Prognostic Value of Cardiac Metaiodobenzylguanidine Imaging in Patients with Heart Failure

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The prognostic value of ^{123}I-metaiodobenzylguanidine (MIBG) imaging was compared with that of other noninvasive cardiac imaging indices in ninety patients (mean age = 52 ± 7 yr) suffering from either ischemic (n = 24) or idiopathic (n = 66) cardiomyopathy. Patients had different measurements taken: cardiac MIBG uptake, radionuclide left ventricular ejection fraction, x-ray cardiothoracic ratio and echographic M-Mode data. Cardiac MIBG uptake was assessed as the heart-to-mediastinum activity ratio measured on the chest anterior view image obtained 4 hr after intravenous injection. The patients then had follow-up for 1–27 mo, at which time 10 patients had transplants, 22 had died and 58 were still alive. Data from patients with transplants were not used in the analysis, in which multivariate stepwise regression discriminant analysis showed that cardiac MIBG uptake was more potent to predict survival than other indices: H/M ($p < 0.0001$), x-ray cardiothoracic ratio ($p = 0.0017$), echographic end-diastolic diameter ($p = 0.0264$) and radionuclide left ventricular ejection fraction ($p = 0.0301$). Moreover, multivariate life table analysis showed that cardiac MIBG uptake was also the best predictor for life duration: H/M ($p = 0.0001$), radionuclide left ventricular ejection fraction ($p = 0.0098$) and x-ray cardiothoracic ratio ($p = 0.0139$); echographic data were not useful. Thus, cardiac MIBG imaging may be helpful for heart transplantation decision making in patients with heart failure.

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The prognosis of patients with congestive heart failure remains poor. Cardiac transplantation represents an alternative treatment for the most severe patients who have no other options. Unfortunately, a discrepancy exists between the number of candidates for heart transplantation and the availability of donors. A method to discriminate between high and low risk patients with regard to mortality could help rationalize the indication of cardiac transplantation and its timing. Of the available measurements, a diminished left ventricular ejection fraction (LVEF) has often been associated with mortality (*1–4*); strata defined by a 20% cutoff value (*3,4*) have been prognostically useful. Measurements of neuro-hormonal system disorders, especially those involving the adrenergic system, have also provided helpful information (*5–8*). However, these indices are not sufficiently discriminatory and the decision for heart transplantation remains difficult in individual patients.

Iodine-123-metaiodobenzylguanidine (MIBG) has been used to study cardiac adrenergic nerve activity. Cardiac MIBG uptake is diminished in patients with congestive heart failure in comparison with normal subjects (*9*). Cardiac MIBG uptake and LVEF are correlated, suggesting that MIBG imaging could be a useful prognostic marker (*9*). However, the prognostic value of cardiac MIBG imaging has not yet been defined in heart failure. The present study was undertaken to examine the prognostic value of MIBG cardiac imaging of patients with heart failure in comparison with noninvasive markers. These markers were either indices of left ventricular systolic function, i.e., radionuclide LVEF and echocardiographic fractional shortening, or indices of left ventricular enlargement, i.e., chest x-ray and echographic end-diastolic and end-systolic diameters.

METHOD

Study Population

Ninety patients, 14 women and 76 men (mean age = 52 ± 7 yr), with at least one episode of decompensated congestive heart failure, entered the study after fulfilling the following criteria: congestive heart failure symptoms for more than 6 mo; these symptoms graded II to IV in the functional classification of the New York Heart Association; radionuclide LVEF lower than

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45%; congestive heart failure related to a dilated cardiomyopathy either idiopathic or ischemic; no concomitant illnesses.

Idiopathic cardiomyopathy was considered to be present (n = 66) when no significant stenosis was detected on the coronary angiogram (no narrowing greater than 50% of the lumen artery) and when no other recognized etiology was evident.

All ischemic patients had severe coronary artery disease (n = 24) based on both clinical history and severe and diffuse coronary lesions shown on the coronary angiogram. At the time of inclusion, these patients were not suitable for revascularization by surgery or angioplasty and had no documented acute myocardial infarction within the previous 6 mo.

Study Protocol

The protocol was approved by the ethical committee of the Henri Mondor University Hospital and each subject gave informed consent. After inclusion in the study, all data were obtained over an 8-day period.

Radionuclide LVEF

Each patient was intravenously injected with 15 to 20 mCi of ^{99m}Tc in vitro labeled red blood cells. Ten minutes after injection, a 5000K count ECG-gated acquisition was performed in the 40° left anterior oblique view. LVEF was calculated using a standard software program (*10*).

MIBG Imaging

Lugol solution (40 mg of iodure a day) was administered orally for 3 days prior to and 3 days after scintigraphic examination. After a 30-min resting period, 3–4 mCi of ^{123}[I]MIBG (International CIS) were intravenously injected. A 10-min static acquisition was performed in the anterior view of the chest, 4 hr after injection, using a GE 400T gamma camera. Cardiac MIBG uptake was measured twice by two independent observers unaware of the clinical status of patients. Left ventricular activity was recorded using both a manually drawn and a 7×7 pixel region of interest (ROI). Size and positioning were checked using the anterior view of the chest x-ray. Another 7×7 pixel ROI was placed over the upper mediastinum area. Heart-to-mediastinum (H/M) activity ratio was then computed to quantify cardiac MIBG uptake. For each patient, the H/M value was taken as the average of measurements performed over his scintigraphic image, by each observer and using each kind of cardiac ROI.

Control value of cardiac MIBG uptake was determined in 12 subjects (mean age = 39 ± 11 yr) showing no sign of cardiac disease after clinical, electrocardiographic and echocardiographic examinations.

M-Mode Echocardiography

Echographic measurements were performed using standard recommendations (*11*). End-diastolic and end-systolic diameters were recorded and the fractional shortening value was calculated.

X-ray Cardiothoracic Ratio

The x-ray cardiothoracic ratio was calculated utilizing the maximal cardiac diameter and the intrathoracic diameter at the level of the right costocardiac border (*12*).

Patient Management and Follow-up

At the time of inclusion, patient treatments included: diuretics (n = 82), angiotensin-converting-enzyme inhibitors (n = 73), nitrates (n = 48), and digitalis (n = 18). Ischemic patients were also treated with nifedipine (n = 9), diltiazem (n = 3), metoprolol (n = 6) and atenolol (n = 2).

After initial examination, patients were followed-up in their respective institution or by their primary physician. No patients were lost to follow-up.

When functional status deteriorated, heart transplantation was considered for suitable patients (*13*).

Data Analysis and Statistics

Cardiac MIBG uptake, radionuclide LVEF, x-ray cardiothoracic ratio, echographic end-diastolic and end-systolic diameter and fractional shortening were the parameters tested. To evaluate the prognostic value of each parameter measured at initial examination, comparisons were made between patients who were still alive at the end of the study and patients who died during the follow-up period. Cardiac death was ascertained either as progressive cardiac failure or as sudden when it occurred within 1 hr of the onset of new symptoms or without premonitory symptoms. Ten patients underwent heart transplantation, indicated for a refractory heart failure. To evaluate the different parameters with regard to life duration, patients with transplants were discarded from the final analysis.

Statistical analysis was performed on a Compaq computer with a Lotus data base and a SAS statistical program package (SAS Institute, North Carolina). Subgroups of patients were compared using variance analysis. The value of parameters as predictors of survival was assessed using a stepwise multifactorial regression discriminant analysis (Proc Discrim). The relationship between life duration and parameters was examined using life table analysis and Wilcoxon testing.

For all tests, a p value of less than 0.05 was considered statistically significant. All parameters were expressed as mean value ± standard deviation.

RESULTS

Parameters Measured at Time of Inclusion

Noninvasive Hemodynamic Parameters. Patients had altered indices of left ventricular systolic function (radionuclide LVEF = 22%±8% and echographic fractional shortening = 17 ± 5 mm), as well as a cardiac enlargement (x-ray cardiothoracic ratio = 55%±6%) associated with a dilated left ventricle (echographic end-diastolic diameter = 67 ± 8 mm).

MIBG Cardiac Uptake. Intra- and interobserver differences for H/M activity ratio measurements were not significant (< 5%). As shown in Figure 1, when calculated using either the 7×7 pixel or the manually drawn myocardial ROI, H/M values were well correlated (r = 0.89, p = 0.0001). MIBG data presented afterward were therefore calculated using the 7×7 pixel ROI.

Cardiac MIBG uptake decreased in patients (H/M = 122%±15%) compared with controls (H/M = 196%± 33%, $p < 0.001$). Figure 2 shows a scintigraphic image of cardiac MIBG uptake in a patient and in a control subject. Cardiac MIBG correlated positively with LVEF (r = 0.50, $p < 0.001$) (Fig. 3). Cardiac MIBG correlated negatively with both x-ray cardiothoracic ratio (r = 0.50, $p < 0.001$) and echographic end-diastolic diameter (r = 0.28, $p < 0.01$).

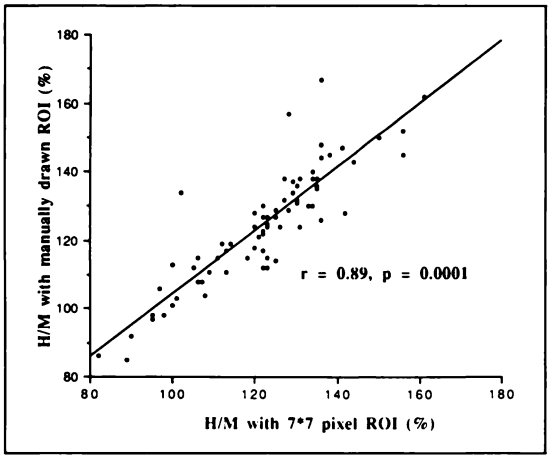

FIGURE 1. Relationship of H/M activity ratio measured either with the 7×7 pixel or the manually drawn ROI. The two H/M values are well correlated (r = 0.89, p = 0.0001).

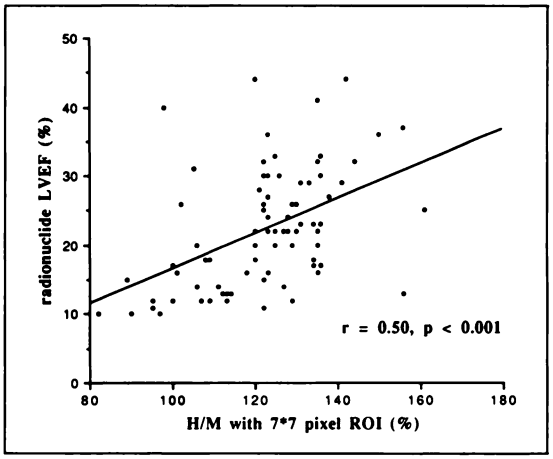

FIGURE 3. Relationship between radionuclide LVEF and the H/M activity ratio, used as an index of cardiac MIBG uptake, in patients with heart failure. The two variables are correlated, but the correlation is weak (r = 0.50, p < 0.001).

Clinical Outcome

Twenty-two patients died (6 sudden deaths and 16 deaths related to progressive cardiac failure: subgroup D). Ten patients underwent heart transplantation (subgroup T). The remaining patients (subgroup A, n = 58) were alive at the end of the follow-up period, which was 7 ± 1.1 mo for subgroup D, 3.9 ± 1.5 mo for subgroup T and 14± 5.5 mo for subgroup A.

Prognostic Value of Parameters

Multivariate analysis revealed that the only predictors for survival were: H/M (p < 0.0001), x-ray cardiothoracic ratio (p = 0.0017), echographic end-diastolic diameter (p = 0.0264) and radionuclide LVEF (p = 0.0301). The other parameters (x-ray cardiothoracic ratio, fractional shortening end-systolic diameter) did not contribute significantly to predict survival. Results were comparable when using either the 7×7 pixel or the manually drawn ROI to measure cardiac MIBG uptake (Tables 1 and 2, respectively). Moreover, when the analysis was performed separately in the two subgroups of patients with either ischemic or idiopathic dilated cardiomyopathy, differences were observed, but the H/M value remained the most important predictor for survival whatever the type of ROI used for quantification (Tables 3 and 4). The value of these parameters as predictors of life duration was examined using multivariate life table analysis. The only significant predictors of life duration (Table 5) were: H/M (p < 0.0001), radionuclide LVEF (p = 0.0098) and x-ray cardiothoracic ratio (p = 0.0139). Echographic data were not useful.

A threshold value of 20% was used to evaluate the accuracy of LVEF to predict survival: sensitivity was 90%, specificity 79%, positive predictive value 62% and negative predictive value 95%.

A threshold value of 120% was found for H/M; lower values had a poor prognosis. When using this cutoff value to predict survival, sensitivity was 95%, specificity 93%, positive predictive value 84% and negative predictive value 98%.

Survival curves with a threshold value of 20% for LVEF and 120% for H/M are shown in Figures 4 and 5, respectively.

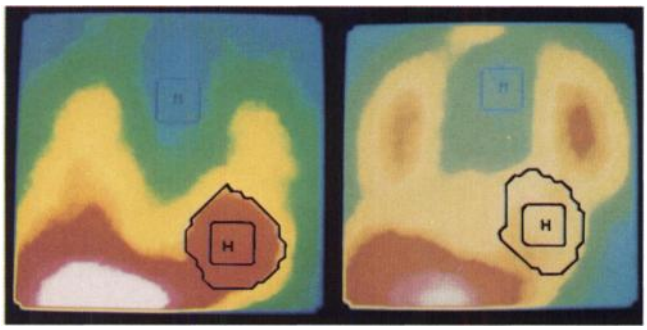

FIGURE 2. Scintigraphic images obtained in the anterior view of the chest 4 hr after MIBG intravenous injection. Cardiac MIBG uptake is quantified as the H/M activity ratio, using ROIs positioned over the heart (H) and over the upper mediastinum (M). In the normal subject (left), the left ventricular myocardium is easily individualizable, indicating a high left ventricular uptake of MIBG. A high but nonspecific uptake is observed in the liver. In this patient (right), a decrease in cardiac MIBG uptake is observed.

TABLE 1
Comparison Among the Predictors for Survival Using Multivariate Analysis (Including MIBG Uptake Calculated with a 7 × 7 Pixel ROI)

Parameter	Fisher	p value
Heart-to-mediastinum activity ratio of MIBG (7 × 7 pixel ROI)	87	<0.0001
X-ray cardiothoracic ratio	10	0.0017
Echographic end-diastolic diameter	5	0.0264
LVEF	5	0.0301

TABLE 2
Comparison Among the Predictors for Survival Using Multivariate Analysis (Including MIBG Uptake Calculated with a Manually Drawn ROI)

Parameter	Fisher	p value
Heart-to-mediastinum activity ratio of MIBG (using manually drawn ROI)	53	<0.0001
X-ray cardiothoracic ratio	9	0.002
Echographic end-diastolic diameter	5	0.0254
LVEF	8	0.004

DISCUSSION

The major finding of the present study was that the level of cardiac MIBG uptake was closely related to life duration and appeared to be a potent prognostic index when compared to noninvasive indices of left ventricular function in either ischemic or dilated cardiomyopathy patients.

Many reports have concerned various approaches to distinguish high and low risk populations in patients with congestive heart failure. In most of these studies, prognostic indicators have involved hemodynamic parameters (*1–4,14–18*). Data showed that x-ray cardiothoracic ratio (*19*) and echographic end-diastolic diameter (*16*) were related to prognosis. Our data agree with these findings. Similarly, LVEF has been associated with mortality in several samples, including either idiopathic cardiomyopathy or idiopathic cardiomyopathy and ischemic patients (*1–4*). Moreover, LVEF is a more potent prognostic marker than right heart catheterization measurements (*2,4*). This suggests that LVEF is a good index to guide indications of heart transplantation and its timing (*4,20*). However, a predictive value for survival of only 59% was reported for LVEF when using a threshold value of 20% (*20*). In the present study, a similar predictive value (62%) was found when using the same threshold value. However, this predictive value appears to be insufficient to accurately define the high risk of mortality for individuals.

Increasing attention has therefore been given to indices of adrenergic dysfunction as prognostic markers (*5–8,20*). An inverse relationship between circulating norepinephrine level and life duration has been observed (*6,8*). However, no single cutoff point for plasma-norepinephrine concentration appeared to be both highly sensitive and specific to predict mortality (*8*). Moreover, plasma norepinephrine derived from adrenergic activity throughout the body, and the circulating concentration of this neurotransmitter may not be an accurate index of changes of cardiac adrenergic activity. Alterations of neuronal function may be important to consider in the failing myocardium since abnormalities of norepinephrine release and reuptake as well as decreased norepinephrine content have been reported (*21,22*).

Part of these abnormalities can be scintigraphically explored using MIBG, radiolabeled with ^{123}I, ^{125}I or ^{131}I, since it shares the same uptake and storage mechanisms as norepinephrine. It is unmetabolizable by catechol-O-methyl transferase or monoamine oxidase (*23*). Two types of uptake systems for norepinephrine and MIBG have been identified in adrenergic tissues: the uptake one system (neuronal uptake) that dominates at low concentrations of the substrates is sodium- and ATP-dependent and is inhibited by tricyclic antidepressants; the uptake two system (extra neuronal uptake), a diffusion system that dominates at high concentrations of norepinephrine or MIBG and is slightly inhibited by tricyclic agents (*24–26*). However, neurons of the heart may also sequester MIBG by the diffusion pathway. Indeed, Sisson et al. have identified quantitative differences between tritiated norepinephrine and MIBG that may be attributable to partial neuronal uptake of MIBG by the diffusion pathway (*24*). However, MIBG administered at the low doses used for clinical applications may enter mainly through the uptake one pathway (*26*). Moreover, a ten-fold difference in cardiac MIBG uptake was found between heart transplanted patients and normal subjects, suggesting that MIBG uptake

TABLE 3
Multivariate Analysis in Patients with Either Ischemic or Idiopathic Cardiomyopathy Using H/M Values and a 7 × 7 Pixel ROI To Calculate H/M Values

	Idiopathic patients		Ischemic patients	
Parameter	Fisher	p value	Fisher	p value
Heart-to-mediastinum activity ratio of MIBG (using the 7 × 7 pixel ROI)	67	<0.0001	17	0.0004
Echographic end-diastolic diameter	—	ns	—	ns
LVEF	—	ns	6	0.02

TABLE 4
Multivariate Analysis in Patients with Either Ischemic or Idiopathic Cardiomyopathy Using the Manually Drawn ROI To Calculate H/M Values

	Iodiopathic patients		Ischemic patients	
Parameter	Fisher	p value	Fisher	p value
Heart-to-mediastinum activity ratio of MIBG	35	<0.0001	16	0.0006
Echographic end-diastolic diameter	5	0.02	—	—
LVEF	4	0.05	5	0.02

TABLE 5
Predictors of Life Duration Using Life Table Analysis

Parameter	Fisher	p value
Heart-to-mediastinum activity ratio of MIBG	37	<0.0001
LVEF	6	0.0098
X-ray cardiothoracic ratio	6	0.0013

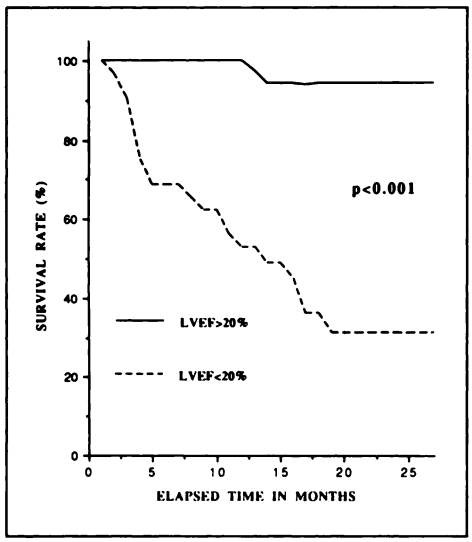

FIGURE 4. Survival curve, using life table analysis, with a threshold value of 20% for LVEF. A large difference is seen for survival between patients with a LVEF lower (dotted line) or greater (unbroken line) than 20% ($p < 0.001$).

is highly dependent on the integrity of neuronal uptake in the human heart (*27*). Since the neuronal accumulation of MIBG reaches its maximum 4 hr after injection, MIBG imaging performed at this time may be the most accurate method to explore neuronal norepinephrine uptake function (*28*).

MIBG imaging represents a tool to assess adrenergic presynaptic activity in heart diseases. Measurement of cardiac MIBG uptake has been used to explore neuronal norepinephrine uptake and storage functions in heart failure. In patients with idiopathic cardiomyopathy, Henderson et al. reported a noticeable increase in MIBG washout and a greater heterogeneity of cardiac MIBG distribution in comparison with controls (*29*). The ability of scintigraphy to measure cardiac MIBG uptake has been tested in patients with idiopathic cardiomyopathy. Schofer et al. showed a correlation ($r = 0.78$, $p < 0.001$) between ^{123}[I] MIBG activity scintigraphically determined and MIBG activity measured from endomyocardial biopsy samples (*9*). In this last study, myocardium-to-mediastinum activity ratio significantly correlated to myocardial norepinephrine content ($r = 0.63$), suggesting that a decreased MIBG uptake is related to a disruption of the sympathetic innervation.

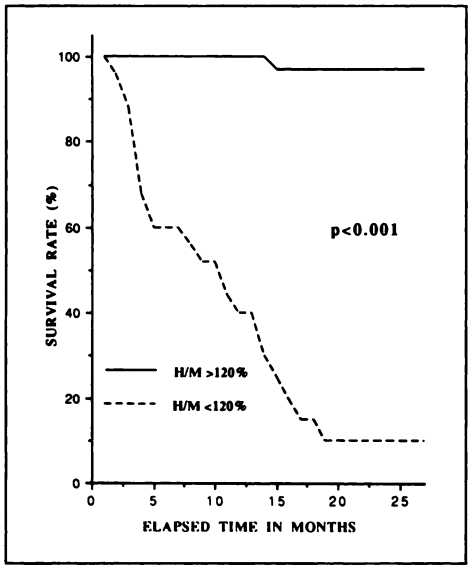

FIGURE 5. Survival curve, using life table analysis, with a threshold value of 120% for H/M activity ratio. A striking difference is seen for survival between patients with H/M lower (dotted line) or greater (unbroken line) than 120% ($p < 0.001$). When compared to Figure 4, this graph shows that survival is much poorer in patients with an H/M below 120% than in those with a LVEF below 20%.

Quantification of myocardial MIBG activity on scintigraphic images had technical limitations. Tomographic imaging provides an opportunity to study the myocardial distribution of MIBG uptake (*29*). In the present study, the drastic decrease in MIBG uptake in severe patients induced difficulties for image reconstruction, therefore hindering the use of tomographic imaging in routine examination. Planar imaging was used to quantify cardiac MIBG uptake. This discrepancy with Henderson's study may be due to the low doses of MIBG used in our study. However, planar imaging has limitations of its own. The ideal cardiac ROI should include myocardial activity and exclude adjacent lung and liver activities. Ventricular enlargement may induce an underestimation of the myocardial activity. Pulmonary crosstalk in the cardiac ROI may induce an overestimation of the myocardial activity. The activity measured over a cardiac ROI is therefore a crude estimate of the actual activity. For these reasons and to minimize the effects of individual attenuation, cardiac activity has to be normalized to enable comparisons between different subjects. No anatomic structure showing MIBG uptake can be individualized in the upper mediastinum on scintigraphic images, suggesting that this is a non-target area for MIBG. In the present study, the upper mediastinum was therefore used for normalization. Cardiac MIBG uptake was evaluated as the heart-to-mediastinum activity ratio. Such an index may be a simple and reproducible way to allow the evaluation of a large number of patients. Interestingly, when using either the 7×7 pixel or the manually drawn ROI to quantify cardiac MIBG uptake, H/M values were closely correlated and similar prognostic values were obtained. This result can appear surprising since the manually drawn ROI is thought to be more appropriate than the 7×7 pixel to encompass the entire heart and to take into account the heterogeneities of MIBG uptake which have been previously described, especially in ischemic patients. This can be explained by the fact that when MIBG uptake is low, as it is in heart failure, the myocardium can be barely individualized from the enlarged left ventricular cavity, the heterogenei-

ties of fixation being only minor or not detectable with planar imaging. The size of the cardiac ROI in such patients does not appear as a significant factor in MIBG uptake quantification whatever the etiology of the heart failure.

The decrease in MIBG uptake found in patients with heart failure remains to be explained. A decreased cardiac MIBG uptake could simply be due to a dilated left ventricle. The relationship between MIBG uptake and indices of ventricular enlargement was therefore examined in the present study. However, if the decreased MIBG uptake correlated with indices of ventricular enlargement, this correlation was weak and similar to the correlation between MIBG uptake and indices of left ventricular function. This correlation may simply be due to the fact that MIBG uptake and indices of ventricular enlargement are linked to the severity of heart failure.

In the present study, the decreased MIBG uptake found in patients with heart failure is likely to be related to an impairment of the neuronal uptake function. This agrees with other data demonstrating an impairment of the uptake one function in the failing heart when using other techniques (*21*). However, an elevation of circulating norepinephrine concentration occurs in patients with heart failure (*5–8*); this elevation could compete with MIBG uptake at the receptor site. Indeed, in patients with pheochromocytoma, Nakajo et al. found that the cardiac MIBG accumulation at 24 and 48 hr after injection was inversely related to plasma concentrations and urinary excretion rate of catecholamines (*30*). In the present study, plasma catecholamine concentrations of patients were not determined. However, in another study, a decreased cardiac MIBG uptake associated with normal circulating norepinephrine concentrations has been observed in patients with moderate heart failure (*31*). This finding suggests that the elevation of circulating norepinephrine concentrations is not the only factor involved in the decrease of MIBG uptake. Further studies are needed to define the respective role of elevated circulating norepinephrine and impaired neuronal norepinephrine reuptake in the decrease of MIBG uptake.

In conclusion, the present data demonstrate that cardiac MIBG scintigraphy is a potent prognosis marker when compared to noninvasive hemodynamic indices. When using a cutoff value of 120% for heart-to-mediastinum ratios, MIBG imaging has a high predictive value for survival. Moreover, decreased MIBG uptake is better related to life duration than is LVEF. Thus, MIBG imaging can be helpful in patients with heart failure in making heart transplantation decisions and evaluating their timing.

REFERENCES

1. Schwartz F, Mall G, Zebe H, et al. Determinants of the survival in patients with congestive cardiomyopathy: quantitative morphologic findings and left ventricular hemodynamics. *Circulation* 1984;70:923–928.
2. Diaz RA, Obasohan A, Oakley CM. Prediction of outcome in dilated cardiomyopathy. *Br Heart J* 1987;58:393–399.
3. Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic cardiomyopathy or to ischemic cardiomyopathy. *Am J Cardiol* 1987;59:634–638.
4. Keogh AM, Freund J, Baron DW, Hickie JB. Timing of cardiac transplantation in idiopathic cardiomyopathy. *Am J Cardiol* 1988;61:418–422.
5. Gottlieb SS, Marrick L, Kukin ML, Ahern D, Packer M. Prognostic importance of atrial natriuretic peptide in patients with chronic heart failure. *J Am Coll Cardiol* 1989;13:1534–1539.
6. Cohn JN, Levine BT, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819–823.
7. Creager MA, Faxon DP, Halperin JL, et al. The determinants of clinical response and survival in patients with congestive heart failure treated with enalapril. *Am Heart J* 1982;104:1147–1154.
8. Rector TS, Olivari MT, Levine TB, Francis GS, Cohn JN. Predicting survival for an individual with congestive heart failure using the plasma norepinephrine concentration. *Am Heart J* 1987;148–152.
9. Schofer J, Spielmann R, Schubert A, Weber K, Schlüter M. Iodine-123 metaiodobenzylguanidine scintigraphy: a noninvasive method to demonstrate myocardial adrenergic system disintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1988;12:1252–1258.
10. Standke R, Hör G, Maul FD. Fully automated sectorial equilibrium radionuclide ventriculography. *Eur J Nucl Med* 1983;8:77–83.
11. Sahn DJ, DeMaria A, Kissio J, Weyman A. Recommendations regarding quantitation in M-Mode echocardiography: result of a survey of echocardiographic measurements. *Circulation* 1978;58:1072–1083.
12. Glover L, Baxley WA, Dodge HT. A quantitative evaluation of heart size measurements from chest roentgenograms. *Circulation* 1973;47:1289–1296.
13. Copeland JG, Emery RW, Levinson MM, et al. Selection of patients for cardiac transplantation. *Circulation* 1987;1975:2–9.
14. Wilson J, Schwartz S, Sutton MJ, et al. Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;2:403–410.
15. Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983;51:831–836.
16. Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy. *Am J Cardiol* 1984;54:147–152.
17. Hofmann T, Meinertz T, Kasper W, et al. Mode of death in idiopathic dilated cardiomyopathy: a multivariate analysis of prognostic determinants. *Am Heart J* 1988;116:1455–1463.
18. Gradman A, Deedwania P, Cody R, et al. Predictors of total mortality and sudden death in mild to moderate heart failure. *J Am Coll Cardiol* 1989;14:564–570.
19. Ikram M, Williamson HG, Won M, Crozier IC, Wells ET. The course of idiopathic dilated cardiomyopathy in New Zealand. *Br Heart J* 1987;57:521–527.
20. Keogh AM, Baron DW, Hickie JB. Prognostic guides in patients with idiopathic or ischemic dilated cardiomyopathy assessed for cardiac transplantation. *Am J Cardiol* 1990;65:903–908.
21. Petch MC, Nayler WG. Uptake of catecholamines by human cardiac muscle in vitro. *Br Heart J* 1979;41:336–339.
22. Chidsey CA, Braunwald E, Morrow AG. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Am J Med* 1965;39:442–451.
23. Wieland DM, Brown LE, Les Roger W, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 1981;22:22–31.
24. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jaques S Jr. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 1987;28:1620–1624.
25. Tobes MC, Jaques S Jr, Wieland DM, Sisson JC. Effect of uptake one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. *J Nucl Med* 1985;26:897–907.
26. Gasnier B, Roisin MP, Scherman D, Coornaert S, Desplanches, Henry JP. Uptake of meta-iodobenzylguanidine by bovine chromaffin granule membranes. *Mol Pharmacol* 1986;29:275–280.
27. Glowniak JV, Turner FE, 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.

28. Nakajo M, Shimabukuro K, Yoshimura H, Yonekura R, Nakabeppu TP, Shinohara S. Iodine-131-metaiodobenzylguanidine intra- and extravesicular accumulation in the rat heart. *J Nucl Med* 1986;27:84–85.
29. Henderson EB, Kahn JK, Corbett JR, et al. Abnormal I-123 myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive heart cardiomyopathy. *Circulation* 1988;78:1192–1199.
30. Nakajo M, Shapiro B, Glowniak J, Sisson JC, Beierwaltes WH. Inverse relationship between cardiac accumulation of meta-131-iodobenzylguanidine (I-131-MIBG) and circulating catecholamines in suspected pheochromocytoma. *J Nucl Med* 1983;24:1127–1134.
31. Merlet P, Dubois-Randé JL, Adnot, S, et al. Myocardial beta adrenergic desensitization and neuronal norepinephrine uptake function in idiopathic cardiomyopathy. *J Cardiovasc Pharmacol* 1991;19:10–16.

EDITORIAL

Prognosis in Congestive Heart Failure: What Information Can Best Predict the Future?

The incidence of chronic congestive heart failure (CHF) has increased drastically during the past decade, with over three million patients in the United States affected. Approximately 400,000 new cases of heart failure are diagnosed each year, despite the widespread use of antihypertensive therapy and the advances made in acute intervention during myocardial infarction. CHF is currently the most common hospital discharge diagnosis in patients over 65 yr of age. Although ischemic heart disease accounts for the majority of cases, other etiologies include hypertensive heart disease, dilated cardiomyopathies (particularly idiopathic, alcoholic, and those consequent to viral myocarditis), and progressive valvular heart disease. Once overt heart failure symptoms have developed, death is usually inevitable, with progressive heart failure accounting for 60% of deaths and sudden deaths the remainder (*1*).

Despite major advances made in the medical and surgical treatment of patients with impaired left ventricular function and symptomatic CHF, it has become evident that a high mortality rate is still associated with chronic heart failure. The Framingham Study suggested a 10% annual mortality rate once symptoms had developed (*2*). The recently published V-HeFT II and SOLVD studies reported 5-yr mortality rates approaching 50% despite medical therapy (*3*, *4*). The CONSENSUS trial reported a 1-yr mortality in patients with severe NYHA Class IV symptoms of 52% despite vasodilator therapy (*5*). The need to prospectively identify those CHF patients who are at greatest risk for early mortality has become increasingly important since cardiac transplantation may serve as an effective treatment option for at least a subgroup of these individuals. A variety of mortality studies have identified clinical, hemodynamic, and laboratory factors that correlate with outcome in CHF patients and have recently been summarized in a review by Vagelos et al. (*6*). Factors associated with increased mortality include heart failure etiology, severity of right and left ventricular systolic dysfunction, extent of neurohumoral and sympathetic nervous system activation, degree of hemodynamic derangement, presence of ventricular arrhythmias, and degree of functional impairment—either determined symptomatically by NYHA classification or objectively on exercise testing.

Clinical features that have proven useful in predicting poor outcome include age greater than 55 yr at presentation, cardiothoracic ratio greater than 0.55 by chest film, the presence of a chronic third heart sound, and evidence for right heart failure (*7*). Most studies have confirmed that CHF due to ischemic heart disease is associated with a poorer prognosis than that associated with idiopathic or alcoholic cardiomyopathy. Although Cohn et al. (*8*) identified plasma renin and norepinephrine levels as independent predictors of mortality and confirmed that the higher the plasma norepinephrine level, the greater the likelihood of death due to progressive CHF, this type of neurohumoral profiling is rarely undertaken in the initial evaluation of patients with heart failure.

The relationship between left ventricular ejection fraction (LVEF) and survival varies depending upon the population study. This relationship is strongest in postmyocardial infarction populations, including those with symptomatic CHF. An LVEF less than 0.30 has consistently been shown to be predictive of excess mortality in patients whose CHF is due to ischemic heart disease. The association between LVEF and outcome in patients with idiopathic dilated cardiomyopathy is less clear, although it certainly exists when systolic function is markedly impaired (LVEF less than 0.20). Only recently has impairment in right ventricular ejection fraction become recognized as an important indicator of prognosis in CHF patients (*9*). Quantitative assessment of maximal oxygen uptake with treadmill or bicycle ergometry can add objective prognostic information. A peak oxygen uptake of less than 10–12 ml/kg/min has been associated with a 1-yr mortality rate approaching 80% (*10*). Despite the useful prognostic information derived from these studies, efforts to extrapolate from the group data the prediction of outcome in an individual CHF patient have proven problematic and argues the need for better noninvasive diagnostic modalities.

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