Cardiac Metaiodobenzylguanidine Uptake in Patients With Moderate Chronic Heart Failure: Relationship With Peak Oxygen Uptake and Prognosis

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OBJECTIVES   This prospective study was undertaken to correlate early and late metaiodobenzylguanidine (MIBG) cardiac uptake with cardiac hemodynamics and exercise capacity in patients with heart failure and to compare their prognostic values with that of peak oxygen uptake (VO_2).

BACKGROUND   The cardiac fixation of MIBG reflects presynaptic uptake and is reduced in heart failure. Whether it is related to exercise capacity and has better prognostic value than peak VO_2 is unknown.

METHODS   Ninety-three patients with heart failure (ejection fraction <45%) were studied with planar MIBG imaging, cardiopulmonary exercise tests and hemodynamics (n = 44). Early (20 min) and late (4 h) MIBG acquisition, as well as their ratio (washout, WO) were determined. Prognostic value was assessed by survival curves (Kaplan–Meier method) and uni- and multivariate Cox analyses.

RESULTS   Late cardiac MIBG uptake was reduced (131 ± 20%, normal values 192 ± 42%) and correlated with ejection fraction (r = 0.49), cardiac index (r = 0.40) and pulmonary wedge pressure (r = −0.35). There was a significant correlation between peak VO_2 and MIBG uptake (r = 0.41, p < 0.0001). With a mean follow-up of 10 ± 8 months, both late MIBG uptake (p = 0.04) and peak VO_2 (p < 0.0001) were predictive of death or heart transplantation, but only peak VO_2 emerged by multivariate analysis. Neither early MIBG uptake nor WO yielded significant insights beyond those provided by late MIBG uptake.

CONCLUSIONS   Metaiodobenzylguanidine uptake has prognostic value in patients with wide ranges of heart failure, but peak VO_2 remains the most powerful prognostic index. (J Am Coll Cardiol 1999; 33:759–66) © 1999 by the American College of Cardiology

Patients with chronic heart failure (CHF) have reduced exercise capacity (1) attributable to both central and peripheral factors (2). Alteration of the cardiac adrenergic pathway is a hallmark of the syndrome (3,4), participating in the reduction in the heart rate and contractile reserves. To what extent it may contribute to the reduction of exercise capacity has not been previously determined. Metaiodobenzylguanidine (MIBG), an analogue of noradrenaline that shares the same reuptake pathway within the cardiac synapse (5), was developed to visualize sympathetic innervation and was recently used to study myocardial adrenergic nerve activity (6,7). Its myocardial fixation depends on the integrity of the sympathetic pathway, is reduced in parallel with the alter-

ation of norepinephrine uptake (8,9) and correlates in experimental heart failure with the myocardial content of norepinephrine (10) and in patients with the degree of myocyte degeneration and necrosis (11). Whether MIBG uptake should be assessed early or late after injection remains debated (12–17); the washout rate of MIBG uptake from early to late imaging may reflect the sympathetic nervous system activity. It is unclear at the present time, however, whether imaging MIBG uptake early and late after injection has some clinical value above only late imaging. The relationships between MIBG uptake and hemodynamics have not been extensively studied (5,18). Finally, it has recently been shown that MIBG uptake had a high prognostic value (19) and may help successfully manage the transplant list (20), but the comparison with another major prognostic index, peak exercise oxygen uptake (peak VO_2) (21,22), has not yet been performed. As the latter has clearly appeared as the best index of prognosis

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Abbreviations and Acronyms

CHF	=	chronic heart failure
EF	=	ejection fraction
H/M	=	heart/mediastinum
MIBG	=	metaiodobenzylguanidine
NYHA	=	New York Heart Association
ROC	=	receiver operating characteristic
VO₂	=	oxygen uptake
WO	=	wash-out

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in most of the recent studies, we wondered which index had the greatest value to predict outcome in patients with various degrees of heart failure.

The aims of the present study were therefore 1) to address the relationships between MIBG cardiac uptake and cardiac hemodynamics and exercise capacity; 2) to prospectively compare the prognostic values of cardiac MIBG uptake and peak VO_2, and 3) to compare early and late MIBG acquisitions, in patients with CHF.

METHODS

Patients. Ninety-three consecutive patients with CHF (88 men, 5 women) were prospectively studied during an 18-month period. Their mean age was 55 ± 10 years (range 32 to 77). The inclusion criteria were a history of chronic heart failure and a left ventricular ejection fraction (EF) lower than 45%. The etiology of heart failure was an ischemic cardiomyopathy in 24 cases and a dilated cardiomyopathy in 69 cases. Forty patients were in New York Heart Association (NYHA) functional class II, 46 in class III and 7 in class IV. All were in stable conditions. At the time of the study, most of the patients were receiving angiotensin-converting enzyme inhibitors (86%) and diuretics (92%); 45% received digoxin, 42% nitrates, 40% amiodarone and 13% a beta-adrenergic blocking agent. Eighty-seven patients had echocardiography for measurement of left ventricular end-diastolic and end-systolic diameters and calculation of fractional shortening. An hemodynamic evaluation was performed in 44 patients, allowing determination of pulmonary arterial pressures and cardiac index. All procedures were approved by the appropriate ethics committee, and subjects provided informed consent to participate in the study.

Exercise tests. Exercise tests were all performed on a bicycle, in an upright position. After an initial workload of 20 W, load was increased by 10 W every minute. Patients were regularly encouraged to pedal until exhaustion at a constant rate. All tests were stopped because of fatigue and/or dyspnea. Heart rate was continuously recorded. Brachial arterial pressure was measured with a mercury manometer at each stage. Respiratory gases were analyzed on a CPX-D Medical Graphics (Minneapolis, MN) system. The equipment was calibrated with a standard gas mixture before each test. Subjects breathed through a mouthpiece with a nose clip. Oxygen consumption (VO₂), carbon dioxide production, minute ventilation and the respiratory exchange ratio were measured on a breath by breath basis. Peak oxygen consumption was defined as the highest averaged oxygen consumption during the test and was expressed in ml/min and ml/min/kg. Indexed peak oxygen consumption (%) was calculated as peak oxygen consumption divided by maximal predicted oxygen consumption (23). The chronotropic reserve was defined as peak minus rest heart rate/rest heart rate. The ventilatory threshold (24) was determined by use of a combination of multiple graphical methods (25). All patients exercised beyond the anaerobic threshold, and the respiratory exchange ratio was always greater than 1.0 at the end of exercise.

¹²³Iodine metaiodobenzylguanidine scintigraphy. Within 15 days of the exercise test, patients underwent myocardial scintigraphy to determine MIBG uptake, used as an index of neuronal norepinephrine reuptake. As exercise-induced myocardial ischemia may decrease MIBG uptake (26,27), a free period of at least 5 days was respected between the exercise test and MIBG scintigraphy when the exercise test was performed first. After a 30-min resting period, patients were injected intravenously with 3 to 4 mCi (111 to 148 MBq) of ¹²³I MIBG (CIS BIO-International, Gif sur Yvette, France). Twenty minutes (early acquisition) and 4 h (late acquisition) after MIBG administration, a 10-min static acquisition was performed in the anterior view of the chest on a Sopha Medical DST gamma-camera (Buc, France). Cardiac MIBG uptake was measured as the heart to mediastinum activity ratio (H/M) on a planar image by two independent observers. Left ventricular activity was recorded using a manually drawn region of interest and mediastinum activity using a 7×7 pixel region of interest placed over the upper mediastinum area (19). For each patient, the H/M value was taken as the average of measurements performed over his scintigraphic image by each observer. The normal late H/M ratio obtained in our laboratory from 20 normal subjects (mean age 48 ± 18 years, range 23 to 78) is $192 \pm 42\%$ (19).

The washout (WO) rate of MIBG within the myocardium was measured as the percent of change in cardiac activity from early to delayed images within the left ventricular regions of interest as follows: (H early − H delayed) × 100/H early, H values being corrected for ¹²³I physical decay.

Follow-up. Outcome was assessed either directly (when the patient's physician was a member of the medical staff), or by contacting the patient's practitioner. The date and cause of death were documented in every case. Ten patients died, and 23 patients underwent cardiac transplantation during follow-up (10 ± 8 months). Since there is no consensus about the best way to consider heart transplantation in survival analyses, we used two methods of analysis: first using both death and transplantation as end points (33

events); second, censoring patients who underwent cardiac transplantation at the time of intervention (considering them alive at this time) (10 events).

Statistical analysis. Numeric values are expressed as means ± standard deviation. Differences between the means of groups was made by analysis of variance or a Student *t* test when appropriate. Linear regression analysis was by least square. P values of 0.05 or less were considered to denote statistically significant differences.

We used the Survival Analysis module of Stat View 4.02 (Abacus Concept, California) for MacIntosh software to analyze survival. Kaplan–Meier cumulative mortality curves were plotted to the end of follow-up to describe trends in mortality over time in each of the risk categories (28). For continuous variables, we used the medians as cutoff values. Survival curves were compared by using the log-rank test.

Age, NYHA class, left ventricular ejection fraction, end-diastolic diameter, early and late MIBG H/M, WO and peak oxygen uptake were the variables entered in the univariate analysis. The Cox proportional hazards regression model was used to determine the significance of variables predictive of outcome by univariate analysis (p < 0.05) as independent predictors of survival in multivariate analysis (backward selection) (29).

Finally, the sensitivity and specificity of values of MIBG H/M and peak oxygen uptake for the prediction of death or of death and cardiac transplantation were determined. Receiver operating characteristic (ROC) curves were constructed by plotting sensitivity against (1 − specificity). The best compromise between sensitivity and specificity was determined graphically.

RESULTS

Baseline values. Mean left ventricular ejection fraction was 25 ± 10%. Mean echocardiographic left ventricular end-diastolic and end-systolic diameters were 70 ± 10 mm and 59 ± 11 mm, respectively. Pulmonary wedge pressure was 16 ± 8 mm Hg and cardiac index was 2.6 ± 0.7 liters/min/kg in the subgroup of patients in whom they were measured.

Peak VO$_2$ was on average 1493 ± 490 ml/min, that is, 20.1 ± 6.0 ml/min/kg (median value 21 ml/min/kg), corresponding to 67 ± 19% of the predicted value. A ventilatory threshold could be clearly determined in 77 patients, and its mean value was 13.3 ± 4.4 ml/min/kg. Heart rate was 86 ± 23 min^{-1} at rest and 141 ± 28 min^{-1} at peak exercise, corresponding to 86 ± 16% of the predicted values. The chronotropic reserve was 137 ± 11%.

Early MIBG H/M ratio was 139 ± 21% (median 138%, range 94% to 208%) and late MIBG H/M ratio was 131 ± 20% (median 127%, range 88% to 191%). Washout was 34.8 ± 6.0 (median 35.5, range 16.9 to 56.3).

Relation with hemodynamic and exercise variables. Late MIBG H/M correlated with left ventricular ejection frac-
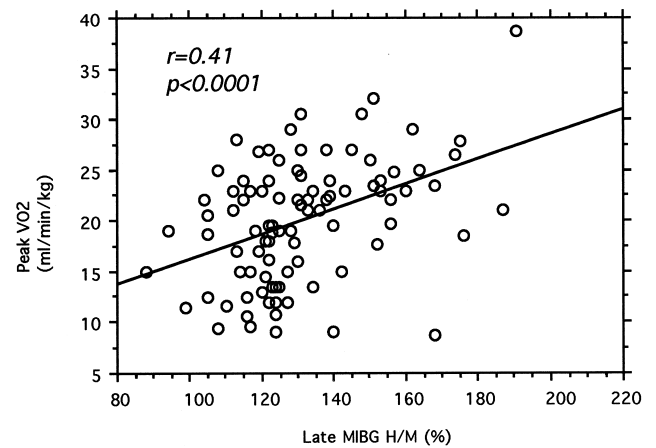

Figure 1. Correlation between late MIBG uptake (MIBG H/M, in percentage) and peak VO$_2$ (in ml/min/kg).

tion (r = 0.49, p < 0.0001), cardiac index (r = 0.40, p < 0.01), mean pulmonary artery pressure (r = −0.36, p < 0.01), pulmonary artery resistances (r = −0.30, p < 0.05) and pulmonary wedge pressure (r = −0.35, p < 0.05). The correlation coefficients between late MIBG H/M and left ventricular end-diastolic and end-systolic diameters and fractional shortening were r = −0.45, r = −0.53 and r = −0.43, respectively (all p < 0.001). Early MIBG H/M correlated with late MIBG H/M (r = 0.87, p < 0.0001) and with the same hemodynamic parameters, albeit less closely. Washout did not correlate with any hemodynamic variable, except ejection fraction and mean pulmonary arterial pressure.

There was a significant correlation between peak VO$_2$ (in ml/min/kg) and late MIBG H/M (r = 0.41, p < 0.0001) (Fig. 1). Expressing peak VO$_2$ in ml/min or in percentage of the predicted values did not change the coefficient of correlation (r = 0.41 and r = 0.40, respectively, both p < 0.0001). When the 12 patients with beta-blockers were excluded, the coefficient of correlation was r = 0.48. The anaerobic threshold also correlated with MIBG uptake (r = 0.35, p < 0.05). There was no correlation between MIBG uptake and the chronotropic reserve (r = 0.17, p = NS), even when patients receiving beta-blockers were excluded.

Prognostic analysis. Patients who died or received transplants had significantly lower peak VO$_2$ and poorer NYHA class than those who survived at the end of the study (Table 1). There was no or only marginal differences among the two groups regarding age, ejection fraction, left ventricular diameters and early and late H/M MIBG or WO.

Survival curves were drawn to identify the factors most predictive of prognosis. Peak oxygen consumption was highly predictive of event-free survival (cutoff median values: 21 ml/min/kg, chi-square = 15, p = 0.0001; and 69% of the predicted values: chi-square = 16, p < 0.0001) (Fig. 2). The median late MIBG H/M cutoff value of 127% also discriminated between patients with good and poor out-

Table 1. Description of Baseline Values in Patients Who Died, in Patients Who Underwent Cardiac Transplantation and in Patients Who Survived

	Death (n = 10)	Cardiac Transplantation (n = 23)	Alive (n = 60)	p
Age (mean ± SD)	56 ± 10	53 ± 9	56 ± 10	0.30
NYHA class				0.054
% I–II	20	13	55	
% III–IV	80	87	45	
Etiology				0.16
% ischemic	10	39	23	
% nonischemic	90	61	77	
Peak VO₂ (ml/min) (mean ± SD)	1,310 ± 539	1,267 ± 509	1,610 ± 440	0.007
Peak VO₂ (ml/min/kg) (mean ± SD)	17.5 ± 5.3	17.0 ± 5.6	21.7 ± 5.7	0.002
Peak VO₂ (% predicted) (mean ± SD)	58 ± 15	56 ± 15	72 ± 17	0.0001
EF (%) (mean ± SD)	21 ± 8	23 ± 9	26 ± 11	0.15
End-diastolic diameter (mm) (mean ± SD)	71 ± 12	70 ± 10	70 ± 10	0.81
Late MIBG H/M (%) (mean ± SD)	123 ± 14	128 ± 21	134 ± 20	0.18
Early MIBG H/M (%) (mean ± SD)	133 ± 19	138 ± 22	141 ± 20	0.48
WO (mean ± SD)	34.5 ± 4.2	34.1 ± 6.2	36.1 ± 6.2	0.30

EF = ejection fraction; H/M = heart/mediastinum; MIBG = metaiodobenzylguanidine; NYHA = New York Heart Association; WO = early to late MIBG H/M ratio.

come (chi-square = 9, p = 0.002) (Fig. 3). Early MIBG had lower prognostic value, whereas WO did not have any.

By univariate analysis (Table 2), peak VO₂ (p = 0.0001) and late MIBG H/M (p = 0.04) were predictive of death or heart transplantation. Neither early MIBG H/M nor WO had prognostic value. Ejection fraction was not discriminant. By multivariate analysis (Table 3), only peak VO₂ remained as an independent predictor of outcome.

When deaths only were considered, only peak VO₂ (p <

0.05) predicted death by univariate analysis. When patients who underwent heart transplantation were excluded from analysis, similar results were obtained (peak VO₂: p = 0.02; late MIBG H/M: p = 0.06).

Finally, ROC curves (Fig. 4) showed a greater area under the curve for peak oxygen uptake than for early or late MIBG H/M, confirming the better prognostic value of the former for predicting death or death and transplantation.
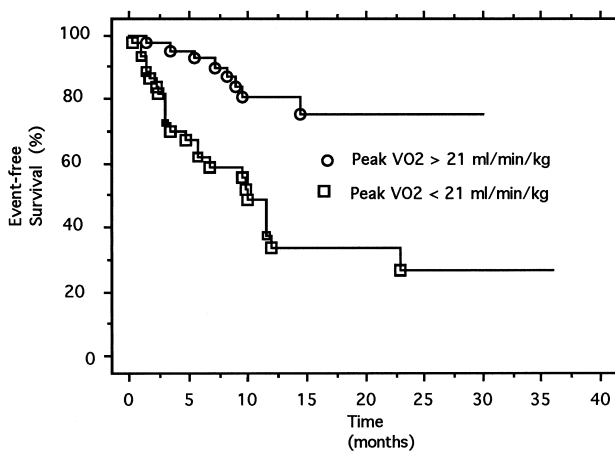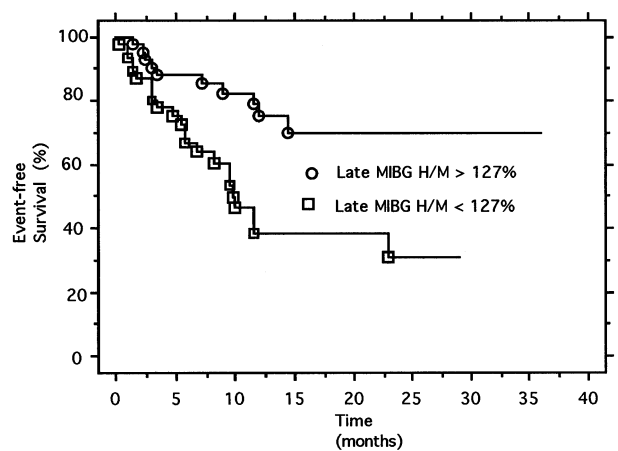

Figure 2. Event-free survival curves according to baseline peak VO₂, using a peak VO₂ cutoff value of 21 ml/min/kg.

Figure 3. Event-free survival curves according to baseline late MIBG uptake, with a MIBG H/M cutoff value of 127%.

Table 2. Univariate Survival Analysis: Cox Model

	Event: Deaths (n = 10)		Events: Deaths or Transplantations (n = 33)	
	Risk Ratio	p	Risk Ratio	p
Age (years)	1.023	0.47	0.99	0.78
NYHA				
I–II	1		1	
III–IV	4.1	0.07	5.3	0.0006
Peak VO₂ (%)	0.97	0.04	0.96	0.0001
Peak VO₂ (ml/min)	0.99	0.03	0.99	0.0001
Peak VO₂ (ml/min/kg)	0.89	0.03	0.88	0.0001
EF (%)	0.96	0.20	0.97	0.13
Late MIBG H/M (%)	0.03	0.09	0.11	0.04
Early MIBG H/M (%)	0.07	0.16	0.25	0.15
WO	1.008	0.90	1.05	0.14
End-diastolic diameter (mm)	1.001	0.68	1.001	0.68

Abbreviations as in Table 1.

DISCUSSION

This study suggests that altered adrenergic nerve function may determine in part exercise capacity and has a prognostic value, which seems, however, to be lesser than that of peak VO₂.

Metaiodobenzylguanidine uptake in heart failure. Altered adrenergic function is a hallmark of the syndrome of heart failure. Abnormal baroreflex function (30), increased spillover of noradrenaline (31) and sympathetic discharge (32,33), down-regulation of the beta-adrenergic receptors (4) and depletion of myocardial sympathetic stores (3) are characteristic features of the disease and probably participate in its pathophysiology. These alterations result in altered contractile state and peripheral vasoconstriction. Cardiac neuronal uptake is the predominant means for terminating the action on beta-adrenoceptors of norepinephrine either released by nerve terminals or removed from coronary circulation (34) and is decreased in chronic heart failure (8,9); this may lead to increased stimulation and down-regulation of beta-adrenoceptors. Metaiodobenzylguanidine myocardial scintigraphy has been shown to explore noradrenaline reuptake within the cardiac synapse (6,7) and thus has the potential to mirror the whole myocardial adrenergic pathway disintegrity. Metaiodobenzylguanidine uptake correlates with the norepinephrine content of the heart (10) and with the increase in myocardial contractility induced by intracoronary beta-adrenergic stimulation (35). Metaiodobenzylguanidine uptake was clearly decreased in our population, although some patients were found to have

Table 3. Multivariate Survival Analysis: Cox Model With a Backward Selection

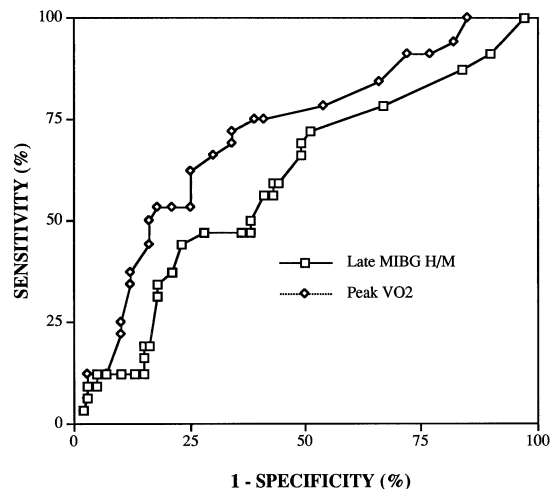|	Events: Deaths (n = 10)	Events: Deaths or Transplantations (n = 33)
	p	p
Age (years)	0.34	0.74
NYHA class	0.56	0.02
Peak VO₂: % predicted	0.04	0.01
Late MIBG H/M (%)	0.27	0.87
Age (years)	0.30	0.81
NYHA class	0.57	0.02
Peak VO₂: % predicted	0.047	0.01
Early MIBG H/M (%)	0.23	0.69

Abbreviations as in Table 1.

Figure 4. Plot showing ROC curves for prediction of death or cardiac transplantation for peak oxygen uptake (% of predicted values) and late MIBG H/M. Peak oxygen uptake ROC curve, situated clearly leftward relative to MIBG curve, suggests better predictive value.

MIBG uptake values only slightly lower than normal, despite clear left ventricular dysfunction; in a recent experimental study, it was found that MIBG uptake was not decreased in the early stages of heart failure (36), a finding also recently observed in men (37). Metaiodobenzylguanidine uptake decrease may thus be a late event in the history of the disease, explaining its prognostic value in end-stage heart failure (19). We found that MIBG uptake correlated with most hemodynamic indexes of left ventricular dysfunction, albeit sometimes loosely.

Metaiodobenzylguanidine washout rate. Metaiodobenzylguanidine uptake within the myocardium decreases with time, and there is evidence that the washout rate of MIBG (WO) measured by calculating the early/late MIBG uptake can be an index of norepinephrine spillover. Various studies demonstrated that the nonneural myocardial uptake of MIBG contributes mainly to the early image and disappears rapidly, whereas the neural uptake contributes to the delayed images (14,38). These findings indicate that the delayed image represents adrenergic nervous system function more faithfully than does the early image. Myocardial retention of MIBG is significantly reduced, and consequently MIBG washout increased in the patients with heart failure (7,12,38,39). We found no additional value of performing early MIBG imaging or calculating WO. In contrast with other studies in mitral stenosis (17) or heart failure (16), the WO did not appear to correlate with hemodynamic parameters or peak VO$_2$, nor did it have prognostic value. Therefore, its medical interest is questionable in patients with CHF.

Metaiodobenzylguanidine uptake and exercise capacity. To our knowledge, no study has attempted to address the relationship between the abnormalities of cardiac norepinephrine reuptake and the circulatory response during exercise in patients with CHF. We found a significant correlation between MIBG uptake and peak VO$_2$. This suggests that the alteration in cardiac adrenergic function may participate in the reduction in exercise tolerance. Adrenergic responsiveness may influence both the contractile (40) and the chronotropic reserves (41). Eisenhofer et al. (9) recently showed that norepinephrine reuptake efficiency is decreased during exercise in heart failure, which may contribute to increased sympathetic drive. Reduced chronotropic reserve, an abnormality the prognostic value of which has been recently emphasized (42), is frequently observed in patients with chronic heart failure (41,43) and has been related more to postsynaptic beta-adrenergic desensitization than to altered norepinephrine kinetics. This may explain the close correlation found in a previous study between the extent of the chronotropic reserve and right ventricular myocardial beta-adrenergic receptor density (44), whereas we found no correlation between MIBG uptake and the chronotropic reserve. Overall, abnormalities of the adrenergic nerve function explain at best 17% of the variance of peak VO$_2$; this underscores the importance of the other determinants of peak VO$_2$, mainly the peripheral ones.

Prognostic value of peak VO$_2$ and MIBG uptake. The increase in plasma norepinephrine has a negative impact on prognosis in CHF patients (45). Increased cardiac sympathetic nervous activity seems to have a greater prognostic value than whole-body sympathetic activity, determined by isotope dilution (46). Metaiodobenzylguanidine uptake, which largely reflects altered cardiac noradrenergic pathway dysfunction, has been found in a previous study to have prognostic value in patients with end-stage CHF (19). Subsequently, this parameter has demonstrated its powerful value in the process of triage of patients referred for cardiac transplantation (20). In that study (19), patients had severe heart failure, and those who underwent cardiac transplantation were excluded from analysis; in addition, exercise capacity was not assessed. On the contrary, numerous studies have demonstrated the great short-term prognostic value of peak VO$_2$ (21,45,47–49). Recently, we found that peak VO$_2$ also had prognostic value in the long term (22). Therefore, we decided to prospectively compare the prognostic value of both parameters. This study is the first comparing the prognostic value of these two variables in patients with various degrees of heart failure. We found that both had greater prognostic value than ejection fraction, and that peak VO$_2$ seems to have a greater prognostic value than MIBG uptake, whatever the way of analyzing outcome. Moreover, in this population, MIBG imaging does not seem to bring significant prognostic information beyond that provided by peak VO$_2$.

Limitations of the study. There are some potential limitations to the present study. As patients remained medicated during the investigation, one cannot exclude that the effects of CHF therapy upon MIBG uptake may have slightly modified the relationships: MIBG uptake was reported to increase after spironolactone (50), angiotensin-converting enzyme inhibitors (51) and perhaps digoxin and amiodarone (52); beta-blocker therapy seems to have neutral effect (53). We did not perform tomographic imaging (54). However, in our experience as well as in others' (12), it is difficult and often impossible to obtain adequate tomographic scans, at least 3 to 4 h after injection, especially in the most severe patients; the reconstruction process is not reproducible enough from one trained observer to another. Myocardial perfusion was not simultaneously assessed by 201 thallium imaging (55). Decrease in perfusion by itself may decrease planar MIBG uptake. However, previous studies have shown that in either ischemic or idiopathic dilated cardiomyopathy, resting myocardial blood flow values were close to normal. Finally, the number of deaths was low, and this was the reason why we decided to consider transplantation as an end point. It is unlikely that peak VO$_2$ or MIBG values differently affected the decision to perform cardiac transplantation, as at the time of the study, we felt that both tests were roughly equally discriminant regarding

the decision of transplantation. Censoring transplantation at the time of surgery or only considering "urgent" transplantation (not reported) did not change the results of the study. It is, however, possible that the prognostic value of MIBG imaging would be greater in patients with severe heart failure. Recently, however, it was shown that even in patients with the most advanced heart failure, peak VO$_2$ indexed by predicted values yielded the greatest prognostic value, as also noticed in other populations with a wide range of heart failure (22,48,56,57).

Conclusions. Metaiodobenzylguanidine uptake, which reflects the reuptake of noradrenaline within the cardiac synapse, only modestly correlates with peak VO$_2$. Thus, although alterations of the sympathetic pathway participate in the alteration of the exercise response in patients with CHF, they are not major determinants of peak VO$_2$. Metaiodobenzylguanidine uptake is a new powerful prognostic variable with prognostic value greater than ejection fraction. The MIBG uptake washout rate does not provide any significant prognostic insight. However, in these patients with predominantly moderate heart failure, peak VO$_2$ remains the better prognostic index.

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