Prognostic Value of MIBG Imaging in Idiopathic Dilated Cardiomyopathy

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Alterations of cardiac sympathetic innervation are likely to contribute to fatal outcomes in patients with heart failure. These alterations can be evaluated noninvasively by ^{123}I-metaiodobenzylguanidine (MIBG) imaging. **Methods:** The hypothesis that impaired cardiac sympathetic innervation, as assessed using MIBG imaging, is related to adverse outcomes was tested in 112 patients with heart failure resulting from idiopathic cardiomyopathy. Main inclusion criteria were New York Heart Association classes II–IV and radionuclide left ventricular ejection fraction (LVEF) < 40%. Patients were assessed for cardiac MIBG uptake, circulating norepinephrine concentration, LVEF, peak Vo_2, x-ray cardiothoracic ratio, M-mode echographic end-diastolic diameter and right-sided heart catheterization parameters. **Results:** During a mean follow-up of 27 ± 20 mo, 19 patients had transplants, 25 died of cardiac death (8 sudden deaths), 2 died of noncardiac death and 66 survived without transplantation. The only independent predictors for mortality were low MIBG uptake ($P < 0.001$) and LVEF ($P = 0.02$) when using multivariate discriminant analysis. Moreover, MIBG uptake ($P < 0.001$) and circulating norepinephrine concentration ($P = 0.001$) were the only independent predictors for life duration when using multivariate life table analysis. **Conclusion:** Impaired cardiac adrenergic innervation as assessed by MIBG imaging is strongly related to mortality. MIBG imaging may help risk stratify patients with heart failure resulting from idiopathic dilated cardiomyopathy.

Key Words: heart failure; idiopathic cardiomyopathy; prognosis; autonomic nervous system; norepinephrine

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Heart failure is a major cause of disability and mortality and represents a growing health problem, despite major therapeutic advances (*1–4*). Clinical trials have shown that angiotensin-converting enzyme inhibitor (*1–2*) or β-blocker therapy can reduce significantly the mortality of patients with congestive heart failure (*3*). In patients with ischemic left ventricular dysfunction but revascularizable lesions, coronary artery bypass graft has been proposed as a treatment leading to good survival with improved ejection fraction and functional state in selected populations (*4*). Moreover, considerable progress toward accurate detection of myocardial viability, especially with the introduction of dobutamine echocardiography, ^{201}Tl tomoscintigraphy with reinjection and flow-metabolism studies with PET, could allow more frequent use of angioplasty or conservative surgery. Despite these efforts, the prognosis for patients with end-stage heart failure remains grim, especially for those with idiopathic dilated cardiomyopathy, because, when medical therapy fails for these patients, the only alternative is heart transplantation. This is the reason why idiopathic dilated cardiomyopathy represents about 50% of patients who undergo heart transplantation, despite the fact that the disease is a less frequent cause of heart failure. Heart transplantation has modified the prognosis for these patients, leading to better quality and prolongation of life (*5*), but this therapeutic procedure can be performed in only a small proportion of patients with heart failure who are eligible (*5,6*). Because most deaths occur soon after evaluation, efficient prioritization of potential transplant recipients depends on accurate risk stratification. Severity of heart failure is evaluated mainly by symptoms, clinical findings, hemodynamic measurements or exercise tolerance (*7–10*). In addition, the assessment of neurohormonal system disorders related to heart failure has proven prognostically useful (*11,12*). Despite these indices, accurate evaluation of the risk of mortality remains difficult on an individual basis.

In heart failure, altered cardiac adrenergic function contributes to arrhythmogenesis and to the progression of myocardial dysfunction. ^{123}I-metaiodobenzylguanidine (MIBG) imaging provides a means to evaluate noninvasively in vivo the cardiac adrenergic nerve activity, because MIBG is subject to the same uptake and storage mechanisms as norepinephrine. MIBG is internalized by the neuronal cells through the uptake-1 system, a transporter- and energy-dependent system, whereas the compound enters the myocytes through the uptake-2 system, the activity of which is very low in the human heart (*13,14*). Cardiac MIBG uptake is decreased dramatically in the failing human heart (*15*), and preliminary data from our laboratory suggest that this decrease is related to mortality (*16*). However, the clinical significance of MIBG imaging as a tool for heart transplantation decision making remains to be confirmed, because no comparison has been made with validated prognostic indices, such as

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right-sided heart catheterization data, exercise tolerance or plasma norepinephrine concentration, and because no information is available on the prediction of sudden death (*16*). Because the prognostic importance of the scintigraphic detection of residual ischemia or viability has long been demonstrated to be the strongest prognostic tool in patients with ischemia, this study aimed to determine the prognostic value of MIBG in comparison with recognized indices in a large population of patients with congestive heart failure resulting from idiopathic dilated cardiomyopathy.

MATERIALS AND METHODS

Patients

One hundred twelve patients (mean age 50 ± 10 y) with heart failure resulting from idiopathic dilated cardiomyopathy were included prospectively in the study after fulfilling the following criteria: congestive heart failure symptoms, classes II–IV in the functional classification of the New York Heart Association, of at least 6-mo duration with at least one episode of decompensation; a radionuclide left ventricular ejection fraction (LVEF) of <40%; no concomitant severe illnesses; and absence of severe intractable arrhythmias.

Idiopathic cardiomyopathy was considered present when no significant stenosis (no narrowing > 50%) was detected on the coronary angiogram and when no other cause was evident.

Study Protocol

The research protocol was approved by the local Institutional Ethics Committee, and each patient gave informed consent. Before entering the study, all patients were stable clinically under medical treatment for at least 2 wk. No patients included in the study were treated with medications known to interact with MIBG uptake, such as tricyclic agents or labetolol.

Radionuclide Left Ventricular Ejection Fraction

All patients underwent equilibrium radionuclide angiography after in vivo labeling of red blood cells with 740 MBq ^{99m}Tc. LVEF was determined from the left anterior oblique view, using a standard, commercially supplied, semiautomated edge detection program. The normal range of LVEF is 55%–70%.

MIBG Imaging

After a 30-min resting period, patients were injected intravenously with 111–148 MBq MIBG (CIS BIO-International, Gif-sur-Yvette, France). Four hours after MIBG administration, a 10-min static acquisition of the anterior view of the chest was performed. Cardiac MIBG uptake was measured twice as the heart-to-mediastinum (H/M) activity ratio by two independent observers, each unaware of the clinical status of the patients. Left ventricular activity was recorded using a manually drawn region of interest (ROI). Mediastinum activity was recorded using a 7 × 7 pixel ROI placed over the upper mediastinum area (*16*). The value of MIBG uptake for each patient was taken as the average of values determined by the observers. The interobserver differences for H/M ratio measurements were not significant (<3%). An H/M ratio value of 195% ± 31% (range 175%–260%) was found in 20 normal subjects (mean age 49 ± 14 y) in our laboratory.

M-Mode Echocardiography

Echographic measurements were performed using standard recommendations. 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 using the maximal cardiac diameter and the intrathoracic diameter at the level of the right costocardiac border.

Plasma Norepinephrine Determination

Blood samples were obtained after a 30-min resting period in the supine position. Plasma norepinephrine concentrations were determined by radioenzymatic assay (*17*).

Right-Sided Heart Catheterization

Right-sided heart catheterization was performed with a Swan-Ganz thermodilution catheter. Baseline measurements of right atrial, mean pulmonary artery and pulmonary capillary wedge pressures were recorded. Thermodilution cardiac output was taken as the mean value obtained by three iced injectates. Cardiac index (CI) was calculated as cardiac-output-to-body-surface-area ratio.

Maximal Oxygen Consumption

To assess the maximal workload, the peak oxygen uptake (peak Vo_2) and the anaerobic threshold, patients performed cycloergometer exercise (Medical Graphics Corporation, St. Paul, MN) with gas analysis for determination of maximal oxygen uptake. The test started at an initial workload of 10 W, with increments of 10 W/min.

Patient Management and Follow-Up

At the time of enrollment in the study, patients' medical treatment included angiotensin-converting enzyme inhibitors (91% of patients), diuretics (86%), digitalis (24%), amiodarone (16%) and β-blockers (18%).

After the initial examination, patients were followed up in their referring institutions or by their primary physicians. No patients were lost to follow-up. When functional status deteriorated, heart transplantation was considered for suitable patients (*5,18*).

Data Analysis and Statistics

The vital status of patients was determined through contacts with their primary physicians, the patients themselves or family members and from the patients' medical records. Information about circumstances and causes of death was collected. Cardiac deaths were categorized either as progressive heart failure or as sudden. Death from progressive heart failure was defined as death in the setting of progressive hemodynamic deterioration. Sudden death was defined as death occurring within 1 h of new symptom onset, without premonitory symptoms or during sleep.

Statistical analysis was performed on a computerized database using the SAS statistical program package (SAS Institute, Cary, NC). Analysis of variance was used to compare three subsets of patients: those still alive at the end of the study, those who died of cardiac death and those who underwent heart transplantation. The variables tested as prognostic indicators were cardiac MIBG uptake, plasma norepinephrine concentration, radionuclide LVEF, x-ray cardiothoracic ratio, echographic end-diastolic and end-systolic diameter, echographic fractional shortening, CI, right atrial pressure, pulmonary capillary wedge pressure and peak Vo_2. To evaluate the different parameters with regard to life duration, patients who underwent transplantation were excluded from the analysis. Patients who died of noncardiac deaths also were excluded from the analysis. The value of variables as predictors of death during the follow-up period was assessed using a multivariate stepwise regression discriminant analysis. The relationship

TABLE 1
Clinical and Laboratory Data

Number of patients	112
Age (y)	50 ± 10
Radionuclide LVEF (%)	21 ± 9
Cardiac MIBG uptake (H/M, %)	123 ± 19
Cardiac index (L/min/m^2)	2.33 ± 0.55
Pulmonary capillary wedge pressure (mm Hg)	19 ± 8
Right atrial pressure (mm Hg)	9 ± 4
Peak Vo_2 (mL/min/kg)	19 ± 5
Echographic end-diastolic diameter (mm)	70 ± 8
X-ray cardiothoracic ratio (%)	57 ± 8
Plasma NE (ng/mL)	1.02 ± 0.77

LVEF = left ventricular ejection fraction; MIBG = ^{123}I-metaiodobenzylguanidine; H/M = heart-to-mediastinum activity ratio; Vo_2 = oxygen uptake; NE = norepinephrine concentration.
Patients with noncardiac deaths (n = 2) are not included.

between life duration and variables was examined using multivariate stepwise regression life table analysis and Wilcoxon testing. Pearson product-moment correlations were used to examine the relationship among variables. Group data are expressed as mean ± SD. The null hypothesis was rejected for $P < 0.05$.

RESULTS

Clinical and Laboratory Data

The mean follow-up period was 27 ± 20 mo. During follow-up, 25 patients died of cardiac death, and 19 patients underwent heart transplantation. Sixty-six patients who did not receive transplants were alive at the end of the study. Among the cardiac deaths, 8 patients died suddenly. Two patients died of noncardiac deaths.

Laboratory and demographic data from the entire population are listed in Table 1. Data from the three subsets of patients defined as survivors, nonsurvivors and transplant recipients are listed in Table 2.

Predictors of Mortality

Multivariate discriminant analysis showed that among all continuous variables tested (cardiac MIBG uptake, plasma norepinephrine concentration, radionuclide LVEF, x-ray cardiothoracic ratio, echographic end-diastolic and end-systolic diameter, fractional shortening, CI, right atrial pressure, pulmonary capillary wedge pressure and peak Vo_2), H/M ratio ($P < 0.0001$) and radionuclide LVEF ($P = 0.02$) were the only independent predictors of mortality. Regarding the prediction of sudden deaths, multivariate discriminant analysis showed that the only independent factor was cardiac MIBG uptake ($P = 0.0015$). When cardiac MIBG uptake was eliminated from the model, multivariate discriminant analysis showed that plasma norepinephrine ($P = 0.002$) was the only independent predictor of mortality.

Multivariate life table analysis showed that the only independent predictors for life duration were H/M ratio ($P < 0.001$) and plasma norepinephrine concentration ($P = 0.001$).

TABLE 2
Group Data According to Outcome

	Living patients (n = 66)	Heart transplant patients (n = 19)	Dead patients (n = 25)
Age (y)	49 ± 9	51 ± 7	52 ± 13
Radionuclide LVEF (%)	24 ± 9	14 ± 5*	18 ± 7†
Peak Vo_2 (mL/min/kg)	20 ± 5	15 ± 7*	18 ± 8
Cardiac MIBG uptake (H/M, %)	134 ± 14	105 ± 15*	110 ± 9†
Cardiac index (L/min/m^2)	2.53 ± 0.56	1.92 ± 0.32*	2.12 ± 0.38*
Pulmonary capillary wedge pressure (mm Hg)	18 ± 7	23 ± 11*	21 ± 8
Right atrial pressure (mm Hg)	8 ± 4	10 ± 5	10 ± 5
End-diastolic diameter (mm)	68 ± 8	75 ± 8*	72 ± 7
X-ray cardiothoracic ratio (%)	56 ± 6	57 ± 14	59 ± 7
Plasma NE (ng/mL)	0.86 ± 0.60	1.05 ± 0.91	1.71 ± 1†‡

*$P < 0.05$ living vs. heart transplant patients.
†$P < 0.05$ living vs. dead patients.
‡$P < 0.05$ dead vs. heart transplant patients.
LVEF = left ventricular ejection fraction; Vo_2 = oxygen uptake; MIBG = metaiodobenzylguanidine; H/M = heart-to-mediastinum activity ratio; NE = norepinephrine concentration.
Patients with noncardiac deaths (n = 2) are not included.

Individual Performance of Prognostic Markers. Each separate variable can be used as a prognostic model by discriminant analysis. A posterior survival probability for each patient is then obtained from the linear discriminant function applied to each prognostic marker. This value, compared with the actual vital status of each patient observed during the follow-up, allows the determination of the number of patients misclassified by the model. Based on this information, the number of true- and false-positives and negatives is determined for each prognostic marker. Sensitiv-

TABLE 3
Individual Performance of Prognostic Markers

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
MIBG uptake	88	91	78	95
LVEF	61	72	41	85
Cardiac index	79	68	42	91
Plasma NE	77	70	40	92
Peak Vo_2	83	76	28	97

MIBG = metaiodobenzylguanidine; LVEF = left ventricular ejection fraction; NE = norepinephrine concentration; Vo_2 = oxygen uptake.

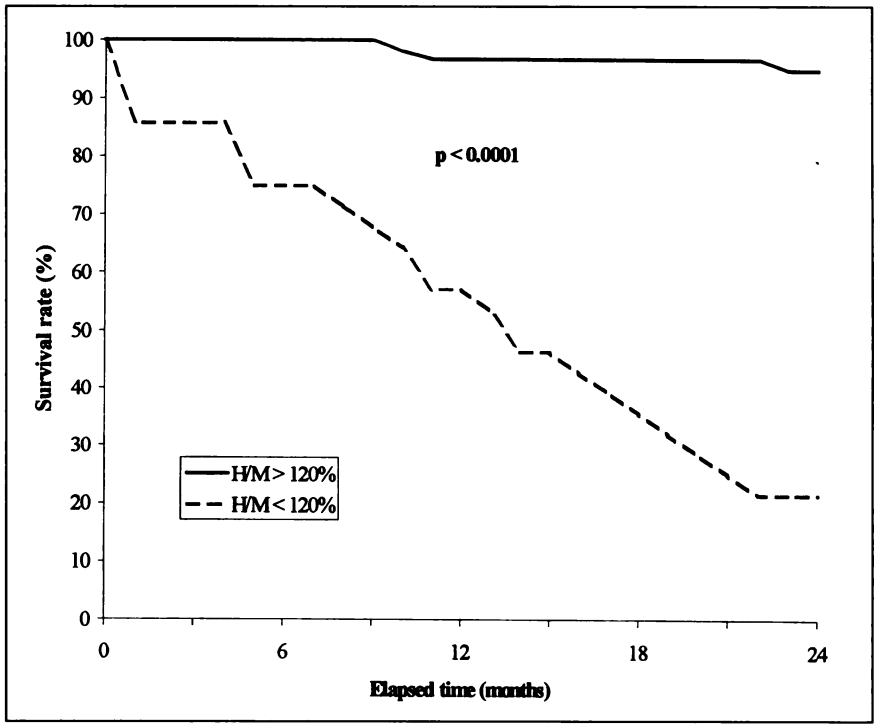

FIGURE 1. Survival curves obtained from life table analysis in patient population using scintigraphic index of cardiac MIBG uptake (H/M) for prognostication. MIBG imaging permits clear delineation between high- and low-risk subsets when using threshold value of 120% for H/M ratio. Patients with low MIBG uptake (dashed line) had poor prognoses when compared with patients with high MIBG uptake (solid line).

ity, specificity and positive and negative predictive values of the prognostic markers are listed in Table 3.

Risk Stratification on the Basis of Predictive Variables. Survival curves with threshold values of 120% for H/M ratio, 20% for LVEF and 1 ng/mL for plasma norepinephrine concentration are shown in Figures 1, 2 and 3, respectively. Each threshold value corresponds to the posterior probability of 0.5 obtained with linear discriminant function for each predictor considered separately as a model for prognostication. The curves show that MIBG imaging permits a better discrimination between high- and low-risk patients than LVEF or norepinephrine.

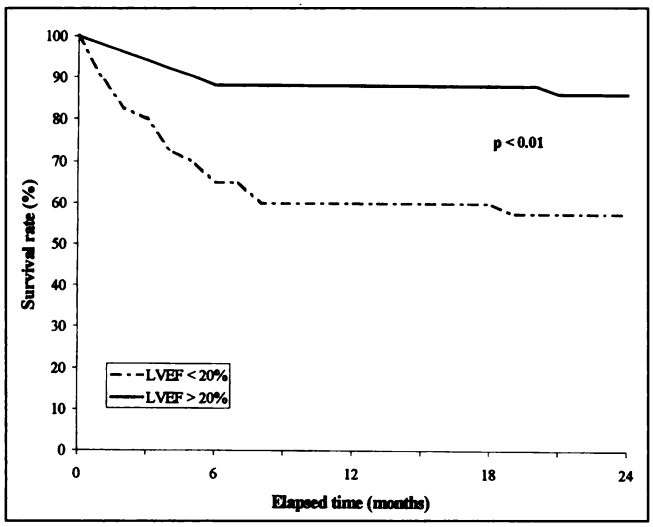

FIGURE 2. Survival curves obtained from life table analysis using LVEF for prognostication. Patient subset with LVEF > 20% (solid line) shows better survival rate than patient subset with LVEF < 20% (dashed line).

DISCUSSION

These data highlight the importance of cardiac sympathetic dysinnervation as a factor of mortality in idiopathic dilated cardiomyopathy. The sympathetic abnormalities detected with MIBG scintigraphy were better able to predict mortality than either circulating norepinephrine or hemodynamic indices.

Prognostic Value of Hemodynamic Variables

Most invasive and noninvasive indicators of cardiac dysfunction (*7–10,19–23*) correlate well with the prognosis. In particular, diminished LVEF has been associated repeatedly with mortality in patients with either idiopathic cardiomyopathy or ischemia (*7–10,23*). Consistent with these data, LVEF appeared as an independent predictor of death in this study.

Peak exercise oxygen consumption provides an objective evaluation of functional capacity and an indirect assessment of cardiovascular reserve and is an important tool for prognostic evaluation (*5,10,24*). In a selected population of ambulatory patients referred for heart transplantation, peak exercise oxygen consumption has proven useful in optimally timing heart transplantation, and a threshold value of 14 mL/min/kg has permitted accurate risk stratification (*10*). Others have reported different threshold values, such as 16 mL/min/kg (*24*) or 12 mL/min/kg (*25*), suggesting that methodologic differences could alter the threshold value. In a study involving 333 patients with advanced heart failure, lower values of peak exercise oxygen consumption were

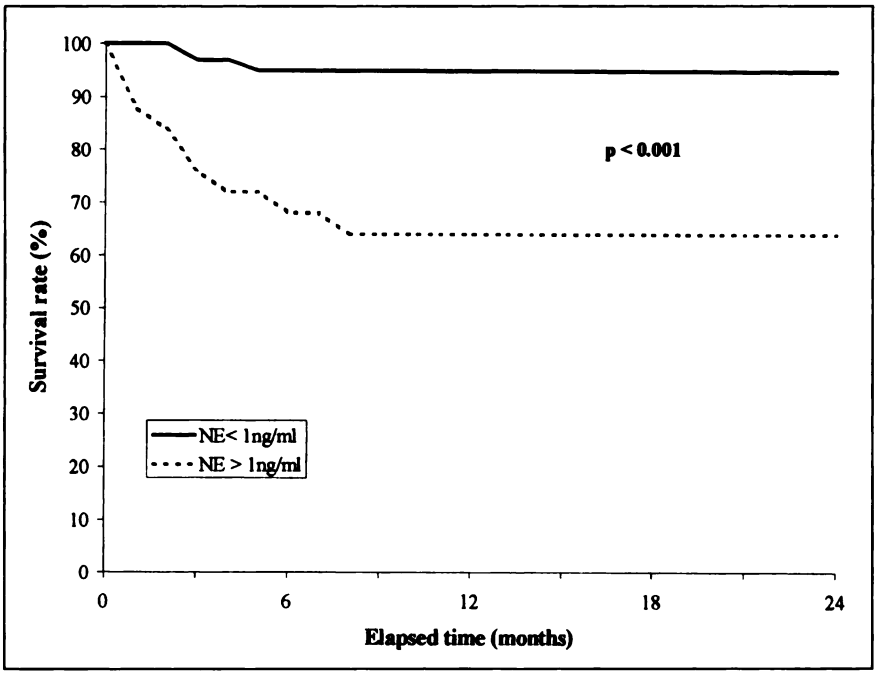

FIGURE 3. Survival curves obtained from life table analysis using plasma norepinephrine concentration (NE) for prognostication. Patients with NE values > 1.0 ng/mL (solid line) had better survival rates than those with CI values < NE values < 1.0 ng/mL (dashed line).

shown by life table analysis to predict the risk of death or the need for urgent transplantation but did not predict sudden deaths (*26*). Although the value of functional disability assessment after referral for heart transplantation may appear limited (*27*), peak exercise oxygen consumption is presently an important tool for the prognostic evaluation (*5*). Patients with preserved functional capacity were found to have a particularly favorable prognosis (*10*). The high negative predictive value for mortality found for peak Vo_2 in this study is consistent with these data. Nevertheless, peak Vo_2 did not appear in this study as an independent prognostic marker when MIBG was included in the analysis.

If all these variables based on measurements of hemodynamic alterations have been shown to correlate well with prognosis, there is a considerable overlap of values regarding the outcome, which makes individual evaluation of the risk of death difficult.

Adrenergic System and Prognosis

In heart failure, compensatory activation of the sympathetic system takes place. As heart failure progresses, circulating norepinephrine concentration is elevated and has been directly related to the degree of left ventricle dysfunction and to the risk of death (*11,28,29*). This study is consistent with these previous data, because when MIBG data were withdrawn from the analysis, the prognostic value of plasma norepinephrine was better than that of any hemodynamic indices. Nevertheless, decreased MIBG uptake was a better predictor of cardiac deaths, whether they occurred suddenly or not, than plasma norepinephrine concentration and hemodynamic markers.

Adrenergic nerve function and integrity are altered in the failing heart. Cardiac stores of norepinephrine are depleted (*30*). Controversial data have been reported regarding norepinephrine release, with an increase found in some studies (*31,32*) and a decrease in others (*33,34*). Although normal fractional extraction of the norepinephrine across the failing heart has suggested normal uptake-1 (*32*), the uptake-1 function has been reported to be diminished in animals (*35*), in postmortem examination of failing human hearts (*36*), in patients with heart failure resulting from valvular disease (*34*) and in patients with ischemic and idiopathic end-stage cardiomyopathies (*37,38*). This decrease in uptake-1 and norepinephrine storage has been found repeatedly using either single-photon imaging with MIBG or PET with ^{11}C-hydroxyephedrine (*15,16,39*).

Decreased MIBG is a consequence of chronic hyperactivation of the sympathetic system. Therefore, the potent prognostic value of cardiac MIBG uptake makes sense if the activation of the sympathetic nervous system is considered as a compensatory response induced when heart failure occurs. Because the evaluation of intrinsic contractility is hindered by the influence of loading parameters, the measurement of this compensatory response may be a better approach in assessing the severity of the disease than any isolated hemodynamic variable.

Limitations of the Study

Although the incidence of ischemic dilated cardiomyopathy has been reported to be higher in patients with congestive heart failure, this study focused on idiopathic dilated cardiomyopathy for two reasons. On the one hand, an impairment of energy supply may modify dramatically the function of the cardiac sympathetic system. Experimental studies have demonstrated that myocardial ischemia may cause extensive myocardial catecholamine depletion and adrenergic denervation in the infarcted area (*40,41*). Thus, in ischemic myocardium, the decrease in MIBG uptake may be

more closely related to the extent of the ischemia than to the deterioration of the contractile function. In patients with ischemia with left ventricular dysfunction, a possible option for a revascularization procedure is obviously the parameter that implies the most important prognostic consequences (*4*). The determination of ischemic but viable myocardium is therefore the first-line issue in the strategy of investigation for patients with ischemia.

The intrinsic limitations of quantification of single-photon imaging hinder the assessment of myocardial sympathetic function, especially in regional distribution. In this study, the drastic decrease in MIBG uptake found in severely ill patients prevented valuable tomographic imaging. The use of PET tracers may overcome these limitations (*39*). Further study is needed to evaluate whether PET can improve the delineation of high-risk patient populations.

CONCLUSION

This study shows that impaired sympathetic innervation and functioning is a major determinant of mortality in heart failure resulting from idiopathic dilated cardiomyopathy, involving either sudden death or progressive heart failure. This finding is concordant with the accumulation of evidence indicating that agents that counteract the adrenergic hyperactivity decrease mortality and morbidity, especially in idiopathic dilated cardiomyopathy (*1–3*). Because patients with idiopathic dilated cardiomyopathy represent half of the population referred for heart transplantation decision making, this study indicates that both MIBG imaging and radionuclide LVEF could help select candidates for heart transplantation.

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