Sympathetic Nerve Alterations Assessed with ^{123}I-MIBG in the Failing Human Heart

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Norepinephrine (NE) reuptake function is impaired in heart failure and this may participate in myocyte hyperstimulation by the neurotransmitter. This alteration can be assessed by ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy. **Methods:** To determine whether the impairment of neuronal NE reuptake was reversible after metoprolol therapy, we studied 18 patients (43 ± 7 y) with idiopathic dilated cardiomyopathy who were stabilized at least for 3 mo with captopril and diuretics. Patients underwent, before and after 6 mo of therapy with metoprolol, measurements of radionuclide left ventricular ejection fraction (LVEF), maximal oxygen consumption and plasma NE concentration. The cardiac adrenergic innervation function was scintigraphically assessed with MIBG uptake and release measurements on the planar images obtained 20 min and 4 h after tracer injection. To evaluate whether metoprolol had a direct interaction with cardiac MIBG uptake and release, six normal subjects were studied before and after a 1-mo metoprolol intake. **Results:** In controls, neither cardiac MIBG uptake and release nor circulating NE concentration changed after the 1-mo metoprolol intake. Conversely, after a 6-mo therapy with metoprolol, patients showed increased cardiac MIBG uptake (129% ± 10% versus 138% ± 17%; P = 0.009), unchanged cardiac MIBG release and decreased plasma NE concentration (0.930 ± 412 versus 0.721 ± 0.370 ng/mL; P = 0.02). In parallel, patients showed improved New York Heart Association class (2.44 ± 0.51 versus 2.05 ± 0.23; P = 0.004) and increased LVEF (20% ± 8% versus 27% ± 8%; P = 0.0005), whereas maximal oxygen uptake remained unchanged. **Conclusion:** Thus, a parallel improvement of myocardial NE reuptake and of hemodynamics was observed after a 6-mo metoprolol therapy, suggesting that such agents may be beneficial in heart failure by directly protecting the myocardium against excessive NE stimulation.

Key Words: idiopathic dilated cardiomyopathy; prognosis; radionuclide left ventricular ejection fraction; norepinephrine; metaiodobenzylguanidine; uptake-1; metoprolol; captopril

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The failing myocardium is characterized by the presence of many alterations of adrenergic nerves such as decreased cardiac norepinephrine (NE) uptake, increased NE release, decreased NE cardiac content and partial denervation (*1–3*). These abnormalities contribute to an elevation of NE concentrations at the synaptic level that is thought to participate in the evolution of cardiomyopathies. Metaiodobenzylguanidine (MIBG) imaging provides the opportunity to explore noninvasively the adrenergic nerve integrity and functioning (*4,5*) because it is an NE analog. A decrease in MIBG uptake was observed in patients with heart failure when compared with healthy subjects (*6,7*). This decrease was correlated to both alterations of left ventricular function indices (*7,8*) and life duration (*9*).

Recent clinical trials have demonstrated that the use of agents that counteract the sympathetic system hyperactivation such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers could be beneficial in the treatment of congestive heart failure. The use of these agents has lead to an improvement of functional status, exercise tolerance and radionuclide ejection fraction, as well as to a better survival in patients with conjestive heart failure, especially in idiopathic dilated cardiomyopathy (*10–18*). Thus, because cardiac MIBG uptake has been shown to be a potent prognostic indicator, it can be hypothetized that the alterations of cardiac adrenergic innervation integrity and functioning could partially recover after a therapy associating both agents.

This study was undertaken in patients with congestive heart failure to test the hypothesis of the reversibility of cardiac innervation disorders as a potential mechanism of hemodynamic improvement in response to therapy. We first studied six healthy subjects before and after a 1-mo intake of metoprolol to determine the potential interaction of this agent with cardiac MIBG uptake. In a group of 18 patients with congestive heart failure stabilized with a therapy associating diuretics and ACE inhibitors, both indices of left ventricular function and cardiac MIBG uptake were studied before and 6 mo after having added metoprolol to the therapy.

SUBJECTS AND METHODS

Study Population

Patients. Eighteen patients, 14 men and 4 women (mean age 43 ± 7 y), 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, symptoms

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graded II to III of the functional classification of the New York Heart Association (NYHA), radionuclide left ventricular ejection fraction (LVEF) below 40%, congestive heart failure related to an idiopathic dilated cardiomyopathy, sinus rhythm, no concomittant illnesses and no contraindication to β-blocker therapy (bradycardia with atrioventricular disturbances, asthma). Idiopathic cardiomyopathy was considered to be present because no significant stenosis (>50% of the lumen) was detected on the coronary angiogram and no other cause was recognized.

Patients were stabilized with a medical therapy, including diuretics and ACE inhibitors for at least 3 mo (mean duration = 8 ± 7 mo).

Controls. Six healthy volunteers (mean age 37 ± 9 y; *P* values were not significant with patients) were included.

All subjects had normal clinical and electrocardiogram (ECG) examinations. Systolic function assessed with echocardiography was normal in the control group with a left ventricular fractional shortening (32% ± 2%) and a normal left ventricular end-diastolic diameter (49.3 ± 2.0 mm). Stress ECG testing was negative. All subjects were free of any medication at the time of inclusion.

Study Protocol

After inclusion in the study, patients had measurements taken of scintigraphic MIBG uptake and release, radionuclide LVEF, peak exercise oxygen consumption, echocardiographic parameters and resting plasma NE concentration. All data were obtained within an 8-d period.

After the initial evaluation, β-blocker treatment (metoprolol) was introduced carefully. Doses were progressively increased each week (12.5 mg/d initially, then 25 mg, 50 mg), up to a maximal dose of 150 mg at 6 wk after initiation of therapy. Final dosage was adapted individually and did not change after the initial 6-wk titration period. The mean dosage obtained at the end of the titration period was 120 ± 23 mg/d. Patients were clinically evaluated twice a month during the first 2 mo and every month thereafter. Six months after patients were included, the initial investigations were repeated.

In the group of healthy subjects, a dose of 200 mg/d of metoprolol was administred orally during 1 mo and scintigraphic examination was repeated. An exercise test was also performed to ensure the efficacy of β-blocker evaluated on the level of maximal heart rate reduction.

The protocol was approved by the ethical committee of our institution and each subject gave informed written consent.

Radionuclide Left Ventricular Ejection Fraction

All patients had equilibrium radionuclide angiography after in vivo labeling of red blood cells using 740 MBq (20 mCi) ^{99m}Tc. A 5000-kct acquisition was performed in the anterior and left anterior oblique views that best separated the right and left ventricles in the plane of the interventricular septum. The processing of the LVEF was performed from the left anterior oblique view with a standard commercially supplied semiautomated edge detection program. The normal range of LVEF is 55%–70%.

MIBG Imaging

Lugol solution (40 mg iodure/d) was administered orally for 3 d before and 3 d after scintigraphic examination. After a 30-min resting period, 111–148 MBq (3–4 mCi) ^{123}I-MIBG (CIS BIO-International, Gif sur Yvette, France) were intravenously injected. A 10-min static acquisition was performed in the anterior view of the chest, 4 h after injection. Cardiac MIBG uptake was measured twice by two independent observers unaware of the clinical status of the patients. Left ventricular activity was recorded with a manually drawn region of interest (ROI). Size and positioning were checked with the anterior view of the chest radiograph. Another 7 × 7 pixel ROI was placed over the upper mediastinum area. Heart-to-mediastinum activity ratio (H/M) was then computed to quantify cardiac MIBG uptake.

MIBG washout rate (WOR) was defined as percentage change in cardiac activity [H] from early to delayed images within the left ventricular ROI as follows: WOR = | ([H] early) − ([H] delayed) | / ([H] early) × 100, data being corrected for ^{123}I physical decay. For each patient, the H/M and WOR values were taken as the average of measurements performed over the scintigraphic image. The interobserver differences for H/M and WOR measurements were not significant (<3%).

Echocardiography

Echographic measurements were performed with standard recommendations. Left ventricular end-diastolic and end-systolic diameters were recorded and the fractional shortening was calculated.

Maximal Oxygen Consumption

For us to assess the maximal workload, the peak oxygen uptake and the anaerobic threshold, all subjects performed a cycloergometer exercise with gas analysis for determination of maximal oxygen uptake on a Medical Graphic Corporation system (St. Paul, MN). The upright bicycle exercise test started at an initial workload of 10 W with increments of 10 W/min. A second determination of maximal oxygen uptake was performed 6 mo later according to the same protocol.

Resting Plasma Norepinephrine Concentrations

Venous blood samples were drawn, after a 30-min resting period in the supine position, at the initial evaluation and after 6 mo of metoprolol therapy. Plasma NE concentrations were determined by radioenzymatic assay.

Statistical Analysis

All results are expressed as mean ± SD. Two-way analysis of variance and paired and unpaired Student *t* testing when appropriate were used to evaluate the changes in the two groups of variables before and after metoprolol. A *P* value <0.05 was considered significant.

RESULTS

Baseline Characteristics of Population

Hemodynamic Parameters in Patients. These data are shown in Table 1.

The mean NYHA functional class was 2.4 ± 0.5. Patients had altered indices of left ventricular dysfunction with a radionuclide ejection fraction of 20% ± 8% and echocardiographic left ventricular dilatation (left ventricular end-diastolic diameter = 68 ± 7 mm). The mean value of maximal oxygen consumption was low (17.6 ± 3.3 mL/min/kg). Patients had a low cardiac output (cardiac index = 2.2 ± 0.4 L/min/m^2) with increased right filling pressure (right atrial pressure = 9 ± 4 mm Hg) and increased left filling pressure (pulmonary capillary wedge pressure = 19 ± 8 mm Hg).

TABLE 1
Clinical and Laboratory Data of Patient Population

Parameter for patients (n = 18)	
Age (y)	43 ± 7
NYHA class	2.4 ± 0.5
LVEF (%)	20 ± 8
MIBG (H/M; %)	129 ± 10
MIBG washout rate (%)	35 ± 6
Vo_{2max} (mL/min/kg)	17.6 ± 3.3
Resting NE concentration (ng/mL)	0.930 ± 0.412
Echocardiographic LVEDD (mm)	68 ± 8
Echocardiographic LVESD (mm)	61 ± 12
Cardiac Index (L/min/m^2)	2.2 ± 0.4
RAP (mm Hg)	9 ± 4
PCWP (mm Hg)	19 ± 7

NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; H/M = heart-to-mediastinum activity ratio; Vo_{2max} = maximal oxygen consumption; NE = norepinephrine; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; RAP = right atrial pressure; PCWP = pulmonary capillary wedge pressure.

Adrenergic Parameters in Controls and Patients. All data are listed in Table 2.

Cardiac MIBG Uptake. Cardiac MIBG uptake determined scintigraphically (H/M) in patient group was 129% ± 10% at baseline and was significantly lower in healthy subjects (188% ± 19%; $P < 0.001$). The cardiac WOR of MIBG was slightly increased in patients compared with healthy subjects (35% ± 6% versus 29% ± 6%; $P = 0.07$), but the difference was not significant.

Resting Plasma Norepinephrine Concentrations. Resting plasma NE concentrations were higher in patients compared with healthy subjects (0.930 ± 0.412 ng/mL versus 0.429 ± 0.173 ng/mL; $P = 0.005$).

Follow-Up After Metoprolol

Alterations of Adrenergic Parameters after Therapy with Metoprolol in Healthy Subjects. The 1-mo intake of metoprolol was well tolerated in healthy subjects, and none of them discontinued the drug before study completion.

No change in either MIBG uptake and release or circulating NE concentration was observed after metoprolol therapy (Table 3 and Figs. 1 and 2).

TABLE 2
Adrenergic Parameters

Parameter	Patients (n = 18)	Controls (n = 6)
Age (y)	43 ± 7	37 ± 10
MIBG (H/M; %)	129 ± 10	188 ± 19*
MIBG washout rate (%)	35 ± 6	29 ± 6
Resting NE concentration (ng/mL)	0.930 ± 0.412	0.429 ± 0.172*

*$P < 0.01$.
H/M = heart-to-mediastinum activity ratio; NE = norepinephrine.

TABLE 3
Effect of Metoprolol Intake in Healthy Volunteers

Parameter for controls (n = 6)	Baseline	1-mo therapy
MIBG uptake (H/M; %)	188 ± 19	173 ± 20
MIBG washout rate (%)	29 ± 6	34 ± 14
Resting NE concentration (ng/mL)	0.429 ± 0.173	0.448 ± 0.110

H/M = heart-to-mediastinum activity ratio; NE = norepinephrine.

Alterations of Hemodynamic and Adrenergic Parameters after Therapy in Patients. Results of hemodynamic parameters are displayed in Table 4. Metoprolol treatment was well tolerated and could be maintained in all patients during the study follow-up. The functional NYHA status improved from 2.4 ± 0.5 to 2.0 ± 0.2 ($P = 0.004$). A worsening in NYHA functional class was noted in only 1 patient. An increase in LVEF was found after the 6-mo therapy (from 20% ± 8% to 27% ± 8%; $P = 0.0005$; Figs. 3 and 5). Maximal oxygen uptake did not change significantly after metoprolol therapy (17.6 ± 3.3 versus 19.33 ± 3.7; P values were not significant; Fig. 3).

In adrenergic parameters cardiac MIBG uptake (H/M) increased from 129% ± 10% to 138% ± 17% ($P = 0.009$) after metoprolol therapy (Table 4 and Figs. 1, 4 and 6), whereas plasma NE concentrations slightly decreased (0.930 ± 412 versus 0.721 ± 0.370 ng/mL; $P = 0.02$; Table 4). The MIBG WOR remained unchanged after therapy (35% ± 6% versus 33% ± 5%; P values were not significant; Fig. 3).

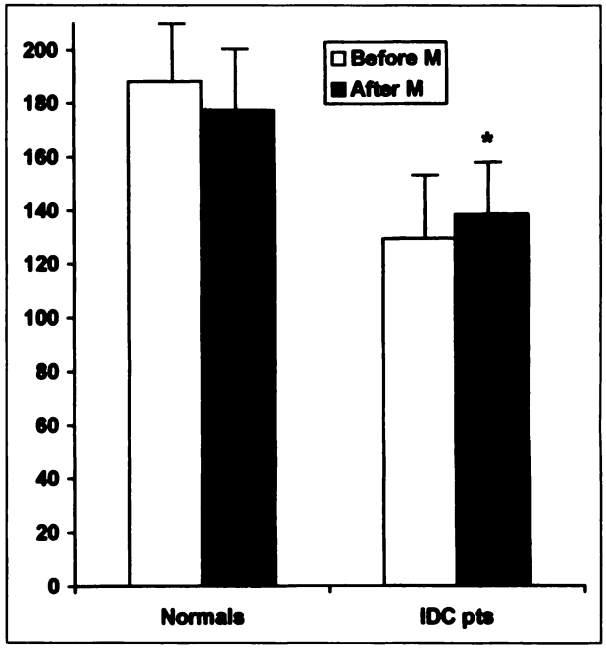

FIGURE 1. Alterations in cardiac MIBG uptake (in %) after metoprolol use in healthy subjects and in patients with idiopathic dilated cardiomyopathy (IDC pts; 1 and 6 mo after metoprolol use). No significant change was observed after 1 mo intake of metoprolol in healthy subjects. Conversely, increase in MIBG uptake was found in patients with idiopathic cardiomyopathy after having added metoprolol to captopril during 6 mo. M = metoprolol.

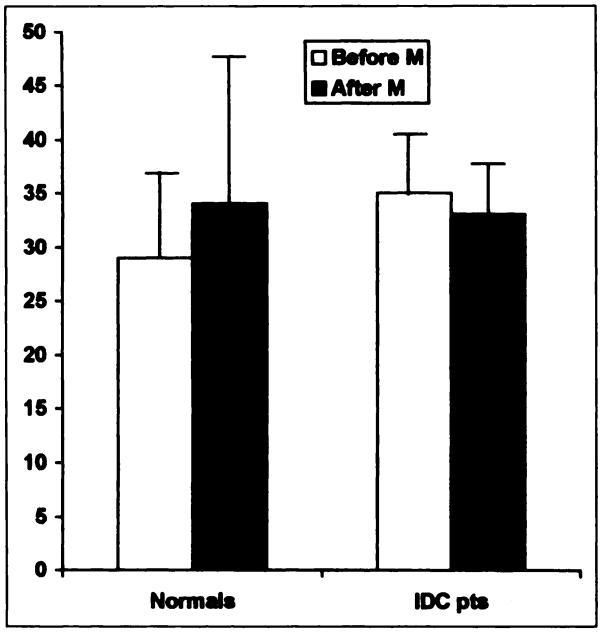

FIGURE 2. Alterations in WOR of MIBG (in %) 1 and 6 mo after metoprolol (M) use in healthy subjects and in idiopathic cardiomyopathy patients (IDC pts). No significant change was observed in either group.

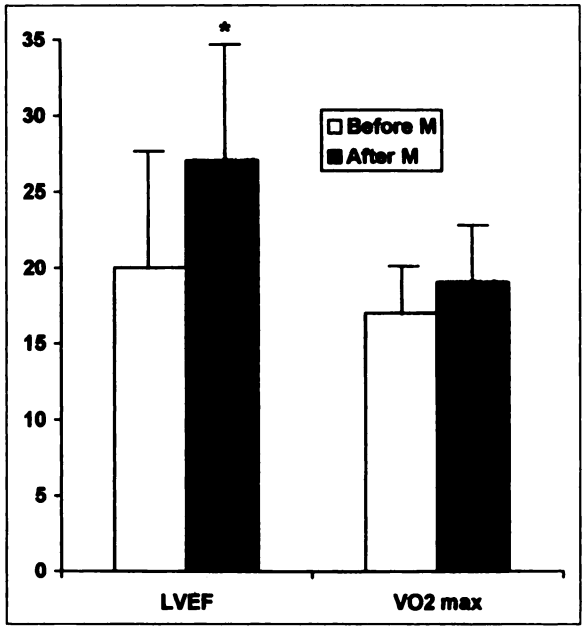

FIGURE 3. Hemodynamic changes observed in patients 6 mo after addition of metoprolol (M). An increase in resting left ventricular function (radionuclide LVEF, in %) was observed. Slight improvement in exercise tolerance (maximal oxygen consumption [Vo_{2max}], in mL/min/kg) was also found, but difference was not statistically significant.

The changes in MIBG uptake correlated with the changes in LVEF ($r = 0.469$, $P = 0.049$) but were not related to the changes in NYHA class, circulating NE concentration or left ventricular end-diastolic diameter.

DISCUSSION

This study shows that the addition of metoprolol to ACE inhibitor therapy in idiopathic dilated cardiomyopathy may be associated with a concomitant improvement in hemodynamics and myocardial adrenergic innervation.

Mechanism of MIBG Uptake

MIBG labeled with ^{123}I shares the same uptake and storage mechanisms as NE (*4*). Two types of uptake systems for MIBG have been identified in adrenergic tissues. The uptake-1 system is mediated by the NE transporter and the uptake-2 system is an extraneuronal system that is low in human beings (*4–6,19*). It is unmetabolized by catechol-O-methyl transferase or monoamine oxidase (*4*).

TABLE 4
Effects of 6-Month Therapy in Patients

Parameter for patients (n = 17)	Baseline	6-mo therapy
NYHA functional class	2.4 ± 0.5	2.0 ± 0.2*
MIBG uptake (H/M; %)	129 ± 10	138 ± 17*
MIBG washout rate (%)	35 ± 6	33 ± 5
Radionuclide LVEF (%)	20 ± 8	27 ± 8*
Vo_{2max} (mL/min/kg)	17.6 ± 3.3	19.3 ± 3.7
Resting NE concentration (ng/mL)	0.930 ± 0.412	0.721 ± 0.370†
Echographic LVEDD (mm)	68 ± 7	66 ± 7
Echographic LVESD (mm)	58 ± 10	54 ± 9†

*$P < 0.01$.
†$P < 0.05$.
NYHA = New York Heart Association; H/M = heart-to-mediastinum activity ratio; LVEF = left ventricular ejection fraction; Vo_{2max} = maximal oxygen consumption; NE = norepinephrine; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter.

Adrenergic Nerve Integrity and Functioning in the Failing Heart

The increase in sympathetic system activity is one of the main mechanisms that compensates the failure of the cardiac pump. The sympathetic nerve function is altered in the failing myocardium. Cardiac stores of NE are depleted (*20*). NE release was found increased in some studies (*21–23*), whereas it was found decreased in others (*24,25*). Although a normal fractional extraction of the NE across the failing heart has suggested a normal neuronal NE uptake (*22,23*), the uptake-1 function has been found to be diminished in animals (*26*), in postmortem examination of human failing hearts (*1*) and in patients with heart failure as a result of valvular heart disease (*24*) and ischemic and idiopathic cardiomyopathies (*27,28*).

Causes of Decreased MIBG Uptake in the Failing Heart

Decreased MIBG uptake in the failing myocardium is likely to be due to impaired uptake-1. Other factors may cause a decrease in MIBG uptake. An elevation of NE concentration at the synaptic level could compete with MIBG uptake. This elevation of NE may be the result of an increase in either circulating NE level or neuronal NE release. Because a significant decrease in cardiac ^{123}I-MIBG uptake was previously reported to be associated with normal

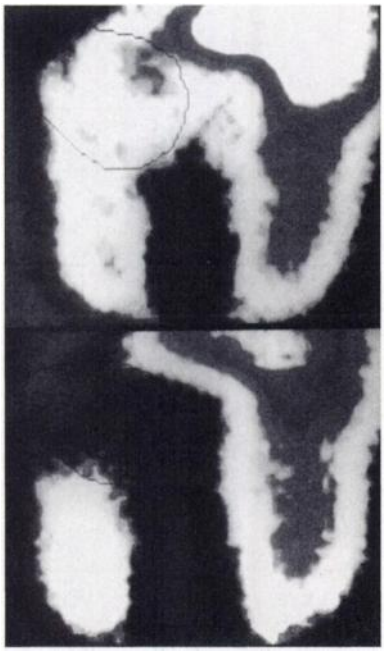

FIGURE 4. Delayed scintigraphic MIBG images obtained in 1 patient with heart failure because of idiopathic dilated cardiomyopathy, before and 6 mo after addition of metoprolol (top and bottom panel, respectively). Cardiac MIBG uptake was quantified as heart-to-mediastinum activity ratio, using regions of interest positioned over heart and over upper mediastinum. Increase in left ventricular MIBG uptake is noticeable when comparing second to first examination.

circulating NE levels, increased circulating concentration of NE may not be an important factor (*8*). In this study, however, if a very low MIBG uptake, despite slightly increased circulating NE levels, was found at the initial evaluation, changes in the cardiac MIBG uptake were associated to changes in the circulating NE levels after 6 mo of therapy.

On the other hand, the increase in NE release reported in some studies could theoretically participate in the diminished MIBG uptake. This hypothesis has been supported by the fact that MIBG washout measured from early to delayed images was increased in patients with idiopathic cardiomyopathy (*5,6,29,30*). However, in this study, no difference in MIBG WOR was observed between healthy subjects and patients and no change was found after therapy with metoprolol in both groups.

Pathophysiological Importance of Altered Uptake-1

The uptake-1 function is the principal means for terminating the action of NE. Reduced uptake-1 function may cause a myocyte hyperstimulation to the neurotransmitter. In dogs, the cardiac response to exogenous NE was prolonged by the uptake-1 blockade but was unchanged by the uptake-2 blockade (*31,32*). In patients with heart failure, the role of reduced uptake-1 as a local factor for altering concentration of NE at the myocyte membranes has been recently demonstrated (*27*). The effectiveness of NE in increasing the force of contraction was decreased in proportion to the importance of heart failure. Conversely, the relative potency of NE was higher in failing than in nonfailing hearts, whereas that of isopreterenol, which is not a substrate of the uptake-1, was reduced. Finally, this relative supersensitivity to extrinsic NE was related to a loss of uptake-1 carrrier protein measured with tritiated mazindol binding assays (*27*).

The impairment of uptake-1 generates an elevation of the NE concentration at the synaptic level, thereby inducing deleterious effects such as hypertrophy, myocyte calcium overload, arrhythmias, increase in myocardial oxygen consumption linked to increase in heart rate and afterload, alteration in coronary artery tone or β-adrenergic desensitization. In particular, the link between the alterations uptake-1 and β-receptor downregulation has been documented. With in vitro measurements, the amount of tritiated NE uptake has been found to be directly proportional to β_1-receptor density in left ventricles of heart failure patients (*33*).

Mechanisms of the Reversibility of Presynaptic Alterations

The increase in cardiac MIBG uptake after therapy with agents counteracting sympathetic system hyperactivity may

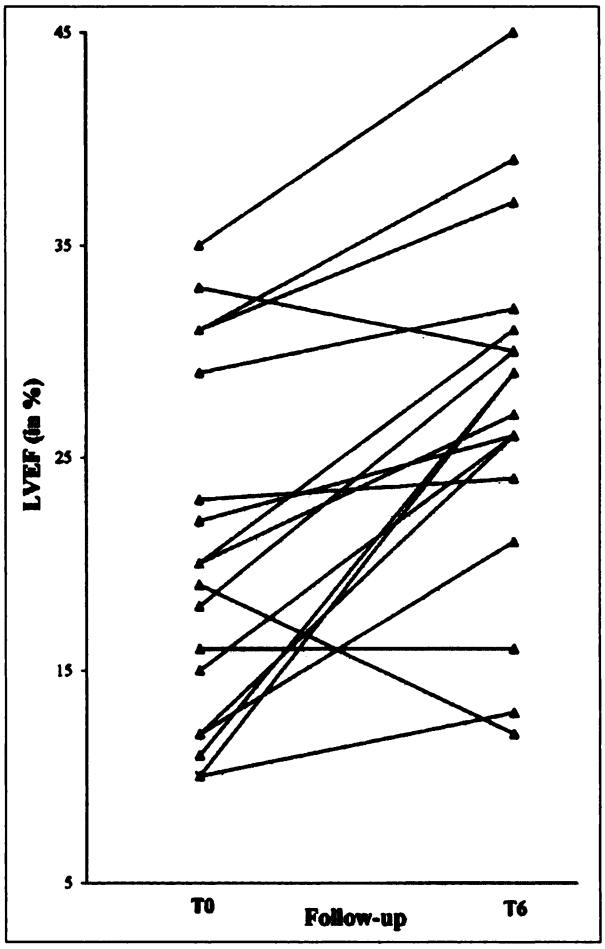

FIGURE 5. Individual left ventricular objection fraction (LVEF) values observed in 18 patients with idiopathic dilated cardiomyopathy before (T0) and after 6-mo metoprolol therapy (T6).

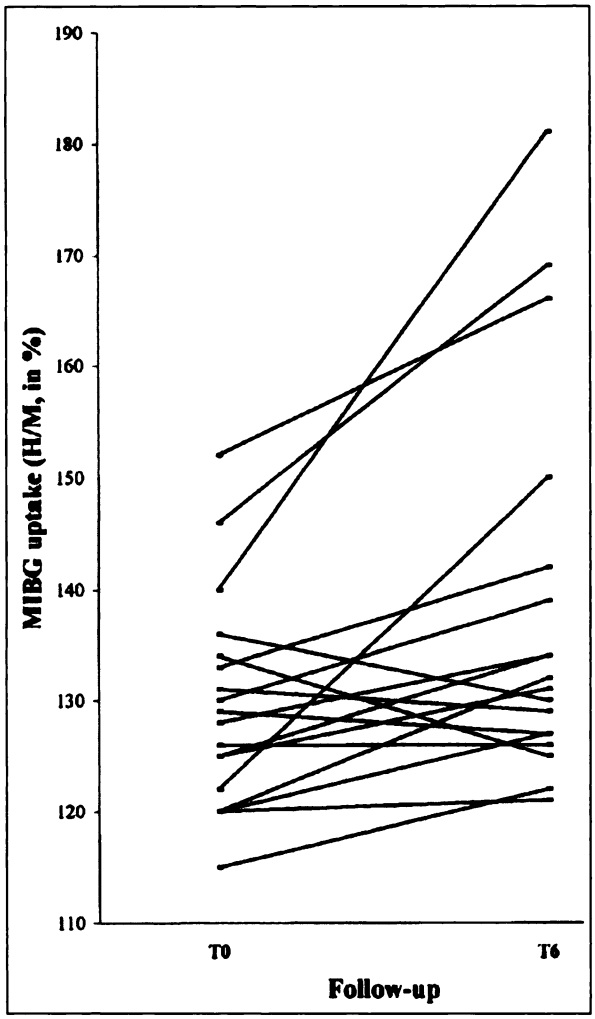

FIGURE 6. Individual MIBG uptake values (delayed H/M) observed in 18 patients with idiopathic dilated cardiomyopathy before (T0) and after 6-mo metoprolol therapy (T6). H/M = heart-to-mediastinum activity ratio.

have different meanings. The influence of systemic adrenergic hyperactivity in patients is possible because plasma NE was found to be elevated at the initial evaluation and to be slightly decreased after treatment. However, the absolute plasma NE level in congestive heart failure is influenced by alterations in neuronal uptake, clearance and metabolism of NE released from the sympathetic nerve endings. Thus, if the observed changes in resting plasma NE levels certainly reflect a reduction in the activity of the adrenergic system, it is likely that either a local improvement in uptake-1 or a decrease in local release occurred.

In this study, the reduction in myocardial adrenergic hyperactivity may have been caused by metoprolol therapy through blockade of presynaptic β_2-adrenoceptors that increase NE release (*34*). Nevertheless, this hypothesis is unlikely because metoprolol displays a relative β_1 selectivity and did not change myocardial MIBG uptake in the healthy subjects.

The improvement in MIBG uptake could be due to an improvement in the uptake-1 function as a result of a decrease in angiotensin II action on neuronal uptake caused by the concomitant ACE inhibition (*35*). Thus, ACE inhibitors used in the present patient population may have antagonized the facilitative effects of angiotensin II on central sympathetic outflow and inhibited NE release at the neuro-effector junction, where it is subject to modulation by prejunctioned angiotensin II receptors (*34*).

Finally, partial reinnervation may have occurred. Indeed, in cardiac transplantation where the myocardium is entirely denervated, PET studies that used ^{11}C-hydroxyephedrine (*36*) have demonstrated that partial reinnervation occurs during the follow-up. It is therefore conceivable that the destruction of adrenergic nerve endings of the failing myocardium may be subject to partial reinnervation after therapy, leading to functional improvement.

Concomitant Improvement of Adrenergic Nerve Function and Left Ventricular Function

Previous work has shown an improvement in hemodynamic parameters under metoprolol therapy in patients with heart failure, including an increase in LVEF and in maximal exercise capacity (*10–11,14,37*). In this study, the hemodynamic improvement after therapy paralleled an improvement in MIBG uptake as suggested by the correlation between the net increase in MIBG uptake (H/M) and the net increase in LVEF. These data are concordant with previous works that have evidenced a link between the regression of different sympathetic disorders and the improvement of left ventricular function after treatment counteracting sympathetic hyperactivity (*10,14,38*). The possibility of improving in parallel the abnormalities of NE uptake and left ventricular function suggests a role of adrenergic innervation disorders in the fatal outcome of patients with heart failure. This is concordant with previous data demonstrating that decreased cardiac MIBG uptake was strongly related to poor prognosis (*9*) and the large trials that have demonstrated that agents lowering adrenergic hyperactivity were able to decrease mortality and morbidity (*10–18*). Nevertheless, the current data are not congruent with those published by Eichhorn et al. (*39*) who have shown that, whereas an increase in functional class was noted after short duration treatment with bucindolol in patients with heart failure, no change in MIBG cardiac uptake or in plasmatic catecholamines was observed. This discrepancy may be due to differences in treatment, follow-up duration or methodology. The current data are in accordance with those obtained in heart failure after enapril therapy (*40*).

MIBG Washout Rate

No clear modification in MIBG washout was observed after use of β-blockers in the current patient population, which contrasts with the observed reduction in systemic sympathetic tone illustrated by the decrease in resting circulating NE levels. This was unexpected because the combined action of ACE inhibitors and β-blockers in heart failure is assumed to favor a decrease in sympathetic tone of

the heart. The mechanisms underlying MIBG clearance remain unclear, although some reports have suggested that MIBG washout may reflect sympathetic nerve tone in patients who had heart failure, a pathophysiological condition recognized to involve sympathetic hyperactivity. Nevertheless, there is no direct evidence until now that increased MIBG washout reflects enhanced neurotransmitter release by the adrenergic nerves of the myocardium. There is no evidence that this parameter can be used as an index of NE spillover in human beings. NE spillover is increased in the failing human heart, but because normally 90% of the released NE is taken back by the neurons, this alteration may be caused by increased NE release, decreased NE reuptake or both. Even though MIBG washout could reflect NE spillover, its increase would not necessarily imply an increase in adrenergic drive.

Finally, a methodologic precaution can explain this discrepancy with previous reports. The MIBG intravenous injection was performed in this study after a 30-min resting period according to the standard recommandations for plasma catecholamine measurements. This may have minimized the difference of MIBG clearance from myocardium in patients with heart failure compared with healthy subjects, or its changes after intake of β-blockers.

Limitations of the Study

Because this study was not a randomized placebo controlled trial, no definite conclusion can be drawn on the direct role of β-blockers in the improvement of cardiac MIBG uptake. This study simply shows that the hemodynamic improvement obtained by the combination of ACE inhibitors and β-blockers parallels a regression of the disorders of cardiac adrenergic innervation.

CONCLUSION

The current data support the hypothesis that the mechanisms contributing to sympathetic nerve dysfunction in heart failure are functional rather than structural and are potentially amenable to modulation. This study suggests that the beneficial hemodynamic action of β-blockers used on top of ACE inhibitors is due in part to a protection against overexposure to NE. Thus, inhibiting sympathetic drive to the heart would be a key factor in the improvement of the prognosis of patients with congestive heart failure. MIBG imaging can provide a noninvasive and sensitive index to follow-up the response to therapy in patients with congestive heart failure who are potential candidates for heart transplantation.

REFERENCES

1. Petch MC, Nayler WG. Uptake of catecholamines by human cardiac muscle in vitro. *Br Heart J.* 1979;41:336–339.
2. Spann JF, Chidsey CA, Pool PE, Braunwald E. Mechanism of norepinephrine depletion in experimental heart failure produced by aortic constriction in the guinea pig. *Circ Res.* 1965;17:312–321.
3. Shofer J, Tews A, Rühwedel H, Reimitz PE, Mathey DG. Myocardial noradrenaline content: a factor not considered up to now for the prognosis of patients with dilated cardiomyopathy. *Z Kardiol.* 1989;78:366–377.
4. Wieland DM, Brown LE, Rogers L, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med.* 1981;22:22–31.
5. Dae MW, De Marco T, Botvinick EH, et al. Scintigraphic assessment of MIBG uptake in globally denervated human and canine hearts—implications for clinical studies. *J Nucl Med.* 1992;33:1444–1450.
6. Glowniak JV, Turner FE, Gray LL, 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.
7. Schofer J, Spielmann R, Schuchert A, Weber K, Schüter M. Iodine-123 metaiodobenzylguanidine scintigraphy: a noninvasive method to demonstrate myocardial adrenergic disintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol.* 1988;12:1252–1258.
8. Merlet P, Dubois-Randé JL, Adnot S, et al. Myocardial β-adrenergic desensitization and neuronal norepinephrine uptake function in idiopathic dilated cardiomyopathy. *J Cardiovasc Pharmacol.* 1992;19:10–16.
9. Merlet P, Valette H, Dubois-Randé JL, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med.* 1992;33:471–477.
10. Heilbrunn SM, Shah P, Bristow MR, Valantine HA, Ginsburg R, Fowler MB. Increased β-receptor density and improved hemodynamic response to catecholamine stimulation during long-term metoprolol therapy in heart failure from dilated cardiomyopathy. *Circulation.* 1989;79:483–490.
11. Waagstein F, Bristow MR, Swedberg K, et al. for the Metoprolol in Dilated Cardiomyopathy Trial Study Group. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet.* 1993;342:1441–1446.
12. The Cardiac Insufficiency Bisoprolol Study (CIBIS) Investigators. A randomized trial of β-blockade in heart failure. *Circulation.* 1994;90:1765–1773.
13. Packer M, Bristow MR, Cohn JN, et al. for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med.* 1996;334:1349–1355.
14. Engelmeier RS, O'Connell JB, Walsh R, Rad N, Scanlon PJ, Gunnar RM. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. *Circulation.* 1985;72:536–546.
15. CONSENSUS Trial Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med.* 1987;316:1429–1435.
16. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991;325:293–302.
17. SOLVD II Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction. *N Engl J Med.* 1992;32:685–691.
18. Pfeffer MA, Braunwald E, Moyé LA, et al. on behalf of the SAVE Investigators. Effects of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med.* 1992;327:669–677.
19. Glowniak J, Kilty J, Amara S, Hoffman BJ, Turner FE. Evaluation of metaiodobenzylguanidine uptake by the norepinephrine, dopamine and serotonin transporters. *J Nucl Med.* 1993;34:1140–1146.
20. Chidsey CA, Braunwald E, Morrow AG. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Am J Med.* 1965;39:442–451.
21. Swedberg K, Viquerat C, Rouleau JL, et al. Comparison of myocardial catecholamine balance in chronic congestive heart failure and in angina pectoris without failure. *Am J Cardiol.* 1984;54:783–786.
22. Hasking GJ, Esler MD, Jenning GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation.* 1986;73:615–621.
23. Meredith IT, Eisenhofer G, Lambert GW, Dewar EM, Jennings GL, Esler MD. Cardiac sympathetic nervous activity in congestive heart failure: evidence for increased neuronal norepinephrine release and preserved neuronal uptake. *Circulation.* 1993;88:136–145.
24. Rose C, Burgess JH, Cousineau D. Tracer norepinephrine kinetics in coronary circulation of patients with heart failure secondary to chronic pressure and volume overload. *J Clin Invest.* 1985;76:740–747.
25. Sandoval AB, Gilbert EM, Rose CP, Bristow MB. Cardiac norepinephrine uptake and release is decreased in dilated cardiomyopathy [abstract]. *Circulation.* 1989;80(suppl II):393.
26. Fisher JE, Horst WD, Kopin IJ. Norepinephrine metabolism in hypertrophied rat heart. *Nature (London).* 1965;207:951–953.
27. Böhm M, La Rosée K, Schwinge RH, Erdmann E. Evidence for reduction of norepinephrine uptake sites in the failing human heart. *J Am Coll Cardiol.* 1995;25:146–153.
28. Eisenhofer G, Friberg P, Rundqvist B, et al. Sympathetic nerve function in congestive heart failure. *Circulation.* 1996;93:1667–1676.

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. Imamura Y, Ando H, Ashihara T, Fukuyama T. Myocardial adrenergic nervous activity is intensified in patients with heart failure without left ventricular volume or pressure overload. *J Am Coll Cardiol.* 1996;28:371–375.
31. Levy MN, Blattberg B. The influence of cocaine and desipramine on the cardiac responses to exogenous and endogenous norepinephrine. *Eur J Pharmacol.* 1978;48:37–49.
32. Masuda Y, Levy MN. The effects of neuronal uptake blockade on the cardiac responses to sympathetic nerve stimulation and norepinephrine infusion in anesthezied dogs. *J Autonom Nerv Syst.* 1984;10:1–17.
33. Beau SL, Saffitz JE. Transmural heterogeneity of norepinephrine uptake in failing human hearts. *J Am Coll Cardiol.* 1994;23:579–585.
34. Francis GS. Modulation of peripheral sympathetic nerve transmission. *J Am Coll Cardiol.* 1988;12:250–254.
35. Khairallah PA. Action of angiotensin on adrenergic nerve endings: inhibition of norepinephrine uptake. *Fed Proc.* 1972;31:1351–1357.
36. Schwaiger M, Hutchkins GD, Kalff V, et al. Evidence for regional catecholamine uptake and storage sites in the transplanted human heart by positron emission tomography. *J Clin Invest.* 1991;87:1681–1690.
37. Eichhorn EJ, Bedotto JB, Malloy CR, et al. Effect of β-adrenergic blockade on myocardial function and energetics in congestive heart failure. *Circulation.* 1990;82:473–483.
38. Woodley SL, Gilbert EM, Anderson JL, et al. β-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. *Circulation.* 1991;84:2426–2441.
39. Eichhorn EJ, McGhie AI, Bedotto JB, et al. Effects of bucindolol on neurohormonal activation in congestive heart failure. *Am J Cardiol.* 1991;67:67–73.
40. Takeishi Y, Atsumi H, Fujiwara S, Takahashi K, Tomoike H. ACE inhibition reduces cardiac iodine-123-MIBG release in heart failure. *J Nucl Med.* 1997;38:1085–1089.