JACC Vol. 26, No. 7
December 1995:1594–9

Iodine-123 Metaiodobenzylguanidine Images Reflect Intense Myocardial Adrenergic Nervous Activity in Congestive Heart Failure Independent of Underlying Cause

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Objectives. **This study was undertaken to assess myocardial adrenergic activity using iodine-123 metaiodobenzylguanidine (MIBG) imaging in patients with heart failure.**

Background. **In patients with congestive heart failure, adrenergic nerve activity is accelerated. However, whether myocardial adrenergic nerve activity reflects the severity of heart failure and its relation to the underlying cause have not yet been elucidated.**

Methods. **Planar MIBG images were obtained from 96 patients with heart failure and compared with images from 9 age-matched healthy subjects. Groups 1 and 2 included 65 patients with heart failure related to impaired myocardial function and whose left ventricular ejection fraction was <40% (group 1 = 40 patients with dilated cardiomyopathy; group 2 = 25 patients with ischemic cardiomyopathy). Group 3 included 31 patients with heart failure related to a mechanical abnormality and whose left ventricular ejection fraction was >40% (mitral regurgitation in 16, aortic regurgitation in 9, aortic and mitral regurgitation in 4, ruptured aneurysm of Valsalva in 2). Myocardial uptake of MIBG was calculated as the heart/mediastinal activity ratio. Storage and release of MIBG were calculated as percent myocardial MIBG washout from 15 min to 4 h after isotope injection.**

Results. **The heart/mediastinal activity ratio in the immediate images (15 min) showed a significant decrease only in patients with severe heart failure (groups 1 and 2). The myocardial washout was accelerated in all three heart failure groups. The level of myocardial washout was related to severity of heart failure and correlated well with New York Heart Association functional classification.**

Conclusions. **In severe heart failure associated with cardiomyopathy, norepinephrine uptake is reduced. In addition, myocardial adrenergic nerve activity is accelerated in proportion to severity of heart failure, independent of the underlying cause.**

(J Am Coll Cardiol 1995;26:1594–9)

In patients with congestive heart failure, it has been demonstrated that plasma norepinephrine levels are increased, generally two to three times the levels observed in normal subjects (1,2), reflecting increased activation of the adrenergic nerve system (3). On the basis of findings of an increased aortocoronary sinus plasma catecholamine gradient (4,5) and an increase in the rate of norepinephrine spillover to plasma from the heart (6,7), intense myocardial adrenergic nervous stimulation has been suggested. Iodine-123 (I-123) metaiodobenzylguanidine (MIBG) is an analog of the adrenergic blocking agent guanethidine and shares many cellular transport properties with norepinephrine (8). It was developed as a clinical tool to visualize sympathetic innervation and was recently used to study myocardial adrenergic nerve activity (9,10). In patients with dilated cardiomyopathy, abnormal findings on myocardial MIBG images, such as a reduced myocardial/mediastinal MIBG activity ratio, heterogeneous distribution of MIBG within the myocardium and increased MIBG washout from the heart have been demonstrated (11–13). These abnormal findings have been implicated as reflecting a loss of myocardial adrenergic nervous system integrity during heart failure, a combination of a reduced uptake (14) and increased release of norepinephrine from adrenergic nerve endings (4).

However, heart failure also develops in the setting of work overload or mechanical abnormality, such as valvular heart disease, and abnormal findings on myocardial MIBG images, such as high MIBG washout from heart, have been observed (15). However, whether these abnormal results vary according to the cause of the heart failure, and whether MIBG imaging is associated with severity of heart failure, is not known. To elucidate the change in myocardial adrenergic nervous activity in patients with heart failure, we investigated MIBG images from 96 patients with heart failure of various causes.

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Manuscript received March 2, 1995; revised manuscript received June 30, 1995, accepted July 13, 1995.

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0735-1097/95/$9.50
0735-1097(95)00374-D

Table 1. Baseline Characteristics of Study Patients

	Group 1 (n = 40)	Group 2 (n = 25)	Group 3 (n = 31)
Age (yr)	61 ± 8	65 ± 14	58 ± 8
Gender (M/F)	26/14	15/10	17/14
LVEF (%)	21 ± 5*	23 ± 6*	56 ± 7
NYHA			
I	11	6	7
II	18	10	15
III/IV	11	9	9
Medical treatment			
Beta-blocker	13 (33)	5 (20)	5 (16)
Ca antagonist	10 (25)	7 (28)	7 (23)
ACE inhibitor	21 (53)	8 (32)	15 (48)
Digoxin	34 (85)	18 (72)	18 (58)

*$p < 0.01$ groups 1 and 2 versus group 3. Data presented are mean value ± SD, number of patients or number (%) of patients. ACE inhibitor = angiotensin-converting enzyme inhibitor; Ca antagonist = calcium channel antagonist; F = female; LVEF = left ventricular ejection fraction measured by routine radionuclide angiography; M = male; NYHA = New York Heart Association functional class.

Methods

Study patients. Participants in the study were 96 patients with heart failure. To clarify the influence of the underlying cause of heart failure on myocardial MIBG imaging, we classified the patients into three different groups. Groups 1 and 2 included 65 patients with heart failure primarily ascribed to diminished myocardial contractility and whose left ventricular ejection fraction, measured by radionuclide angiography, was <40%: *group 1* = 40 patients with dilated cardiomyopathy; *group 2* = 25 patients with ischemic cardiomyopathy with global severe hypokinesia by radionuclide angiography. *Group 3* = 31 patients with heart failure primarily ascribed to mechanical abnormalities, such as valvular heart disease, whose left ventricular systolic function was preserved (>40%) (16 with mitral regurgitation, 9 with aortic regurgitation, 4 with mitral and aortic regurgitation, 2 with ruptured aneurysm of Valsalva). Patients with cardiomyopathy and significant valvular dysfunction, and those with valvular heart disease whose left ventricular ejection fraction was <40%, were excluded to clarify the difference between groups 1 and 2 and group 3. Baseline characteristics of each group are shown in Table 1. Patients were taking a variety of medications at the time of the study, but none were taking tricyclic antidepressant or sympathomimetic agents or other drugs known to interfere with MIBG uptake.

Control group. Nine normal subjects (four men, five women; mean [±SD] age 58 ± 3 years) who underwent clinical, hematologic and biochemical screening, chest radiography, rest and exercise electrography and echography before admission to the study formed the control group.

Protocol and imaging. Blood samples were drawn from 66 inpatients for plasma human atrial natriuretic peptide (hANP) and norepinephrine determinations after supine rest for a minimum of 1 h on the morning of the day of the MIBG imaging study. All medications, including digitalis preparations, diuretic drugs, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors and calcium channel antagonists, were continued; 2 mg of potassium iodide was given orally from 1 day before to 4 days after the study to block thyroid uptake of I-123 MIBG. Patients were placed in the supine position, and an intravenous catheter was placed in an antecubital vein. Iodine-123 MIBG was obtained commercially (Daiichi Radioisotope Laboratory, Tokyo, Japan); 111 MBq of I-123 MIBG was injected and flushed with normal saline solution. Myocardial images were acquired using a standard-field gamma camera equipped with a low energy, parallel-hole collimator (SNC-500R, Shimazu, Kyoto, Japan). A 20% window centered at 159 keV was used. Planar imaging was performed with converging collimators in the anterior view of the chest. The first acquisition began 15 min after tracer injection (*immediate image*). Identical acquisition was obtained at 4 h after tracer injection (*delayed image*). Images were collected in a nuclear medicine computer for later analysis (Scintipac 2400, Shimazu).

Gated radionuclide angiography was performed using a single-crystal scintillation camera (ZLC 3700, Siemens, Solna, Sweden) and the method of in vivo labeling of technetium-99m (Tc-99m) red blood cells with 740 MBq of Tc-99m. Processing of the data was accomplished with the Scintipac 2400.

Image analysis. Left ventricular I-123 MIBG activity was measured using a manually drawn region of interest around the left ventricular myocardium. A 20 × 20-pixel region of interest was placed over the upper mediastinal area. Background subtraction was performed using the upper mediastinal region of interest. To evaluate the myocardial accumulation of MIBG, the heart/mediastinal (H/M) activity ratio was calculated by the following formula from scintigrams obtained at 15 min (immediate image) and 4 h (delayed image) after isotope injection:

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

where [H] = mean count/pixel in the left ventricle; and [M] = mean count/pixel in the upper mediastinum. Myocardial MIBG washout was defined as percent change in activity from the immediate and delayed images within the left ventricle as follows (10):

$$\{([H] - [M])_{\text{immediate}} - ([H] - [M])_{\text{delayed}}\}/([H] - [M])_{\text{immediate}} \times 100(\%).$$

Because systemic sympathetic activity is altered in patients with heart failure, accumulation and washout of MIBG in the liver, which does not have dense adrenergic innervation, were also measured and compared with those in the heart. A 20 × 20-pixel region of interest was placed over the right lobe in the anterior view and analyzed in the same manner.

Left ventricular diastolic function. In group 3, left ventricular systolic function was preserved, and we analyzed diastolic function. The indexes were 1) peak filling rate, determined by calculating the first derivative of the time–activity curve at the time of peak filling and expressed as end-diastolic cps; and 2) time to peak filling rate, the time interval between end-systole to the time of peak left ventricular filling rate (16).

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Neuroendocrine measurement. Blood samples for norepinephrine were withdrawn into prechilled tubes containing reduced glutathione and calcium chelator ethylenediaminetetraacetic acid (EDTA) as preservative for norepinephrine analysis. The samples were centrifuged at 4°C at 2,500 rpm for 12 min. The norepinephrine analysis was performed by Biomedical Laboratories (Tokyo, Japan) with high performance liquid chromatography with electrochemical detection. Blood samples for plasma hANP were withdrawn into evacuated EDTA tubes and centrifuged at 4°C at 2,500 rpm for 12 min. Plasma hANP was also measured by Biomedical Laboratories with a simplified radioimmunoassay using commercially available antibodies.

Statistical analysis. Data are presented as mean value ± SD. The chi-square test was used to compare categoric variables. Comparison of more than two groups was performed by analysis of variance followed by the multiple comparison test (modified *t* test according to Bonferroni). Differences were considered statistically significant at $p < 0.05$.

Results

Plasma norepinephrine and hANP levels. Patients in New York Heart Association functional classes II and III/IV had significantly higher norepinephrine levels, and to the same extent, than patients in functional class I (0.25 ± 0.07, 0.49 ± 0.25, 0.56 ± 0.31 ng/ml for functional classes I, II and III/IV, respectively, $p < 0.01$, class I vs. class II and class I vs. class III/IV). hANP levels were also higher in patients in functional class III/IV (33.8 ± 21.1, 75.0 ± 45.0, 155.9 ± 102.7 pg/ml for functional classes I, II and III/IV, respectively, $p < 0.01$, classes I and II vs. class III/IV).

Myocardial accumulation of MIBG. In the immediate images, the heart/mediastinal activity ratio (Fig. 1) did not show any significant differences in Group 3 between any functional class or the control group. However, in group 1 and 2 patients in functional class III/IV, the heart/mediastinal activity ratio was decreased ($p < 0.01$) (Fig. 1, top). In the delayed images, the heart/mediastinal activity ratio decreased in group 1 and 2 patients in functional classes II and III/IV and in group 3 patients in functional class III/IV ($p < 0.01$) (Fig. 1, bottom).

Myocardial washout of MIBG. Myocardial washout of MIBG was increased in proportion to severity of congestive heart failure in all groups. There were no significant differences between groups for any functional class (Fig. 2). Myocardial washout correlated positively with plasma norepinephrine levels, but its correlation was weak ($r = 0.38$, $p < 0.01$) (Fig. 3, top). Myocardial washout also correlated positively with plasma hANP concentrations ($r = 0.56$, $p < 0.01$) (Fig. 3, bottom).

Left ventricular diastolic function. The peak filling rate in group 1 and 2 patients in functional classes II and III/IV was significantly decreased (2.23 ± 1.05, 1.47 ± 0.46, 1.08 ± 0.41 cps for functional classes I, II and III/IV, respectively, $p < 0.01$, class I vs. class II and class I vs. class III/IV), and the time to peak filling was prolonged in patients in functional class III/IV (200 ± 76, 202 ± 58, 268 ± 99 ms for functional classes I, II and III/IV, respectively, $p < 0.01$, classes I and II vs. class III/IV). The myocardial washout rate correlated inversely with the peak filling rate ($r = -0.47$, $p < 0.01$) (Fig. 4, top) and positively with the time to peak filling, although its correlation was weak ($r = 0.31$, $p < 0.05$) (Fig. 4, bottom).

However, in group 3, the peak filling rate tended to be

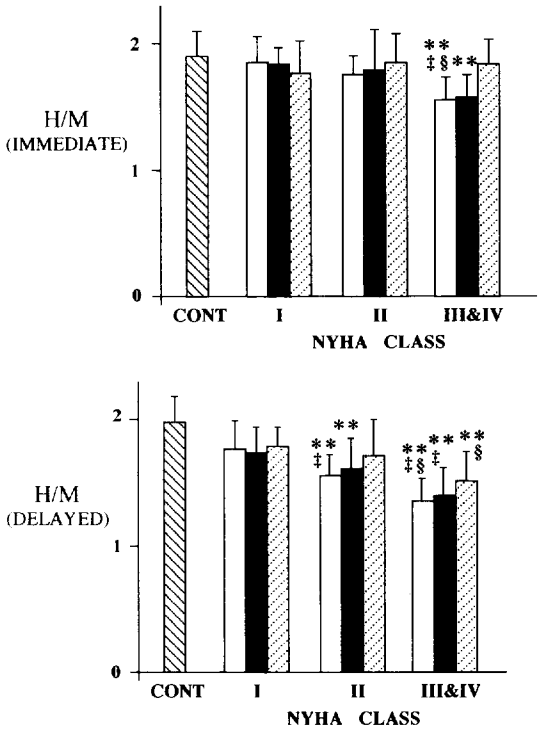
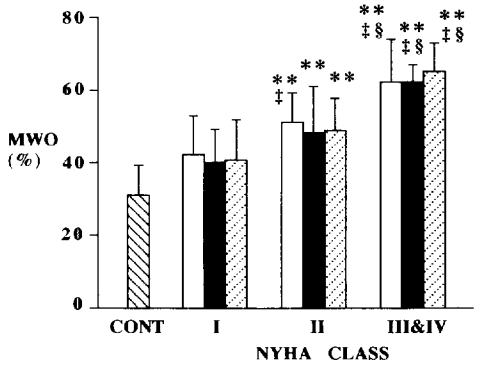


Figure 1. Functional cardiac status (New York Heart Association [NYHA] classification) versus heart/mediastinal (H/M) activity ratio for each heart failure group. **Top**, Immediate images (after 15 min). **Bottom**, Delayed images (after 4 h). **Open bars** = group 1; **solid bars** = group 2; **dotted bars** = group 3. Results are mean value (**bars**) ± SD (**vertical lines**). **p < 0.01 versus control group (CONT). ‡p < 0.01 versus functional class I. §p < 0.01 versus functional class II.

Figure 2. Functional cardiac status (New York Heart Association [NYHA] classification) versus myocardial washout (MWO) of MIBG in each heart failure group. **p < 0.01 versus control group (CONT). ‡p < 0.01 versus functional class I. §p < 0.01 versus functional class II. Other symbols as in Figure 1.



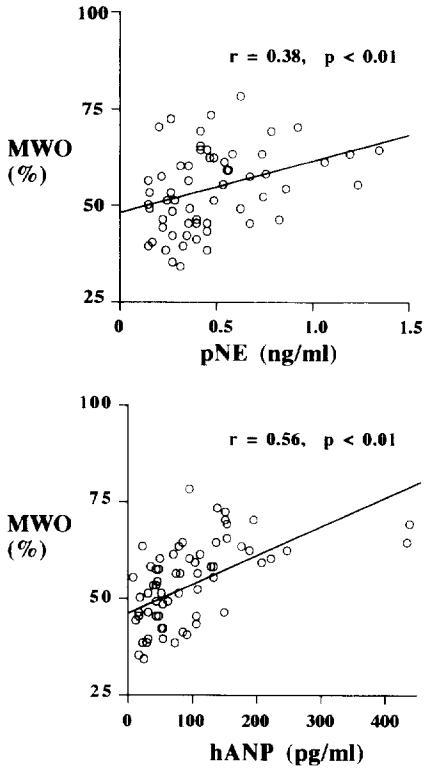


Figure 3. Relation between myocardial washout (MWO) and the concentration of plasma norepinephrine (pNE [**top**]) and plasma human atrial natriuretic peptide (hANP [**bottom**]). Myocardial washout and plasma norepinephrine levels were weakly correlated ($r = 0.38$, $p < 0.01$); myocardial washout and hANP levels had a stronger correlation ($r = 0.56$, $p < 0.01$).

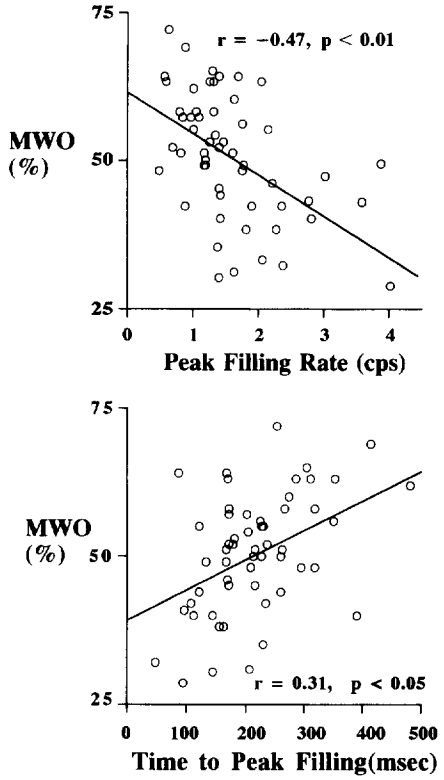


Figure 4. Relation between myocardial washout (MWO) and peak filling rate (**top**) and time to peak filling (**bottom**). Myocardial washout and peak filling rate and time to peak filling were weakly correlated ($r = -0.47$, $p < 0.01$, myocardial washout vs. peak filling rate; $r = 0.31$, $p < 0.05$, myocardial washout vs. time to peak filling).

decreased, and the time to peak filling tended to be prolonged, but not significantly (peak filling rate: 2.56 ± 0.42, 2.33 ± 0.63, 2.16 ± 0.67; time to peak filling: 174 ± 31, 174 ± 50, 241 ± 148 ms for functional classes I, II and III/IV, respectively). Myocardial washout did not show a significant correlation with these indexes ($p = 0.72$, myocardial washout vs. peak filling rate; $p = 0.55$, myocardial washout vs. time to peak filling).

Accumulation and washout of MIBG in liver. The liver/mediastinal activity ratio was 2.91 ± 0.52 in the immediate image and 3.01 ± 0.49 in the delayed image, and washout of MIBG in the liver was 32 ± 15% in the control group. Accumulation and washout of MIBG in the liver did not show any significant differences in any functional class of any study group or the control group.

Discussion

The major finding of the present study is that patients with congestive heart failure have an accelerated myocardial washout of I-123 MIBG that corresponds to the severity of heart failure; MIBG imaging results for the liver were similar in patients and control subjects. This evidence suggests that myocardial washout of MIBG increases, reflecting the intensified myocardial adrenergic nervous activity in patients with heart failure.

The MIBG is taken up by adrenergic tissues, and two types of uptake systems for MIBG have been identified: the neuronal uptake system, which predominates at low concentrations of MIBG, and the extraneuronal uptake system (17,18). The myocardial uptake of MIBG at low concentrations, used for clinical applications, represents mainly neuronal uptake (13,19,20). The MIBG is also taken up by liver, which does not have dense adrenergic innervation (21). In our study, MIBG images of the liver were similar for all heart failure groups and the control group. Therefore, the abnormal myocardial MIBG imaging results observed in our study were assumed to be related specifically to adrenergic nervous activity in the heart.

Myocardial uptake of MIBG. In the immediate images, the heart/mediastinal activity ratio was decreased only in Group 1 and 2 patients in functional class III/IV. Controversy exists regarding the uptake ability of norepinephrine in a failing heart. Evidence has emerged to support both normal and reduced neuronal uptake of norepinephrine by cardiac adrenergic nerves (6,7,22). The initial uptake ability for MIBG with heart failure patients is also controversial. Our data agree with earlier studies (13,15) showing that initial MIBG uptake is reduced in cardiomyopathy and normal in valve diseases but disagree with a study (12) showing that in patients with cardiomyopathy, initial MIBG imaging results are normal (12). However, in the latter study, patients with heart failure of

varying severity were compared with normal control subjects, and the extent of heart failure actually present in their study participants is unclear. Recently, a preliminary study (22) using human ventricular electrically stimulated cardiac preparations obtained from patients with cardiomyopathy demonstrated that uptake-1 activity is reduced in patients with severe heart failure. On the basis of these findings, we consider that our data indicated that the initial uptake of MIBG varied according to severity of heart failure and that it was reduced in patients with severe heart failure caused by cardiomyopathy.

The reason that the heart/mediastinal activity ratio in the immediate images from group 3 was not reduced is not certain. It has been demonstrated (23,24) that when myocardial function fails, an alteration of neuronal function follows. In our study, patients with valve disease and an ejection fraction <40% were excluded. Thus, myocardial function in group 3 was presumably preserved. The lack of myocardial dysfunction may be the reason for the normal heart/mediastinal activity ratio. Consequently, the low heart/mediastinal activity ratio observed in group 1 and 2 patients in functional class III/IV may reflect the possibility that the uptake ability of norepinephrine is reduced in severe congestive heart failure caused by cardiomyopathy because of myocardial injury.

In the delayed images, the heart/mediastinal activity ratio was reduced in all three heart failure groups. This finding agrees with other studies (11,25) demonstrating that the heart/mediastinal ratio obtained 2 or 4 h after isotope injection is reduced in patients with heart failure due to cardiomyopathy. However, the heart/mediastinal activity ratio in the delayed images has limited use as an index of uptake ability or turnover of MIBG because it is affected by both the initial uptake and washout of MIBG. Our data demonstrated that the heart/mediastinal ratio in the immediate images differed between groups and that washout of MIBG also differed. In cases associated with altered MIBG initial uptake and washout, the heart/mediastinal activity ratio in the delayed images may not precisely represent uptake ability or turnover. Therefore, on the basis of findings obtained from the immediate images, we consider that the uptake of norepinephrine was reduced only in patients with severe heart failure caused by cardiomyopathy.

Myocardial washout of MIBG. Myocardial washout of MIBG was accelerated in proportion to severity of heart failure in all groups. There were no significant differences between the groups for any functional class. Acceleration of washout was not observed in the liver and thus was not a general change in patients with heart failure. These results are supported by earlier studies (4–7) demonstrating that neuronal norepinephrine turnover in the heart is increased in patients with heart failure. From our results, we consider that regardless of the cause, intensification of the cardiac adrenergic nervous system was elicited according to severity of heart failure, which in turn accelerated MIBG release in proportion to adrenergic nervous activity.

We believe that in contrast to the heart/mediastinal activity ratio, washout is more useful as an index of adrenergic nervous activity because it is independent of the number of neurons available, whereas the heart/mediastinal activity ratio is not. Therefore, although the heart/mediastinal activity ratio and washout represent different functions of adrenergic presynaptic activity, washout may be a more accurate marker of severity of heart failure.

Left ventricular diastolic function. Left ventricular diastolic function was impaired in patients in groups 1 and 2, and washout correlated weakly with diastolic function. Our findings corroborated previous reports (26–28) that in patients with dilated cardiomyopathy and ischemic heart disease, left ventricular diastolic function was depressed, which contributed to congestive heart failure.

Although left ventricular diastolic function tended to be depressed in patients in group 3, but not statistically significant, there was no correlation between washout and diastolic function. These results may have occurred because left ventricular diastolic function is not a primary factor in determining severity of heart failure. These results also implied that whether there is myocardial dysfunction in patients with heart failure, an intense myocardial adrenergic activity is elicited.

Plasma norepinephrine and hANP. Concentrations of hANP correlated positively with myocardial washout. Plasma norepinephrine levels also showed a significant but weak correlation with myocardial washout. The hANP has an inhibitory effect on sympathetic nerve activity (29), but an increase in myocardial washout preceded the increase in concentration of hANP. Contrary to its sympathoinhibitory effect, myocardial washout showed a positive correlation with hANP concentrations. Accordingly, direct inhibition of MIBG kinetics by hANP was presumably small. In congestive heart failure, excessive levels of hANP have been reported (30), as well as a positive correlation between plasma hANP concentration and severity of heart failure (31,32). We therefore consider that the myocardial washout and hANP may represent severity of heart failure independently, myocardial washout by reflecting intensified adrenergic nervous activity and hANP by reflecting elevated atrial pressure.

It is possible that an increase in norepinephrine levels could compete with MIBG. However, the correlation with plasma norepinephrine and myocardial washout was weak, and between functional classes II and III/IV, although the norepinephrine concentration was almost the same, a significant difference in myocardial washout was observed. Our data indicate that interference between plasma norepinephrine levels and MIBG kinetics is weak, if present at all. In patients with heart failure, elevation of endogenous catecholamine levels has been demonstrated, but its correlation with severity of heart failure is controversial. Because plasma norepinephrine levels reflect overall systemic adrenergic activity, the circulating catecholamine concentration is not an accurate index of changes in cardiac adrenergic activity (2,33). With MIBG imaging, it is possible to assess cardiac adrenergic activity specifically by setting the region of interest on the heart. Therefore, we consider MIBG imaging to be a more accurate way of evaluating myocardial adrenergic activity.

Conclusions. Iodine-123 MIBG imaging reflects myocardial adrenergic activity in patients with heart failure. Although the initial uptake ability of MIBG was different among various underlying diseases, storage and release of MIBG, calculated as the washout rate of MIBG from the heart, represents intensified activity of adrenergic activity independent of the underlying cause. Analysis of MIBG imaging, especially its washout rate from the heart, is a useful, noninvasive tool for evaluating severity of heart failure.

We thank Higashi Akihiko, Ikemoto Toshinari, Hisa Takeshi, Ochi Kunio and Hiraoka Akio for technical assistance and Hirano Akemi for secretarial assistance.

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