular mortality.

Prognostic value of MIBG

Myocardial MIBG activity is reportedly affected by treatment with angiotensin-converting enzyme (ACE) inhibitors or β-blocker. For this reason, patients were examined once they had become stabilized after receiving medication.

The present results disagree with those of an earlier study showing that heart/mediastinal activity had a powerful predictive value but the MIBG washout rate did not.[13] This difference may be due to the different methods used to calculate the myocardial MIBG washout rate, in our study and that by Cohen-Solal et al.[13] The most important difference was that to calculate the myocardial washout rates we applied background correction, whereas they did not. It is clearly shown in Table 2, that the prognostic value of the myocardial washout rate is low without BG correction. The mechanism of myocardial washout of MIBG has not been well elucidated. In the present study, myocardial washout rates showed a better correlation with plasma norepinephrine levels and the left ventricular ejection fraction after BG correction. The myocardial washout rate without BG correction scarcely correlated with the plasma norepinephrine level and left ventricular ejection fraction but showed a strong correlation with the aortic disappearance rate. In the upper mediastinal area, where only the aortic arch exists, the MIBG disappearance rate in the upper mediastinal area may mainly reflect the disappearance of MIBG from blood. These lines of evidence indicate that the myocardial washout rate without BG correction reflects MIBG disappearance from blood and this index is not useful to estimating myocardial adrenergic nerve activity. The importance of background correction in calculating myocardial washout has been indicated in patients with HF.[14] Especially, in patients with severe HF due to cardiomyopathy, the heart/mediastinal activity rate is low, less than two, so that the myocardial washout rate without BG correction is susceptible to the disappearance of MIBG counts in the blood pool, and therefore the prognostic value of myocardial washout rate is low without BG correction.

The prognostic value of the myocardial washout rate with background correction was somewhat superior to that of the heart/mediastinal activity ratio. But our data did not deny the predictive value of the heart/mediastinal activity ratio. It is shown in Table 2, that the chi-square value for the heart/mediastinal activity ratio regarding mortality due to HF was high. The heart/mediastinal activity ratio is affected by both the initial uptake and washout of MIBG. Patients with HF have an accelerated myocardial washout of MIBG that corresponds to the severity of HF, and it is possible that when the washout rate is high, the heart/mediastinal activity ratio in delayed image decreases.[5] Therefore, it is very likely that both the heart/mediastinal activity ratio and the washout rate provide prognostic information in patients with HF.

Therapeutic implications

The results of this study suggest that patients with a high myocardial MIBG washout rate are at a high risk of mortality due to HF. Reportedly, the washout of MIBG from the heart is accelerated in patients with HF independent of underlying causes,[5] and the myocardial MIBG washout rate was similar idiopathic and ischemic patients groups in this study. The present findings implications are of great therapeutic importance: therapies that decrease adrenergic nerve activity may be of therapeutic value in patients with HF from any cause. In medical therapy for HF, angiotensin-converting enzyme inhibitors and β-blockers are reported to improve the prognosis and this effect is partially related to the suppression of adrenergic nerve activity.[15,16] By means of MIBG imaging, it is possible to assess adrenergic nerve activity specifically in the heart, and so that MIBG imaging may become a useful tool to evaluate the efficacy of medical treatment by estimating adrenergic nerve activity.

CONCLUSIONS

Iodine-123 MIBG imaging, especially its washout rate from the heart is useful to evaluating the severity and prognosis of cardiomyopathy. But background correction is essential to calculate the myocardial washout of MIBG.

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