Iodine-123 Metaiodobenzylguanidine Imaging of the Heart in Idiopathic Congestive Cardiomyopathy and Cardiac Transplants

Jerry V. Glowniak, Fredrick E. Turner, Lori L. Gray, Robert T. Palac, Manuel C. Lagunas-Solar, and William R. Woodward

Nuclear Medicine Service and Medical Service, Cardiology Section, Veterans Administration Medical Center; Department of Diagnostic Radiology and Neurology, Oregon Health Sciences University, Portland, Oregon; Crocker Nuclear Laboratory, University of California, Davis, California

Iodine-123 metaiodobenzylguanidine ([^{123}I]MIBG) is a norepinephrine analog which can be used to image the sympathetic innervation of the heart. In this study, cardiac imaging with [^{123}I]MIBG was performed in patients with idiopathic congestive cardiomyopathy and compared to normal controls. Initial uptake, half-time of tracer within the heart, and heart to lung ratios were all significantly reduced in patients compared to normals. Uptake in lungs, liver, salivary glands, and spleen was similar in controls and patients with cardiomyopathy indicating that decreased MIBG uptake was not a generalized abnormality in these patients. Iodine-123 MIBG imaging was also performed in cardiac transplant patients to determine cardiac nonneuronal uptake. Uptake in transplants was <10% of normals in the first 2 hr and nearly undetectable after 16 hr. The decreased uptake of MIBG suggests cardiac sympathetic nerve dysfunction while the rapid washout of MIBG from the heart suggests increased cardiac sympathetic nerve activity in idiopathic congestive cardiomyopathy.

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Adrenergic nerves of the sympathetic nervous system (ANS) play a major role in regulating cardiac function. These nerves have a stimulatory effect on cardiac contraction and are a major support system for the heart. In congestive heart failure after myocardial infarction, for example, adrenergic blockade with beta blocking drugs can cause cardiac decompensation (*1*). The ANS, however, may contribute to or cause cardiac dysfunction. Beta blocking drugs given after myocardial infarction decrease infarct size and mortality (*2*). In idiopathic congestive cardiomyopathy (ICC), beta blockade has resulted in improvement in signs and symptoms of congestive heart failure (*3*) suggesting that ANS overactivity may be causative of or contributory to the manifestations of heart failure in ICC. Means of studying the cardiac ANS in vivo, however, are limited. Noninvasive tests which measure heart rate or blood pressure responses depend on the integrity of afferent nerves as well as the myocardium and the vascular system. Receptor studies measure the response of the myocardial cells to adrenergic stimulation. Electrical recording from cardiac sympathetic nerves provides a direct measure of sympathetic activity (*4*) but is highly invasive, and thus cannot be used in humans.

Metaiodobenzylguanidine (MIBG) is a norepinephrine (NE) analog which was developed as an imaging agent for pheochromocytoma (*5,6*). MIBG is taken up by adrenergic tissues by a specific, high affinity mechanism (uptake 1) as well as a nonspecific mechanism (uptake 2) which is probably due to diffusion (*7,8*). The dense sympathetic innervation of the heart allows imaging of the cardiac ANS with [^{123}I]MIBG. Animal and human studies using [^{123}I]MIBG have shown that the normal heart is easily visualized (*9–11*). Cardiac MIBG uptake is decreased in diseases or conditions in which NE content and/or uptake is reduced, such as myocardial infarction (*12*), congestive heart failure (*13*), cardiac denervation (*14*), and fasting (*15*). Dogs with myocardial infarction had regional loss of MIBG uptake in areas that showed denervation by electrophysiologic recordings (*16*). Patients with severe diabetic auto-

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For reprints contact: Jerry V. Glowniak, MD, Nuclear Medicine Service, Veterans Administration Medical Center, PO Box 1034, Portland, OR 97207.

nomic neuropathy had markedly decreased cardiac uptake of MIBG (*11,17*). These results suggest that MIBG may be useful in evaluating the adrenergic nerves of the heart. In this study, [^{123}I]MIBG was used to study patients with ICC and the results were compared to normal controls and patients with cardiac transplants.

MATERIALS AND METHODS

Subjects

Eight male paid volunteers constituted the normal control (NC) population. All were in good health without acute illness at the time of the study. NC were screened by history and physical exam. None had a history of cardiac, renal, liver, or systemic illness. All had normal results on maximal treadmill exercise testing, echocardiogram, and multiple biochemical blood studies. NC ranged in age from 37 to 56 yr with an average age of 43 yr. None of the NC were taking drugs including over the counter drugs.

Patients were referred for study by the cardiology services of the Portland Veterans Administration and the Oregon Health Sciences University. The patients were six males who ranged in age from 36 to 61 yr with an average age of 46 yr. All had clinically symptomatic congestive heart failure. Three had New York Heart Association class II failure and three had class III failure. The patients had varying degrees of investigation for the cause of their failure, but all had normal coronary angiograms. No patient had a history suggestive of angina or myocardial infarction, and resting thallium studies showed no evidence of a previous myocardial infarction. Right heart biopsies showed varying degrees of fibrosis and myocardial cell loss in all patients, but in none was a definable etiology discovered. None of the patients had hypertension, diabetes, renal insufficiency (creatinine > 2.0), liver disease, valvular abnormalities, or neurologic abnormalities. All patients were taking drugs including diuretics, and five patients were taking digoxin. None of the patients were taking tricyclic antidepressants, sympathomimetics, or other drugs known to interfere with the uptake of MIBG.

A third group of subjects consisted of four males with cardiac transplants. Since all cardiac sympathetic nerves are destroyed in the transplant process, this group of subjects was studied to determine the cardiac, nonneuronal uptake of MIBG. Subject ages were 44, 46, 48, and 63 yr. Donor hearts were from male head trauma victims <40 yr of age who had normal echocardiograms, stable hemodynamic parameters for 48 hr prior to transplantation and no history of cardiac disease. The patients were studied 4 to 16 wk after surgery. None were in active rejection at the time of the study. All were taking prednisone, cyclosporine, and azathioprine. Some of the patients were taking other drugs, but none were taking sympathomimetics or other drugs known to interfere with MIBG uptake. Renal function was normal in three patients as judged by the creatinine and slightly elevated (1.7 mg%) in one patient. Liver function tests were more variable. The SGOT and bilirubin were normal in three patients and twice the upper limit of normal in the fourth patient. The alkaline phosphatase was elevated in three patients ranging from 1.5 to 2.5 times the upper limit of normal.

No patients were taking theophylline, and all participants abstained from drinking coffee or caffeine containing beverages during the course of the study. All subjects signed informed consent forms approved by the Portland Veterans Administration human use committee. MIBG labeling and all imaging studies were performed in the Veterans Administration Nuclear Medicine Department.

Iodine-123 MIBG Labeling

Unlabeled MIBG was purchased from the University of Michigan. High purity, research grade ^{123}I sodium iodide prepared by the (p,5n) reaction was purchased from Crocker Nuclear Laboratory, University of California, Davis, California. Radionuclide purity at calibration time was greater than 98.6% ^{123}I with the remainder being ^{125}I. MIBG labeling was performed according to published methods using the ammonium sulfate decomposition, solid-phase, heat-mediated exchange method (*18*). Free iodide was removed from the reaction product using anion exchange chromatography. The final radiochemical purity was >99%. Specific activity was in the range of 107–179 GBq/mmol (9–15 mCi/mg). All subjects were injected with [^{123}I]MIBG within 5 hr of calibration time.

Imaging Studies

Subjects were pretreated with stable potassium iodide (SSKI), two drops t.i.d. from 1 day before to 3 days after injection of [^{123}I]MIBG. Subjects were placed supine, and an i.v. catheter was placed in an antecubital vein. Approximately 20 min later, a sample of blood was drawn for NE determination from the catheter, placed on ice, and immediately centrifuged. Plasma was stored at −70°C for later determination of NE by reverse phase, high performance liquid chromatography (*19*). After drawing the blood sample, the subjects were injected with 370 MBq (10 mCi) of [^{123}I]MIBG through the indwelling catheter over 10 sec. All subjects had electrocardiographic monitoring during the injection and for the next 15 min. No arrhythmias or change in blood pressure or pulse were noted in any subject. Approximately one-third of patients noted a metallic taste, feeling of heat in the chest, or dizziness immediately after injection, but all symptoms disappeared within 30 sec after the injection.

Images were obtained using a GE 400-AT large field-of-view gamma camera with a LEAP collimator. Data was simultaneously stored on a GE STAR computer. A 20% window centered on 159 keV was used for imaging. To compensate for downscatter from high-energy photons which have an abundance of 2.3% (*20*), a high-energy downscatter image of the same window width (180–212 keV) was simultaneously acquired just above the 159 keV imaging window (*21*). Measurement of full field counts in both patients and in phantom studies showed that 8–14% of the counts in the imaging window were a result of downscatter from high-energy photons.

Images of the heart were obtained in the left anterior oblique (LAO) view. Additional images were obtained of the anterior and posterior chest, posterior abdomen, and anterior and posterior head. Imaging was performed at 1, 2, 16, and 24 hr after injection. Images at 1 and 2 hr were for 5 min each and those at 16 and 24 hr were for 10 min.

Data Analysis

The high-energy down scatter images were subtracted from the 159-keV centered images, and the subtracted images were used for data analysis. Cardiac activity at each time point was

quantified by drawing regions of interest (ROIs) around the left ventricular myocardium (LV) in the LAO view. Background subtraction was performed using a mediastinal ROI. Because of possible inclusion of lung or liver activity in the heart ROI, especially in the patients where heart uptake was low and the myocardial activity was often difficult to visualize, septal activity was measured by placing rectangular ROIs over the mid-septum (Fig. 1). In patients in whom uptake was so low that the septum could not be adequately visualized, horizontal profiles were drawn across the mid-septal region, and the region of highest counts was defined as the septum. To correct for possible attenuation effects between patients, septal to right lung ratios were calculated at each time point. Square ROIs were placed over the right midlung fields in the anterior and posterior views, and the geometric mean was calculated. A mediastinal ROI was used to correct for lung background activity.

Since catecholamine dynamics are altered in patients with cardiomyopathy, uptake in salivary glands, spleen, and liver was quantified and compared to controls. Rectangular ROIs were placed over the parotid glands in the anterior and posterior views using the brain for background subtraction. To compensate for rotation, the right and left sided counts were added. The geometric mean of anterior and posterior counts was then calculated. For the liver, a square ROI was placed over the right lobe in the anterior and posterior views with the mediastinum used as background, and the geometric mean was calculated. For the spleen, a rectangular ROI was placed posteriorly and an abdominal ROI used for background subtraction.

Counts were decay corrected to the 1 hr imaging time. Counts in the 1- and 2-hr images were doubled so that all results are expressed as counts per 10 min of imaging time. Except for total left ventricular counts, results are expressed as counts per pixel divided by the body surface area in square meters.

NE has been shown to be lost from the heart (*22,23*), spleen (*23*), lungs (*24*), and liver (*25*) by first-order kinetics (exponential loss). To determine if MIBG follows similar kinetics in these organs, regression lines were calculated for each NC, ICC, and transplant patient, and the correlation coefficients were determined. Linear regression was performed using the natural logarithm of the counts versus time. Half-times of MIBG loss were calculated from the slopes of the resulting regression lines. The y-axis intercept of the regression line was the natural logarithm of the counts at zero time. The individual half-times, initial (zero time) counts, and correlation coefficients were averaged and the standard deviations calculated (*26*). Organs which showed a correlation coefficient of 90% or greater were considered to show a good fit to an exponential decay curve.

Statistical Analysis

The two-tailed Student's t-test was used to compare half-times of MIBG loss and initial counts (*26*) between the NC and ICC patients. Significance was accepted at the $p < 0.05$ level. For heart to lung ratios, plasma norepinephrine levels, the lungs for which multiple comparisons were made, and organs which did not follow an exponential loss of activity, ANOVA was used to compare the different groups. Analysis was performed by a computer program (SPSS/PC+ V 2.0, SPSS Inc., Chicago, IL) which takes into account equal and unequal variances between groups.

RESULTS

In NC, heart uptake of MIBG was prominent at 1 hr and at all later imaging times (Fig. 2). The left and right ventricular myocardium and the septum were visualized at all times although right heart uptake tended to

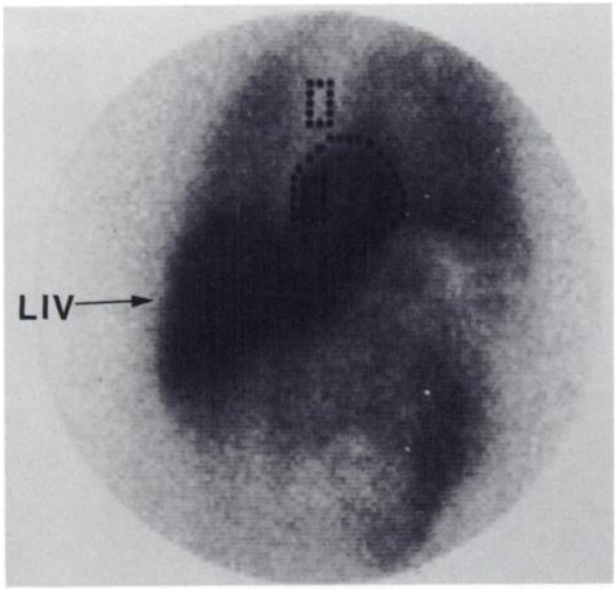

FIGURE 1
Two-hour LAO image in a normal subject showing ROIs over the left ventricular myocardium, the septum, and the mediastinum. Liver (LIV) activity is prominent.

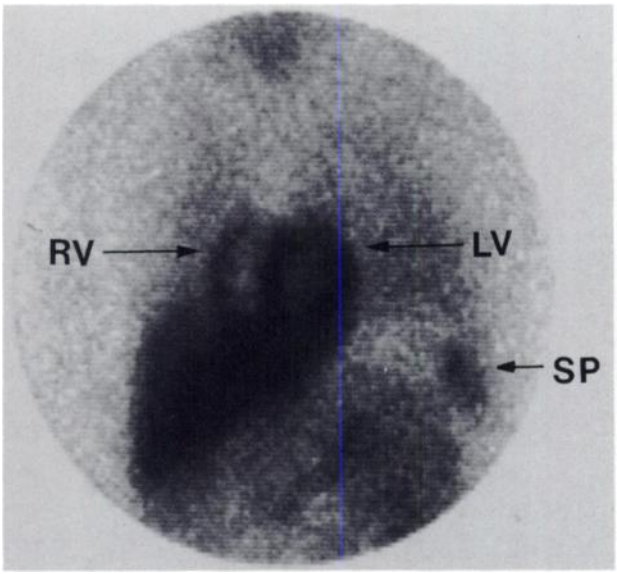

FIGURE 2
Sixteen-hour LAO image. Same subject as in Figure 1. The heart-to-lung ratio has increased. The left ventricular (LV) and right ventricular myocardium (RV) are well seen. Splenic (SP) activity is also seen.

be less prominent than left, especially at the early time points. The atrial myocardium was inconstantly visualized and was always less than that of the ventricles. LV activity was relatively constant during the first 2 hr and fell with time (Table 1). Activity at 2, 16, and 24 hr was 95%, 55%, and 42% of that at 1 hr. Septal uptake was also relatively constant during the first 2 hr, and values at 2, 16, and 24 hr were 101%, 62%, and 47% of the 1-hr value (Table 1). Septum to lung ratios are shown in Table 2. The maximal septum to lung ratio occurred at 16 hr and was nearly three times the 1 hr value. The ratio at 16 hr was significantly greater than the 1- and 2-hr values.

In ICC, heart uptake was moderately to severely decreased in a uniform manner. Patients with class III failure generally had less uptake than those with class II failure (Figs. 3 and 4), but there was overlap between the two classes. Heart to lung ratios were less than one at all times (Table 2) and remained relatively constant with time. When the ratios were tested by ANOVA, ICC was significantly different from the NC group. Heart uptake compared to NC was 72%, 51%, 34%, and 25% at 1, 2, 16, and 24 hr after injection. Septal uptake was even more severely decreased with values of 45%, 36%, 24%, and 15% compared to NC at 1, 2, 16, and 24 hr (Table 1).

In transplant patients, myocardial activity was not visible in any patient (Fig. 5) except at high levels of image contrast. LV activity at 1, 2, 16, and 24 hr was 5.6%, 8.7%, 0.37%, and 0.19% of NC, respectively (Table 1). Septal uptake was 3.2%, 6.0%, 0.26%, and 0.71% compared to NC at these times (Table 1). At no time was activity significantly different from zero.

Half-time values of myocardial activity are shown in Table 3. Half-time activity within the LV for NC was 19 ± 11.8 hr and for the septum was 22.7 ± 12 hr. The correlation coefficients were r = −0.968 and −0.944, respectively, indicating a good fit to an exponential decay curve for both structures. The y-axis intercepts were 170 ± 44 thousand counts for the LV and 180 ± 50 cts/pixel for the septum which correspond to the theoretical zero time activities assuming total uptake of the tracer at this time. In ICC, both LV and septal activity showed a good fit to an exponential decay curve (r = −0.981 and r =−0.978, respectively). Washout of tracer was significantly more rapid from the LV and septum with a half-times of 7.98 ± 4.27 hr for the LV and 8.66 ± 2.77 hr for the septum (p = 0.038 and p = 0.013, respectively). The initial activity of the ICC group (77 ± 37 counts/pixel for the septum and 123 ± 40 thousand counts for the LV) was significantly different

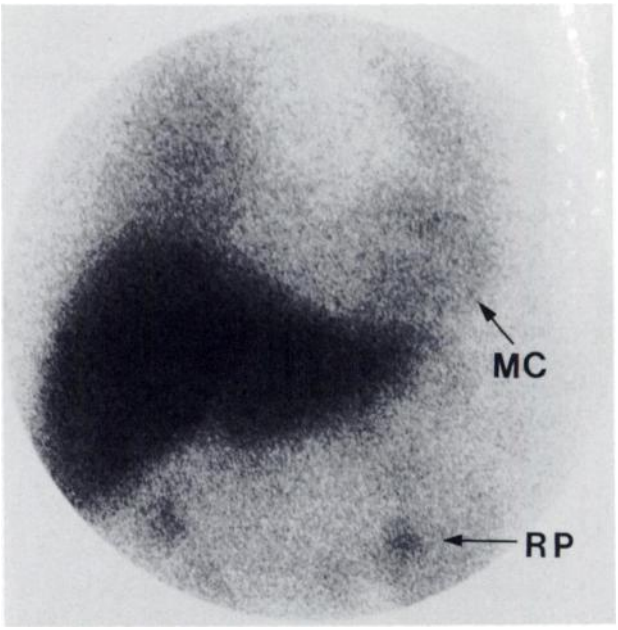

FIGURE 3
Two-hour anterior chest image of a patient with class II cardiomyopathy. Myocardial (MC) activity is approximately equal to lung. Tracer is seen in the renal pelves (RP).

TABLE 1
Cardiac Activity of [^{123}I]MIBG

	1 hr	2 hr	16 hr	24 hr
	Left ventricular myocardium (1000's of counts)			
Controls	158 ± 31	150 ± 34	88 ± 38	67 ± 28
Cardiomyopathy	113 ± 52	76 ± 51	30 ± 18	17 ± 12
% of controls	72%	51%	34%	25%
Transplants	8.9 ± 10	13 ± 17	0.33 ± 0.66	0.13 ± 0.22
% of controls	5.6%	8.7%	0.37%	0.19%
	Septum (counts/pixel/sq. meter)			
Controls	170 ± 37	172 ± 56	105 ± 56	80 ± 37
Cardiomyopathy	77 ± 32	61 ± 34	25 ± 19	12 ± 9.4
% of controls	45%	36%	24%	15%
Transplants	5.5 ± 11	10 ± 10	0.28 ± 0.57	0.57 ± 0.98
% of controls	3.2%	6.0%	0.26%	0.71%

Mean ± s.d.

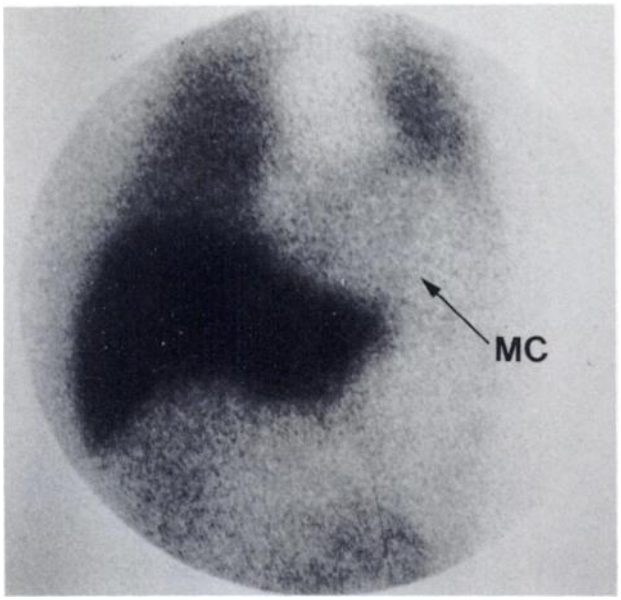

FIGURE 4
Two-hour anterior chest image in a patient with class III cardiomyopathy. Myocardial (MC) activity is less than lung.

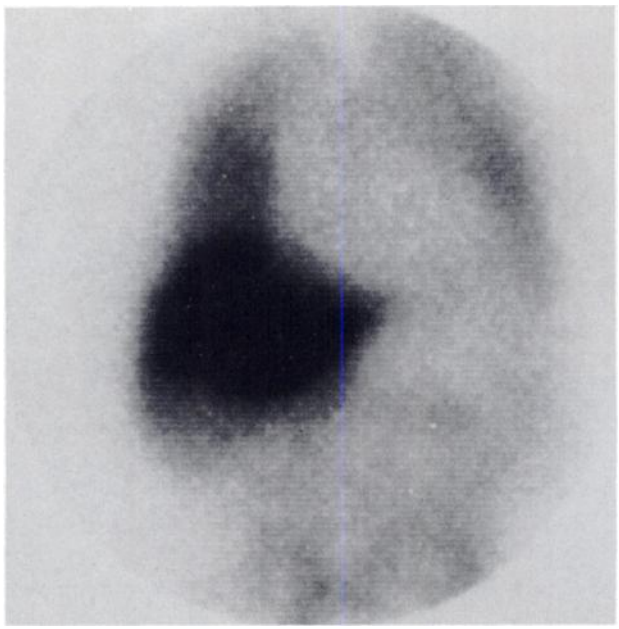

FIGURE 5
One-hour LAO chest image in a patient with a cardiac transplant. No discernible cardiac activity is seen.

from the initial activity of the controls for the septum ($p = 0.001$) but not the the LV ($p = 0.063$). Since about one-half of the data points in the transplant patients were zero, it was impossible or inappropriate to fit exponential decay curves with their values. ANOVA was used to compare their values at each time point against NC and ICC patients. Values for the transplants were all significantly decreased compared to both groups.

Lung activity showed a good fit to an exponential for all three groups ($r = -0.980$ for NC, $r = -0.978$ for ICC, $r = -0.945$ for transplants). The half-times of tracer loss and initial activities are shown in Table 3. Table 4 shows the lung counts of the various groups at each time point. The initial activities and half-times of the transplants were greater than the NC but the differences were not significant.

Liver activity also showed a good fit to an exponential decay curve (Table 3). The half-time of liver activity in NC was 11.1 hr and in ICC was 13.0 hr which were not significantly different. Initial activities were also not significantly different. Spleen activity (Table 4) was relatively constant in ICC and NC and could not be fit by linear or exponential curves. These data were compared by ANOVA and no significant difference was found between NC and ICC. Salivary gland activity was well delineated in NC and ICC (Fig. 6). Activity tended to rise with time, and there was a positive linear correlation between time and activity ($r = 0.831$ in NC and $r = 0.769$ in ICC). There was, however, no significant difference between groups and no significant difference between time points within a group when compared by ANOVA. Adrenal activity was not well seen at 1 and 2 hr but became more prominent at the later imaging times. Activity appeared similar between the NC and ICC patients but was not specifically evaluated.

Plasma NE was 1.76 ± 0.781 pmol/ml (297 ± 132 pg/ml, mean ± s.d.) in NC, 3.42 ± 1.97 pmol/ml (578 ± 333 pg/ml) in ICC, and 1.56 ± 0.988 pmol/ml (263 ± 167 pg/ml) in transplants. There was a significant difference between the NC and ICC patients ($p < 0.05$) which was an expected finding (*27*). There was no significant difference between NC and transplant pa-

TABLE 2
Septum to Right Lung Ratios

	1 hr	2 hr	16 hr	24 hr
Controls	1.29 ± 0.485	1.65 ± 0.370	3.79 ± 2.40*	3.76 ± 2.62
Cardiomyopathy	0.609 ± 0.300	0.590 ± 0.349	0.691 ± 0.520	0.601 ± 0.451
Transplants	0.085 ± 0.069	0.065 ± 0.058	0.004 ± 0.009	0.011 ± 0.019

Mean ± s.d.
* Significantly greater than 1- and 2-hr control values ($p < 0.05$)

TABLE 3
Parameters of Exponentially Fitted Data

	LV	Septum	Lung	Liver
		Half-times of MIBG loss (hr)		
Controls	19.0 ± 11.8	22.7 ± 12.0	9.28 ± 1.92	11.1 ± 1.84
Cardiomyopathy	7.98 ± 4.27*	8.66 ± 2.77†	10.7 ± 6.0	13.0 ± 3.30
Transplants	ND	ND	14.1 ± 6.56	ND
		Initial activities		
Controls	170 ± 44	180 ± 50	124 ± 28	586 ± 196
Cardiomyopathy	123 ± 40‡	77 ± 37§	134 ± 38	418 ± 169
Transplants	ND	ND	222 ± 174	ND
		Correlation coefficients		
Controls	−0.968 ± 0.038	−0.944 ± 0.064	−0.980 ± 0.011	−0.982 ± 0.013
Cardiomyopathy	−0.981 ± 0.019	−0.978 ± 0.023	−0.978 ± 0.015	−0.985 ± 0.010
Transplants	ND	ND	−0.945 ± 0.083	ND

Mean ± s.d.
LV activity is in thousands of counts, the other activities are in counts/pixel/sq. meter.
LV = left ventricular myocardium; ND = not done.
* $p = 0.038$ compared to controls, † $p = 0.013$ compared to controls; ‡ $p = 0.063$ compared to controls, § $p = 0.001$ compared to controls

tients. Since NE can inhibit the uptake of MIBG (*7*), elevated levels of NE might have cause decreased cardiac MIBG uptake. An attempt was made to determine if elevated NE levels could account for the decreased uptake seen in ICC patients. Initial cardiac uptake of MIBG was plotted against plasma NE levels, and regression lines were calculated for the LV and septum. In both cases, an inverse correlation was found. The correlation for LV uptake was poor ($r = -0.395$), while septal uptake was better ($r = -0.798$). Using the septal regression line, one can evaluate the uptake that would occur at the plasma values of NE found in the normal controls. At this value, only 22% of the difference in septal uptake between ICC and NC is accounted for by elevated plasma NE.

DISCUSSION

The ANS is felt to play an important part in several cardiac diseases. The study of the cardiac ANS, how-

TABLE 4
Organ activity of [^{123}I]MIBG

	1 hr	2 hr	16 hr	24 hr
		Lungs		
Controls	123 ± 31	105 ± 23	24 ± 12	23 ± 6.3
Cardiomyopathy	138 ± 39	117 ± 37	47 ± 28	38 ± 24
Transplants	132 ± 31	139 ± 32	62 ± 6.1	50 ± 3.9
		Liver		
Controls	582 ± 177	457 ± 69	177 ± 38	135 ± 29
Cardiomyopathy	413 ± 169	382 ± 168	162 ± 89	136 ± 90
		Spleen		
Controls	32 ± 13	43 ± 21	41 ± 13	47 ± 25
Cardiomyopathy	32 ± 22	31 ± 15	34 ± 22	37 ± 25
		Salivary glands		
Controls	180 ± 33	199 ± 33	225 ± 98	213 ± 94
Cardiomyopathy	177 ± 96	198 ± 108	224 ± 79	195 ± 75

Means ± s.d. All values are given as counts/pixel/sq. meter.

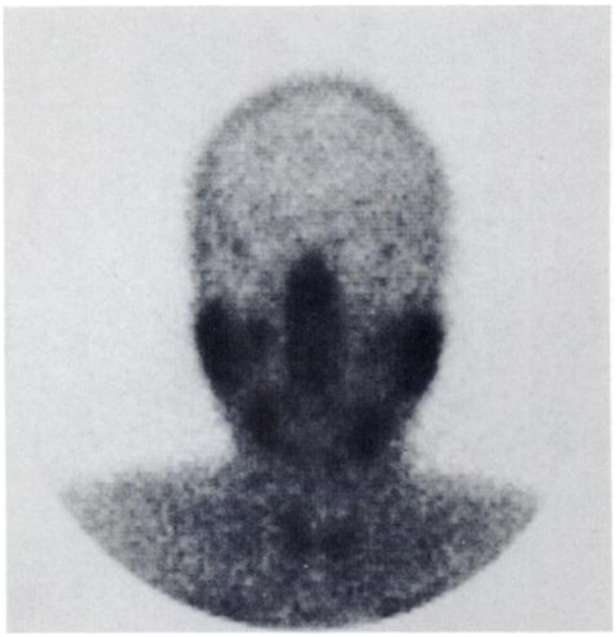

FIGURE 6
Sixteen-hour anterior head image in a normal subject. Parotid glands, submandibular glands, nasopharyngeal activity is seen.

ever, is difficult, and its role in cardiac disease is largely speculative. MIBG is a NE analog which, when labeled with ^{123}I, allows study of the cardiac ANS in vivo. Previous studies have shown that the cardiac ANS is readily visualized with [^{123}I]MIBG in normals (*10,11*). MIBG appears to follow the kinetics of NE in the heart in several circumstances (*12–15*) suggesting that MIBG may be used to study the cardiac ANS.

In the present study, cardiac MIBG uptake in NC was compared to uptake in ICC. Rather than compare uptake between groups at each time point and activity within a group at different time points, the half-times of MIBG loss and initial uptakes were compared between groups. Not only are these parameters more meaningful physiologically, but this method is also appropriate statistically (*26*). Since MIBG loss from the LV, septum, lungs, and liver of ICC and NC showed a good fit to an exponential curve, for these organs the half-times and initial activities were compared. Patients with ICC showed decreased uptake and faster loss of activity from the septum compared to NC. The half-time was also shorter for the entire LV, but initial activity showed only a borderline difference ($p = 0.063$). Since it was often difficult to define LV borders in patients with low uptake, the septal values are probably more accurate. The decreased uptake of MIBG may reflect damage to the sympathetic neurons, while the shortened half-time may represent increased ANS activity. In humans, data on the cardiac ANS in heart failure is sparse. Cardiac stores of NE are decreased in heart failure (*28*). Plasma NE levels are elevated (*27*) suggesting increased ANS activity. Other studies, however, have shown that increased plasma levels of NE are a result of decreased clearance (*29,30*). Directly evaluating sympathetic neuronal activity in vivo is possible with microneurography (*31*). However, only skin and muscle nerve sympathetic activity (MSA) can be recorded. In one study, MSA has been measured in heart failure (*32*), and increased sympathetic activity was found. In the cardiomyopathic Syrian hamster, cardiac NE turnover is increased suggesting increased ANS activity (*23*).

While the present study demonstrated decreased uptake and faster washout of cardiac MIBG in ICC, the results cannot be quantitatively applied to NE kinetics. In the rat, cardiac washout of MIBG was approximately twice as fast as NE in the fed and fasted state (*15*). Similarly, in vitro studies with bovine chromaffin cells show quantitative differences between the kinetics of MIBG and NE although qualitatively the results are similar (*7,8*). Thus MIBG is a marker of sympathetic function rather than a quantitative analog of NE.

Several possible causes of artifactually decreased cardiac activity in the ICC patients were evaluated. Since NE and MIBG share the same uptake mechanism, it is possible that elevated levels of NE might block cardiac uptake of MIBG. Decreased cardiac uptake of [^{131}I] MIBG has, in fact, been found in patients with elevated NE levels who were being evaluated for pheochromocytoma (*33*). In that study, cardiac visualization was evaluated at 24 hr in a semiquantitative manner. Patients with decreased uptake had NE levels above 2.96 pmol/ml (500 pg/ml). In the present study, the average plasma NE level was 3.42 pmol/ml (578 pg/ml). Three patients had levels below 2.96 pmol/ml (500 pg/ml) and three had levels above 2.96 pmol/ml (500 pg/ml). Uptake in both groups was decreased compared to NC although uptake was more severely decreased in the latter group. Linear regression analysis showed a fair correlation between plasma NE and septal uptake of MIBG. A correlation, however, does not imply cause and effect. The relationship between NE and MIBG uptake is complex since two different mechanisms (uptake-1 and uptake-2) which have different kinetics are responsible for NE and MIBG uptake. It is probable, therefore, that a linear relationship does not exist between plasma NE levels and MIBG uptake. Based on the data of Jaques et al., (*7*), the concentration of NE which caused 50% inhibition of type-1 (specific) uptake of 0.5 μM MIBG (which is probably close to the plasma value of MIBG for the first few minutes after injection) was 2.4 μM (2.4 nmol/ml, 406 ng/ml). Since the highest concentration of plasma NE among the ICC patients was 6.77 pmol/ml (1,144 pg/ml), it is unlikely that there was significant inhibition of type-1 uptake. Type-2 uptake is inhibited even less by NE (*7*). Thus it seems

unlikely that elevated NE levels caused any significant inhibition of MIBG uptake.

Tissue attenuation can vary from individual to individual, and this could affect the measured cardiac activity. To account for this, septal activity corrected for body weight and septum to lung ratios were calculated. In both instances, ICC patients showed decreased cardiac activity.

Cardiac uptake of MIBG as measured in this study represents uptake in neuronal and nonneuronal structures. If nonneuronal uptake is high, even marked changes in neuronal uptake would be difficult to quantify. To determine the nonneuronal uptake of MIBG, patients with cardiac transplants were studied, a group in whom all cardiac sympathetic nerves have been destroyed. Since damaged sympathetic nerve axons can regrow if the cell bodies are intact (*34*), patients were studied soon (within 4 mo) after surgery. The results indicate that nonneuronal uptake of MIBG is low, amounting to <10% in the first 2 hr after injection, and is essentially undetectable by 16 hr. Thus, except in severely damaged neurons, cardiac uptake of MIBG represents neuronal uptake.

Catecholamine kinetics are disturbed in several disease states, and patients were excluded who had diseases known to affect catecholamine or MIBG kinetics. Since 85% of an injected dose of epinephrine is taken up by the liver (*35*), liver disease may alter catecholamine metabolism. Diabetes causes neuropathy, and in diabetic autonomic neuropathy, MIBG uptake by the heart is severely decreased (*11,17*). Approximately 50% of MIBG is excreted in the urine in the first 24 hr (*10*). CNS disease can have obvious effects on sympathetic outflow. For these reasons, patients with liver, renal, or CNS disease or diabetes were excluded from the study.

Congestive heart failure in our patient population is largely (~90%) secondary to myocardial infarction. This group has direct injury to sympathetic neurons in a regional manner and thus these patients were considered inappropriate for studying global cardiac ANS dysfunction. Patients were also excluded who had heart failure due to hypertension, valvular disease, infiltrative disease, or alcoholism. The patient study group, however, may not have represented a homogeneous population. Since ICC is a disease of exclusion, it is possible that several disease states are represented in this group each of which may have different effects on catecholamine metabolism.

To exclude a generalized effect on the ANS in ICC as the cause for decreased cardiac uptake of MIBG, uptake was evaluated in other sympathetically innervated organs (parotid gland, liver, lung, and spleen) and in organs which metabolize catecholamines (liver and lung). Uptake in the parotid glands and spleen was very similar between the two groups. Uptake in the liver was more variable but not significantly different from controls. In fact, liver uptake tended to be less in ICC suggesting that tracer had not been shunted to the liver. Lung uptake was also similar in both groups. There was, however, a trend to increased lung uptake in ICC and in the transplant patients. The lung metabolizes NE and serotonin and has a high first-pass uptake (25–50% and 80–95%, respectively) of these amines (*36*). First-pass extraction of [^{123}I]MIBG has been measured in humans and a value of 25% has been reported (*37*). Lung uptake of biogenic amines is even higher when pulmonary artery pressure is elevated (*38*), and the increased uptake of MIBG in the transplant patients (in whom pulmonary artery pressure was very high immediately prior to transplant) may be a manifestation of this phenomenon. Lung uptake of amines (*36,38*) and MIBG (*37*) is primarily in endothelial cells, and increased uptake may continue when pulmonary artery pressure has normalized after transplantation. Cardiovascular abnormalities (impaired vasodilation) have been shown to persist for up to 4 mo after transplantation (*39*).

Salivary gland activity tended to rise with time in both groups, but no significant difference was found between groups or within a group at different time points. Salivary gland activity probably includes a large nonneuronal component (*40*), and the results in this study are similar to those reported previously (*11*). Splenic activity was low. In the Syrian hamster, there is prominent sympathetic innervation of the spleen, and NE shows an exponential loss with time. There are no data on splenic NE kinetics in humans. The relatively constant levels of MIBG in the spleen may reflect species differences in NE kinetics or a high nonneuronal splenic uptake of MIBG.

CONCLUSIONS

We have shown that patients with ICC have decreased uptake and more rapid washout of MIBG from the heart than normal controls. The decreased uptake of MIBG suggests dysfunction of cardiac sympathetic neurons. The rapid washout of MIBG from the heart suggests increased cardiac sympathetic nerve activity in ICC. MIBG appears to be useful for studying the sympathetic nervous innervation of the heart noninvasively which provides a unique means of investigating a relatively unexplored area of cardiac physiology.

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REFERENCES

1. Chadda K, Goldstein S, Byington R. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986; 73:503–510.
2. Braunwald E, Muller JE, Kloner RA, Maroko PR. Role of beta-adrenergic blockade in the therapy of patients with myocardial infarction. *Am J Med* 1983; 74:113–123.
3. Waagstein F, Hjalmarson A, Swedeberg K, Wallentin I. Beta-blockers in dilated cardiomyopathies: they work. *Eur Heart J* 1983; 4:173–178.
4. Honda T, Ninomiya I, Azumi T. Cardiac sympathetic nerve activity and catecholamine kinetics in cat hearts. *Am J Physiol* 1987; 252:H879–H885.
5. Sisson JC, Frager MX, Valk TW. Scintigraphic localization of pheochromocytoma. *N Engl J Med* 1981; 305:12–17.
6. Shapiro B, Copp JE, Sisson JC, Eyre PL, Wallis J, Beierwalter WH. Iodine-131 metaiodobenzylguanidine for the locating of suspected pheochromocytoma: experience in 400 cases. *J Nucl Med* 1985; 26:576–585.
7. Jaques S, Tobes MC, Sisson JC, Baker JA, Wieland DM. Comparison of the sodium dependency of uptake of meta-Iodobenzylguanidine and norepinephrine into cultured bovine adrenomedullary cells. *Mol Pharm* 1984; 26:539–546.
8. Tobes MC, Jaques S, Wieland DM, Sisson JC. Effect of uptake-one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. *J Nucl Med* 1985; 26:897–907.
9. Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu JL, Clinthorne NH, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 1981; 22:22–31.
10. Kline RC, Swanson DP, Wieland DM, Thrall JH, Gross MD, Pitt B, et al. Myocardial imaging in man with I-123 meta-iodobenzylguanidine. *J Nucl Med* 1981; 22:129–132.
11. Sisson JC, Shapiro B, Myers L, Mallette S, Mangner TJ, Wieland DM, et al. Metaiodobenzylguanidine to map the adrenergic nervous system in man. *J Nucl Med* 1987; 28:1625–1636.
12. Dae M, Herre J, Botvinick E, Huberty J, O'Connell W, Davis J, et al. Scintigraphic detection of denervated myocardium after infarction. [Abstract]. *J Nucl Med* 1986; 27:949.
13. Schofer J, Spielman R, Schuchert A, Weber K. Meta-(123) iodobenzylguanidin (MIBG-) scintigraphy in idiopathic dilated cardiomyopathy (icd): a noninvasive method to assess myocardial catecholamine depletion? [Abstract] *Circulation* 1987; 76(suppl IV):308.
14. Dae M, Davis J, Bovinick E, Huberty J, O'Connell W, Fujii C, et al. Scintigraphic assessment of regional cardiac adrenergic density. [Abstract]. *Circulation* 1985; 72(suppl III):444.
15. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jaques S. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 1987; 28:1620–1624.
16. Tuli M, Minardo J, Mock B, Weiner R, Siddiqui A, Zipes D, et al. SPECT with high purity I-123-MIBG after transmural myocardial infarction (TMI), demonstrating sympathetic denervation followed by reinnervation in a dog model [Abstract]. *J Nucl Med* 1987; 28:669.
17. Glowniak JV, Sisson JC, Shapiro B, Meyers L, Mallett S, Beierwaltes WH. Scintigraphic mapping of autonomic neuropathy [Abstract]. *Clin Res* 1984; 32:730A.
18. Wieland DM, Wu JL, Brown LE, Mangner TJ, Swanson DP, Beierwalter WH. Radiolabeled adrenergic neuron-blocking agents: adrenomedullary imaging with [I-131]iodobenzylguanidine. *J Nucl Med* 1980; 21:349–353.
19. Nutt JG, Woodward WR, Hammerstad JP, Carter JH, Anderson JL. The "on-off" phenomenon in Parkinson's disease: relation to levodopa absorption and transport. *N Engl J Med* 1984; 310:483–488.
20. Sorenson JA, Phelps ME. Physics in nuclear medicine. Orlando: Grune & Stratton, Inc., 2nd ed. 1987: 553.
21. Graham LS, Lake R, Cohen MB. Removal of septal penetration effects in images obtained with high purity I-123 [Abstract]. *Clin Nucl Med* 1984; 9:P32.
22. Landsberg L, Young JB. Fasting, feeding and regulation of the sympathetic nervous system. *N Engl J Med* 1978; 298:1295–1301.
23. Sole MJ, Lo CM, Laird CW, Sonnenblick EH, Wurtman RJ. Norepinephrine turnover in the heart and spleen of the cardiomyopathic Syrian hamster. *Circ Res* 1975; 37:855–862.
24. Johnson TS, Young JB, Landsberg L. Norepinephrine turnover in lung: effect of cold exposure and chronic hypoxia. *J Appl Physiol* 1981; 51:614–620.
25. Young JB, Landsberg L. Effect of diet and cold exposure on norepinephrine turnover in pancreas and liver. *Am J Physiol* 1979; 236:E524–E533.
26. Feldman HA. Families of lines: random effects in linear regression analysis. *J Appl Physiol* 1988; 64:1721–1732.
27. Thomas JA, Marks BH. Plasma norepinephrine in congestive heart failure. *Am J Cardiol* 1978; 41:233–243.
28. Chidsey CA, Braunwald E, Morrow AC. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Am J Med* 1965; 39:442–451.
29. Davis D, Zelis R. The sympathetic nervous system in congestive heart failure. *Heart Failure* 1986; 2:21–32.
30. Davis D, Sinoway LI, Robison J, Minotti JR, Day FP, Baily R, et al. Norepinephrine kinetics during orthostatic stress in congestive heart failure. *Circ Res* 1987; 61(suppl I):I87–I90.
31. Wallis BG, Fagius J. The sympathetic nervous system in man–aspects derived from microelectrode recordings. *Trends in Neurosci* 1986; 9:63–67.
32. Leimbach WN, Wallin BG, Victor RG, Aylward PG, Sundlof G, Mark AL. Direct evidence form intra neural recordings for increased central sympathetic outflow in patients with heart failure. *Circ* 1986; 73:913–919.
33. Nakajo M, Shapiro B, Glowniak JV, Sisson JC, Beierwaltes WH. Inverse relationship between cardiac ac-

cumulation of meta-131-I-iodobenzylguanidine (I-131-MIBG) and circulating catecholamines: observations in patients with suspected pheochromocytoma. *J Nucl Med* 1983; 24:1127–1134.
34. Kaye MP, Tyce GM. Norepinephrine uptake as an indicator of cardiac reinnervation in dogs. *Am J Physiol* 1978; 253:H289–H294.
35. LaBrisse EH, Hertting G. Biliary excretion of dl-epinephrine metabolites. *Fed Proc* 1964; 19:398–404.
36. Gillis CN, Pitt BR. The fate of circulating amines within the pulmonary circulation. *Ann Rev Physiol* 1982; 44:269–281.
37. Slosman DO, Morel DR, Alderson PO. A new imaging approach to quantitative evaluation of pulmonary vascular endothelial metabolism. *J Thorac Imag* 1988; 3:49–52.
38. Gillis CN, Cronau LH, Greene NM, Hammond GL. Removal of 5-hydroxytryptamine and norepinephrine from the pulmonary vascular space of man: influence of cardiopulmonary bypass and pulmonary arterial pressure on these processes. *Surgery* 1974; 76:608–616.
39. Sinoway LI, Minotti JR, Davis D, Pennock JL, Burg JE, Musch TI, et al. Delayed reversal of impaired vasodilation in congestive heart failure after heart transplantation. *Am J Cardiol* 1988; 61:1076–1079.
40. Sisson JC, Wieland DM, Jaques S, Sherman P, Fisher S, Mallette S, et al. Radiolabeled meta-iodobenzylguanidine and the adrenergic neurons of salivary glands. *Am J Physiol Imaging* 1987; 2:1–9.
41. Glowniak JV, Turner FE, Gray LL, Palac RT, Lagunas-Solar MC, Hosenpud JD. I-123 metaiodobenzylguanidine (MIBG) cardiac imaging in idiopathic congestive cardiomyopathy (ICC) [Abstract]. *J Nucl Med* 1987; 28:667.
42. Glowniak JV, Turner FE, Gray LL, Palac RT, Lagunas-Solar MC, Hosenpud JD. Evaluation of non-neuronal cardiac uptake of I-123 metaiodobenzylguanidine (I-123 MIBG) in humans [Abstract]. *J Nucl Med* 1988; 29:842.