Sympathetic Reinnervation of Cardiac Allografts Evaluated by ^{123}I-MIBG Imaging

Montserrat Estorch, Marta Campreciós, Albert Flotats, Carina Marí, Lluís Bernà, Ana María Catafau, Manel Ballester, Jagat Narula and Ignasi Carrió

Departments of Nuclear Medicine and Cardiology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; and Cardiac Unit, Allegheny University of Health Sciences, Philadelphia, Pennsylvania

Some heart-transplant patients present with improved heart rate response to exercise and anginal pain suggesting reinnervation of allografts. Studies performed up to 5 y post-transplantation have suggested that reinnervation is a slow process that occurs only after 1 y post-transplantation. The purpose of this study was to evaluate the extent of sympathetic reinnervation in heart-transplant patients and its relation to cardiac function. **Methods:** We performed ^{123}I-metaiodobenzylguanidine (MIBG) studies and rest/exercise radionuclide ventriculography in 31 heart-transplant patients 6 mo to 12 y post-transplantation. Intensity of myocardial MIBG uptake was quantified by a heart-to-mediastinum ratio (HMR), and the regional distribution of MIBG was determined by tomographic studies. **Results:** HMR correlated positively with time after transplantation ($r = 0.607$, $P < 0.001$). Patients studied from 2 to 12 y post-transplantation had an HMR significantly higher than patients studied before 2 y post-transplantation (1.62 ± 0.2 versus 1.34 ± 0.2, $P < 0.05$). Myocardial MIBG uptake was anterolateral in 16 patients, anterior in 3 and anterolateral and septal in 3. Myocardial MIBG uptake was absent in 9 patients. Vasculopathy developed in 8 patients, and 5 of them (63%) had decreased myocardial MIBG uptake. Peak filling rate was higher in patients studied from 2 to 12 y post-transplantation (2.7 ± 0.8 end-diastolic volume (EDV)/s versus 2.16 ± 0.5 EDV/s, $P = 0.02$). **Conclusion:** Sympathetic reinnervation increases with time after heart transplantation and is seen more frequently after 2 y post-transplantation. Complete reinnervation of the transplanted heart does not occur even up to 12 y post-transplantation. Early vasculopathy may delay the process of sympathetic reinnervation.

Key Words: ^{123}I-metaiodobenzylguanidine; sympathetic reinnervation; heart transplantation; cardiac function; graft vasculopathy

J Nucl Med 1999; 40:911–916

During orthotopic heart transplantation, the entire recipient heart is excised except for the posterior atrial walls, to which the donor atria are anastomosed. During the process, the allograft becomes completely denervated. Lack of autonomic nerve supply is associated with major physiologic limitations (*1*). The inability to perceive pain does not allow symptomatic recognition of accelerated allograft vasculopathy, and heart-transplant recipients often develop acute ischemic events or left ventricular dysfunction or die suddenly (*2,3*). Coronary disease develops in as many as 50% of heart-transplant patients within 5 y after transplantation, and surveillance angiography is performed annually to detect coronary involvement early (*2,4*). In addition, denervation of the sinus node does not allow adequate acceleration of heart rate during stress and efficient increase in cardiac output (*5*). Furthermore, loss of vasomotor tone may adversely affect the physiologic alterations in coronary blood flow, produce altered hemodynamic performance at rest and during exercise and decrease exercise capacity (*6,7*).

The clinical observations of gradual improvement in heart rate response to exercise and complaints of typical anginal pain by some heart-transplant recipients suggest that reinnervation of allografts occurs after transplantation (*4,8,9*). Recent clinical and experimental studies have provided evidence of partial reinnervation. Release of norepinephrine in response to intracoronary administration of tyramine (*10*) and scintigraphic uptake of norepinephrine analogs such as ^{123}I-metaiodobenzylguanidine (MIBG) (*11,12*) and ^{11}C-hydroxyepinephrine (*13*) support the concept of reinnervation. All studies performed up to 5 y after heart transplantation have suggested that reinnervation is likely to be a slow process and occurs only after 1 y post-transplantation (*11,12*). Electrophysiologic studies have demonstrated that partial functional reinnervation of the sinus node is possible in long-term transplantation patients (*14*). Despite these results, the functional consequences of a partially reinnervated heart and the progression of sympathetic reinnervation later than 5 y post-transplantation are still unknown.

This study was performed with cardiac allograft recipients from 6 mo to 12 y post-transplantation to evaluate the extent of sympathetic reinnervation and to determine whether evidence of reinnervation is related to functional status and vascular damage resulting from allograft rejection. Studies before 6 mo post-transplantation were not performed, because previous reports have documented the absence of sympathetic reinnervation during this early time period (*15,16*).

Received Apr. 30, 1998; revision accepted Oct. 20, 1998.

For correspondence or reprints contact: Montserrat Estorch, Department of Nuclear Medicine, Hospital de la Santa Creu i Sant Pau, Pare Claret 167, 08025 Barcelona, Spain.

MATERIALS AND METHODS

Patients

We studied 31 patients (27 men, 4 women; age range 19–68 y, mean age 52 y) 6 mo to 12 y after heart transplantation. Disease before transplantation was dilated cardiomyopathy in 17 patients, ischemic cardiomyopathy in 10, hypertrophic cardiomyopathy in 3 and valvular disease in 1. Nine patients were studied from 6 mo to 2 y post-transplantation, and 22 patients were studied from 2 to 12 y post-transplantation. Endomyocardial biopsies and antimyosin scans were performed on all patients at regular intervals to detect acute cellular rejection. Coronary angiograms, ^{99m}Tc-tetrofosmin myocardial perfusion scans and antimyosin scans were performed annually. When one or more of these studies was positive, an endomyocadial biopsy was performed to detect acute cellular rejection, allograft vasculopathy or myointimal proliferation. At the time of this study, none of the patients were in active rejection, none had anginal symptoms and all had normal myocardial perfusion scans. All patients received immunosuppresive therapy consisting of prednisone, cyclosporine and azathioprine. Patients did not suspend their regular medications during the study. None were taking symphaticomimetics or other drugs known to interfere with MIBG uptake, all abstained from drinking coffee or caffeine-containing beverages and all fasted 8 h before the study. None of the patients included in this study had diabetes mellitus or other neuropathy that could affect sympathetic cardiac reinnervation. Patients underwent ^{123}I-MIBG study and rest/exercise radionuclide ventriculography within 2 wk of each other. The protocol was approved by the Institutional Ethical Committee of the Hospital de la Santa Creu i Sant Pau, and all patients gave informed consent.

^{123}I-MIBG Scintigraphy

Thirty minutes after thyroid ^{123}I uptake blockade by oral administration of 500 mg potassium perchlorate, 370 MBq ^{123}I-MIBG (Nycomed Amersham, Ibérica, Spain) were administered intravenously. Planar scintigraphic images of the heart were acquired 15 min and 4 h after injection. SPECT studies also were performed 4 h after injection. Planar images were acquired using a large-field-of-view camera with a low-energy, high-resolution collimator linked to a dedicated computer (Siemens Orbiter ZLC, Microdelta computer; Siemens, Madrid, Spain). A 20% window centered at 159 keV was used. Anterior and 45° left anterior oblique (LAO) views of the thorax were stored in 128 × 128 frames. MIBG uptake was quantified by calculating a heart-to-mediastinum ratio (HMR) after drawing regions of interest (ROIs) over the mediastinum on the anterior view and over the myocardium on the LAO view. The oblique view provides the best separation between myocardial and left-lung activities. The myocardial ROI was drawn over only the visible myocardial regions. Average counts per pixel in the myocardium were divided by average counts per pixel in the mediastinum. For this study, intensity of myocardial MIBG uptake was considered normal when the HMR was >1.8 (*17*), moderate when between 1.8 and 1.6, mild when between 1.6 and 1.3 and absent when <1.3. Intraobserver variability of HMR was <2%, and interobserver variability (two observers) was <5%.

SPECT studies were obtained using a tomographic camera (Helix HR; Elscint, Haifa, Israel) with a low-energy, parallel-hole, general-purpose collimator. SPECT studies were performed only on patients with myocardial MIBG uptake. A single pass of 60 steps at 30 s per step (64 × 64 matrix) was obtained starting at a 45° right anterior oblique projection and proceeding counterclockwise to the 45° left posterior oblique projection. The data were reconstructed in short-axis, horizontal long-axis and vertical long-axis views, and neither scatter correction nor attenuation correction were applied. SPECT slices were used to assess the regional distribution of myocardial MIBG uptake.

Rest/Exercise Radionuclide Ventriculography

Studies were performed after labeling patients' red blood cells with 925 MBq ^{99m}Tc. Acquisition was gated to the QRS complex of the electrocardiogram to obtain sixteen 64 × 64 frames during the cardiac cycle. A large-field-of-view camera with a high-resolution, parallel-hole collimator linked to a dedicated computer (Siemens Orbiter ZLC, Microdelta computer) with a 20% window centered at 120 keV was used. Rest and exercise studies were acquired from the LAO view, taking into account the anatomically oriented left lateral displacement of the transplanted heart and looking for the best separation between the ventricles. Rest studies were acquired with the patients supine. Exercise studies were performed using a supine bicycle ergometer, starting at a workload of 25–50 W according to the patient's clinical condition and increasing 25 W every 3 min. Heart rate, blood pressure and electrocardiogram readings were monitored throughout the exercise test. Rest-to-exercise left ventricular ejection fraction (LVEF), peak emptying rate and peak filling rate were determined.

Statistical Analysis

Results are expressed as mean ± SD with nonparametric analysis of groups using the Mann-Whitney and Wilcoxon tests. Regression analysis was used to assess correlation between variables. The chi-square method was used to analyze potential differences related to previous disease.

RESULTS

Characteristics and Evolution of Myocardial MIBG Uptake

Using intensity of myocardial MIBG uptake related to time after heart transplantation, a positive correlation between HMR and time was found ($r = 0.607$, $P < 0.001$; Fig. 1). Four of 9 patients (44%) studied from 6 mo to 2 y post-transplantation and 18 of 22 patients (82%) studied from 2 to 12 y post-transplantation had myocardial MIBG uptake. HMR of patients studied 2 y post-transplantation and beyond was significantly higher than that of patients studied before 2 y post-transplantation (1.62 ± 0.2 versus 1.34 ± 0.2, $P < 0.05$; Table 1). Table 1 shows the relationship between HMR and intensity of myocardial MIBG uptake in the two patient groups.

Myocardial MIBG uptake was apparent in the anterolateral myocardial region in 16 patients. In 2 patients studied from 6 mo to 2 y post-transplantation and in 1 patient studied from 2 to 12 y post-transplantation, MIBG uptake was apparent in only the anterior myocardial region. In these patients, intensity of myocardial MIBG uptake was mild (mean HMR = 1.35 ± 0.03). Three patients studied from 2 to 12 y post-transplantation had myocardial MIBG uptake in the anterolateral and septal regions, with normal HMR (Table 2, Fig. 2).

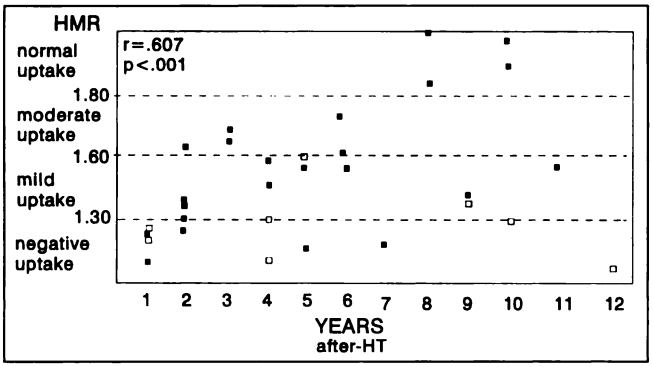

FIGURE 1. Correlation between intensity of myocardial ^{123}I-MIBG uptake, expressed as HMR and time after heart transplantation (HT). Open squares indicate patients in whom graft vasculopathy developed.

Functional Rest/Exercise Parameters

None of the patients experienced a drop in blood pressure during exercise, and none had chest pain or other cardiac symptoms related to exercise. Heart rate response to exercise was within the normal range in heart-transplant patients. No significant differences were observed in rest versus exercise cardiac functional parameters in the two patient groups, except in peak emptying rate of patients studied from 2 to 12 y post-transplantation, which was lower than that of patients studied 6 mo to 2 y post-transplantation (2.44 ± 0.5 end-diastolic volume (EDV)/s versus 2.98 ± 0.6 EDV/s, $P < 0.01$; Table 3).

In patients studied from 6 mo to 2 y post-transplantation, heart rate increased with exercise from 84 ± 11 bpm to 115 ± 7 bpm ($P < 0.01$). In patients studied from 2 to 12 y post-transplantation, heart rate increased with exercise from 96 ± 11 bpm to 125 ± 16 bpm ($P < 0.005$).

Exercise peak filling rate was higher in patients studied from 2 to 12 y post-transplantation than in patients studied from 6 mo to 2 y post-transplantation (2.7 ± 0.8 EDV/s versus 2.16 ± 0.5 EDV/s, $P = 0.02$; Table 3). Heart rate at rest, increment of heart rate with exercise and rest/exercise LVEF did not correlate with intensity of myocardial MIBG uptake.

TABLE 2
Pretransplant Disease, Heart-to-Mediastinum Ratio (HMR) and Regional MIBG Uptake

Pretransplant disease / Patient no.	Time post-transplantation (y)	HMR 15 min p.i.	HMR 4 h p.i.	Regional MIBG uptake
Dilated cardiomyopathy				
1*	1	1.19	1.22	—
2	1	1.20	1.24	—
3	2	1.44	1.27	—
4	2	1.42	1.31	ant-lat
5	3	1.76	1.64	ant-lat
6*	4	1.39	1.31	ant-lat
7*	4	1.23	1.16	—
8*	5	1.54	1.60	ant-lat
9	5	1.22	1.18	—
10	5	1.63	1.57	ant-lat
11	6	1.40	1.61	ant-lat
12	6	1.88	1.70	ant-lat
13	8	1.90	2.06	ant-lat-sep
14	8	2.05	1.85	ant-lat-sep
15	9	1.57	1.44	ant-lat
16	10	1.60	1.30	ant-lat
17*	12	1.25	1.10	—
Ischemic cardiomyopathy				
18	1	1.16	1.14	—
19	2	1.37	1.34	ant
20	3	2.09	1.69	ant-lat
21	4	1.40	1.45	ant-lat
22	4	1.80	1.59	ant-lat
23	6	1.29	1.57	ant-lat
24	7	1.54	1.19	—
25	10	1.97	1.90	ant-lat
26	10	2.01	1.97	ant-lat-sep
27	11	1.48	1.57	ant-lat
Hypertrophic cardiomyopathy				
28*	1	1.50	1.27	—
29	2	1.48	1.63	ant-lat
30*	9	1.55	1.38	ant
Valvular disease				
31	2	1.42	1.33	ant

*Indicates presence of vasculopathy.
MIBG = ^{123}I-metaiodobenzylguanidine; p.i. = postinjection; ant = anterior; lat = lateral; sep = septal.

TABLE 1
Heart-to-Mediastinum Ratio (HMR) and Intensity of MIBG Uptake

Patient group	n	HMR Global uptake	HMR Absent uptake	MIBG uptake Mild	MIBG uptake Moderate	MIBG uptake Normal
6 mo–2 y post-transplant	9	1.34 ± .2*	1.14 ± 0.2 (56%)	1.34 ± 0.2 (44%)	—	—
2–12 y post-transplant	22	1.62 ± .2*	1.16 ± 0.04 (18%)	1.46 ± 0.12 (23%)	1.65 ± 0.05 (41%)	1.95 ± 0.09 (18%)

*$P < 0.05$.
MIBG = ^{123}I-metaiodobenzylguanidine.
Percentage in parentheses is percentage of patients.

FIGURE 2. Tomographic slices of patient studied 10 y after heart transplantation (patient 26). Myocardial ^{123}I-MIBG uptake is visible in anterolateral and septal regions in horizontal short-axis (HSA) and vertical long-axis (VLA) slices.

Myocardial MIBG Uptake, Pretransplant Diagnosis and Post-Transplant Vasculopathy

Patients with previous dilated cardiomyopathy had an HMR of 1.45 ± 0.3 with a significant correlation with time after transplantation (r = 0.550, P = 0.04). In 6 patients (35%), vasculopathy developed after heart transplantation, demonstrated by coronary angiography and/or myocardial perfusion study (1 patient before and 5 patients after 2 y post-transplantation). Five (83%) had decreased myocardial MIBG uptake (HMR = 1.22 ± 0.09) (Table 2, Fig. 1).

Patients with previous ischemic cardiomyopathy had an HMR of 1.48 ± 0.3 with a significant correlation with time after transplantation (r = 0.668, P = 0.03). Vasculopathy did not develop in any of these patients ($P < 0.01$). In 2 patients with hypertrophic cardiomyopathy, vasculopathy developed. Their HMRs were 1.27 and 1.38, respectively.

DISCUSSION

MIBG is an analog of the adrenergic false neurotransmitter guanidine and is taken up by myocardial sympathetic postganglionic presynaptic neurons by an energy-dependent mechanism in a manner similar to norepinephrine (*18–20*). It is trapped in the vesicles, and it is not catabolized by either monoamine oxidase or catechol *O*-methyltransferase (*18*). Scintigraphic evidence of myocardial uptake of a norepinephrine analog reflects sympathetic reinnervation of cardiac allografts (*11,12*). This study confirms that MIBG uptake is observed after the first year post-transplantation and progressively increases over time. The results of this study also suggest that reinnervation begins from the base of the heart and spreads toward the apex. Uptake is primarily observed in the anterior, anterolateral and septal regions. MIBG uptake is not apparent in the posterior or inferior myocardial regions, except for some basal posterior localization. Several diseases may result in myocardial damage that can potentially affect MIBG uptake. In this study, care was taken to exclude patients with diabetes mellitus or other neuropathies as well as patients in active rejection. Similarly, none of the patients in this study had positive antimyosin scans indicative of active myocardial damage at the time of the studies.

These results confirm previous reports regarding the evolution of the reinnervation process (*11,12*). Although MIBG uptake improves quantitatively with time after transplantation, global innervation is not observed even up to 12 y post-transplantation. Higher uptake in the anterior and basal myocardial regions is consistent with greater adrenergic nerve density in these regions in the normal heart (*21*). It is likely that higher availability of nerve fiber basal lamina sheaths in the nerve-rich anterior myocardial region may provide a track for the development of reinnervation (*22*). The experimental studies in transplant models and earlier scintigraphic reports demonstrated preferential regeneration in these myocardial regions (*23*). Lack of reinnervation in the inferior myocardial regions may partially explain the inability of morphologic studies to identify increases in neuronal density in right ventricular endomyocardial biopsy specimens (*24*). However, a significant increase in heart rate after direct tyramine injection in the sinus nodal artery argues against the lack of reinnervation of the inferior myocardial surface (*25*). It is likely that the tiny region of reinnervation of the proximal inferior wall may be sufficient for nodal reactivity.

In a recent PET perfusion and sympathetic reinnervation study of heart-transplant patients, Di Carli et al. (*26*) demonstrated that blood flow increases in response to sympathetic stimulation in the territory of the left anterior descending artery. This territory has the highest uptake of ^{11}C-hydroxyephedrine, whereas in the other territories, increase in flow and uptake of ^{11}C-hydroxyephedrine are minor. The study by DiCarli et al. also showed that basal flow in transplant recipients is similar in all coronary territories despite differences in sympathetic reinnervation. These findings suggest that cardiac-efferent adrenergic signals play an important role in modulating myocardial blood flow during activation of the sympathetic nervous system.

TABLE 3
Functional Rest/Exercise (r/e) Parameters

Patient group	n	LVEF(r)	LVEF(e)	PER(r)	PER(e)	PFR(r)	PFR(e)
6 mo–2 y post-transplant	9	58.3 ± 16.5	57.5 ± 15	2.47 ± 0.8	2.83 ± 0.4	2.50 ± 0.6	2.16 ± 0.5†
2–12 y post-transplant	22	55 ± 14	55.6 ± 9.7	2.44 ± 0.5*	2.98 ± 0.6*	2.85 ± 0.9	2.70 ± 0.8†

*$P < 0.01$.
†$P = 0.02$.
LVEF = left ventricular ejection fraction; PER = peak emptying rate; PFR = peak filling rate.

This coronary vasomotor function may be preserved in long-term heart-transplant survivors (*27*).

Although the number of patients studied is small, the results of this study show that patients with pretransplant dilated cardiomyopathy may have a higher incidence of vasculopathy compared with those with ischemic cardiomyopathy and that patients with vasculopathy has less reinnervation than the others. On the basis of similar observations, De Marco et al. (*12*) hypothesized that the underlying pathophysiology of heart failure might influence eventuality of reinnervation after transplantation. Patients with dilated cardiomyopathy develop a variety of autoantibodies against extracellular and intracellular cardiomyocytic antigens including B-1 adrenoreceptors (*21,28*). De Marco et al. suggested that development of antineuronal antibodies such as those demonstrated in diabetes may interfere with regeneration of sympathetic nerves (e.g., diabetics with autonomic neuropathy demonstrate attenuation of myocardial MIBG uptake) (*29*). We also reported that serial studies with ^{201}Tl allows detection of early vasculopathy episodes that may be similar to those described by vasculitis or vascular rejection in endomyocardial biopsy specimens (*30*). It is likely that relative ischemia resulting from vascular rejection may be associated with lower likelihood of nerve regeneration. In nontransplanted hearts, ischemic episodes are known to result in nerve damage and low MIBG uptake (*31*). Defects in myocardial MIBG uptake observed in transplanted hearts could be related to eventual episodes of myocardial ischemia, although the pattern of MIBG uptake was similar in all patients included in the study. On the other hand, it is known that cumulative episodes of acute cellular rejection are not associated with lack of reinnervation (*32*).

The clinical advantages of partial reinnervation over no reinnervation are not clear. It is also not known whether reinnervation of a graft provides physiologic competence comparable with primary innervation of the heart. The results of this study show that LVEF does not increase with exercise and that patients studied 2 y post-transplantation have a higher peak filling rate at exercise. As other studies also suggest (*33*), this finding could be related to a gradual improvement of functional status of allografts with time, but the functional status of heart-transplant patients remains impaired in comparison with that of healthy individuals.

CONCLUSION

Our findings show that sympathetic reinnervation, measured by regional distribution and intensity of myocardial MIBG uptake, increases with time after heart transplantation, and it is more frequently seen in allografts 2 y post-transplantation. Sympathetic reinnervation first appears in the anterior or anterolateral regions and later in the septal region. Complete reinnervation of the transplanted heart does not occur even up to 12 y post-transplantation. The results of this study suggest that the incidence of early vasculopathy may inhibit the process of sympathetic reinnervation of the transplanted heart.

REFERENCES

1. Olivari MT, Kubo SH, Braunlin EA, et al. Five-year experience with triple-drug immunosuppressive therapy in cardiac transplantation. *Circulation.* 1990;82:276–280.
2. O'Neill BJ, Pflugfelder PW, Singh NR. Frequency of angiographic detection and quantitative assessment of coronary arterial disease one and three years after cardiac transplantation. *Am J Cardiol.* 1989;63:1221–1226.
3. Gao SZ, Schroeder JS, Alderman EL. Prevalence of accelerated coronary artery disease in heart transplant survivors: comparison of cyclosporin and azathioprine regimens. *Circulation.* 1989;80(suppl III):III-100–III-105.
4. Schroeder JS, Hunt SA. Chest pain in heart-transplant recipients. *N Engl J Med.* 1991;324:1805–1807.
5. Kavanagh T, Yacoub M, Mertens D, et al. Cardiorespiratory responses to exercise training after orthotopic cardiac transplantation. *Circulation.* 1988;77:162–171.
6. Hosenpud JD, Morton MJ, Wilson RA, et al. Abnormal exercise hemodynamics in cardiac allograft recipients 1 year after cardiac transplantation. *Circulation.* 1989;80:525–532.
7. Pflugfelder PW, Purves PD, McKenzie FN, Kostuk WJ. Cardiac dynamics during supine exercise in cyclosporine-treated orthotopic heart transplant recipients: assessment by radionuclide angiography. *J Am Coll Cardiol.* 1987;10:336–341.
8. Hartmann A, Maul FD, Huth A, et al. Serial evaluation of left ventricular function by radionuclide ventriculography at rest and during exercise after orthotopic heart transplantation. *Eur J Nucl Med.* 1993;20:146–150.
9. Stark R, McGinn A, Wilson R. Chest pain in cardiac-transplant recipients—evidence of sensory reinnervation after cardiac transplantation. *N Engl J Med.* 1991;324:1791–1794.
10. Wilson RF, Christensen BV, Olivari MT. Evidence for structural sympathetic reinnervation after orthotopic cardiac transplantation in humans. *Circulation.* 1991;83:1210–1220.
11. Guertner C, Krause B, Klepzig H Jr, et al. Sympathetic re-innervation after heart transplantation: dual-isotope neurotransmitter scintigraphy, norepinephrine content and histological examination. *Eur J Nucl Med.* 1995;22:443–452.
12. De Marco T, Dae M, Yuen-Green MS, et al. Iodine-123 metaiodobenzylguanidine scintigraphic assessment of the transplanted human heart: evidence for late reinnervation. *J Am Coll Cardiol.* 1995;25:927–931.
13. Schwaiger M, Hutchins GB, Kalff V. Evidence for regional catecholamine uptake and storage sites in the transplanted human heart by positron emission tomography. *J Clin Invest.* 1991;87:1681–1690.
14. Halpert I, Goldberg AD, Levine AB, et al. Reinnervation of the transplanted human heart as evidenced from heart rate variability studies. *Am J Cardiol.* 1996;77:180–183.
15. Dae M, De Marco T, Botvinick E, et al. Scintigraphic assessment of MIBG uptake in globally denervated human and canine hearts: implications and clinical studies. *J Nucl Med.* 1992;33:1444–1450.
16. Gill JS, Hunter GJ, Gane G, Camm AJ. Heterogeneity of the human myocardial sympathetic innervation: in vivo demonstration by iodine 123-labeled metaiodobenzylguanidine scintigraphy. *Am Heart J.* 1993;126:390–398.
17. Estorch M, Carrió I, Bernà L, López-Pousa J, Torres G. Myocardial iodine-labeled metaiodobenzylguanidine 123 uptake relates to age. *J Nucl Cardiol.* 1995;2:126–132.
18. Wieland DM, Brown LE, Rogers WL, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med.* 1981;22:22–31.
19. Sisson JC, Wieland DM, Sherman P, Mangner IJ, Tobes MC, Jacques S. Meta-iodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med.* 1987;28:1620–1624.
20. Dae MW, De Marco T, Botvinick EH, et al. Scintigraphic assessment of regional cardial adrenergic innervation. *Circulation.* 1989;79:634–644.
21. Magnusson Y, Marullo S, Hoyer S, et al. Mapping of a functional autoimmune epitope on the B1-adrenergic receptor in patients with idiopathic dilated cardiomyopathy. *J Clin Invest.* 1990;86:1658–1663.
22. Kaye MP, Randall WC, Hageman CR. Chronology and mode of re-innervation of the surgically denervated canine heart: functional and chemical correlates. *Am J Physiol.* 1977;233:H431–H437.
23. Kondo Y, Matheny J, Hardy J. Autonomic reinnervation of cardiac transplants: further observations in dogs and rhesus monkeys. *Ann Surg.* 1972;176:24–28.
24. Rowan RA, Billingham ME. Myocardial innervation in long-term heart transplant survivors: a quantitative ultrastructural survey. *J Heart Transplant.* 1988;7:448–452.
25. Wilson RF, Laxson DD, Christensen BV, McGinn AL, Kubo SH. Regional differences in sympathetic reinnervation after human orthotopic cardiac transplantation. *Circulation.* 1993;88:165–171.
26. Di Carli MF, Tobes MC, Mangner T, et al. Effects of cardiac sympathetic innervation on coronary blood flow. *N Engl J Med.* 1997;336:1208–1215.

27. Anderson TJ, Meredith IT, Uchata A, et al. Functional significance of intimal thickening as detected by intravascular ultrasound early and late after cardiac transplantation. *Circulation*. 1993;88:1093–1100.
28. Sundkvist G, Lind P, Bergstrom B, Lilja B, Rabinowe SL. Autonomic nerve antibodies and autonomic nerve function in type 1 and type 2 diabetic patients. *J Intern Med*. 1991;229:505–510.
29. Mantysaari M, Kuikka J, Mustonen J, et al. Noninvasive detection of cardiac sympathetic nervous dysfunction in diabetic patients using [^{123}I]metaiodobenzylguanidine. *Diabetes*. 1992;41:1069–1075.
30. Ballester M, Obrador D, Carrió I, et al. Reversal of rejection-induced coronary vasculitis detected early after heart transplantation with increased immunosuppresion. *J Heart Transplant*. 1989;8:413–417.
31. Matsuo S, Takahashi M, Nakamura Y, Kinoshita M. Evaluation of cardiac sympathetic innervation with iodine-123-metaiodobenzylguanidine imaging in silent myocardial ischemia. *J Nucl Med*. 1996;37:712–717.
32. Wahlers T, Fieguth HG, Jurmann M, et al. Graft coronary vasculopathy in cardiac transplantation. Evaluation of risk factors by multivariate analysis. *Eur J Cardiothorac Surg*. 1996;10:1–5.
33. Mandak JS, Aaronson KD, Mancini DM. Serial assessment of exercise capacity after heart transplantation. *J Heart Lung Transplant*. 1995;14:468–478.