Abnormal I-123 Metaiodobenzylguanidine Myocardial Washout and Distribution May Reflect Myocardial Adrenergic Derangement in Patients With Congestive Cardiomyopathy

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I-123 metaiodobenzylguanidine (MIBG) is a new radiopharmaceutical with properties that allow the characterization of the sympathetic innervation of several organ systems. In this study, we used MIBG with tomographic imaging to evaluate noninvasively the differences in myocardial sympathetic innervation in 14 healthy volunteers and 16 patients with severe dilated cardiomyopathy (CM). Initial (15-minute) images demonstrated no significant differences in MIBG concentration in the hearts of patients with CM and of healthy volunteers. However, the myocardial retention of MIBG was significantly reduced in the patients with CM. Expressed as the percent washout from 15 to 85 minutes, the patients with CM had a $28 \pm 12\%$ washout rate compared with $6 \pm 8\%$ in the controls ($p<0.001$). A small subset of patients from each group imaged at 4-hour intervals demonstrated even greater disparity in washout rates. In addition, the patients with CM had significantly greater heterogeneity in the MIBG activity distribution within the myocardial images. There was $47 \pm 15\%$ intrimage variability in MIBG distribution in the patients with CM and $22 \pm 9\%$ variation in the controls ($p<0.001$). We conclude from these data that the myocardial distribution and kinetics of MIBG in images obtained from patients with CM differ significantly from those of controls and that the MIBG patterns may be used as a relatively noninvasive means to evaluate the severity of altered adrenergic innervation in the hearts of these patients. (Circulation 1988;78:1192-1199)

Radioiodinated metaiodobenzylguanidine (MIBG), an analogue of the adrenergic blocking agent guanethidine, was originally described by Wieland et al at the University of Michigan Medical Center. Research conducted over the last decade has helped to clarify mechanisms of uptake, storage, and release of MIBG and has led to its development as a useful clinical tool to visualize various neuroendocrine tumors.\(^2,3\) In addition, organs with rich adrenergic innervation, such as the heart, spleen, and salivary glands, have been noted to have substantial MIBG uptake and potential for scintigraphic imaging.\(^4\) Kline et al\(^5\) originally described the use of MIBG for myocardial imaging in human volunteers, and other relatively preliminary reports of myocardial imaging with MIBG have followed.\(^4,6,7\)

Abnormalities of adrenergic innervation and catecholamine stores in human myocardium subjected to chronic pressure and/or volume overload have been recognized since the early 1960s.\(^8-10\) Reported findings include depressed tissue levels of norepinephrine in cardiac muscle, patchy attrition of myocardial neurons, and depressed activity of the sympathetic neuronal catecholamine uptake system(s).\(^10-12\)

Despite differences in the pharmacokinetics of MIBG and norepinephrine (NE) as demonstrated in studies with chemical depletion of NE and blockade of MIBG accumulation,\(^13,21\) MIBG and NE appear to share common normal uptake and storage mechanisms.\(^14\) MIBG has, therefore, been labeled as a
“nonmetabolizable norepinephrine” that is incorporated by catecholamine uptake pathways and stored in intraneuronal vesicles. Thus, myocardial scintigraphy with MIBG should reflect the status of myocardial sympathetic innervation, and because dramatic differences in adrenergic innervation exist between patients with severe dilated congestive cardiomyopathy (CM) and controls, MIBG myocardial images of hearts of patients with CM would be expected to differ dramatically from images obtained from hearts of controls. Therefore, this study was designed to test the hypothesis that the imaging characteristics of MIBG in patients with congestive CM differ significantly from the imaging characteristics of MIBG in controls and, further, that these differences might include abnormalities of the myocardial uptake, distribution, and turnover (washout) of MIBG that would reflect marked alterations in myocardial adrenergic innervation.

Subjects and Methods

Subjects

Fourteen normal volunteers (10 men and four women) were recruited for this study. Their mean age was 28.1 ± 4.8 years (range, 23–37 years). None had clinical evidence of organic heart disease or other significant medical problems.

Sixteen patients (10 men and six women) with severe left ventricular (LV) dysfunction were recruited. Their mean age was 44.8 ± 9.5 years (range, 31–60 years). Eleven of the patients had undergone cardiac catheterization and were found to have normal coronary arteries with depressed LV function. The remaining five patients had no clinical history to suggest coronary artery disease and were believed on clinical grounds to have “nonischemic” dilated cardiomyopathy. Thirteen of the 16 patients had recent assessment of LV ejection fraction by radionuclide ventriculography (RVG), and all 16 patients underwent echocardiographic assessment. Overall, 14 of the 16 patients had objective assessment (catheterization and/or RVG) of LV ejection fraction (EF), and their mean LVEF was 0.22 ± 0.08. Three patients had a history of significant alcohol consumption, and two patients had postpartum CM. The etiology of the myocardial dysfunction was unclear (idiopathic) in 11 patients.

Indications of exclusion from this study were inability to provide informed consent, known or suspected coronary artery disease, concomitant thyroid disease, history of allergy to iodine, or consumption of a medication known to interfere with MIBG uptake (i.e., tricyclic antidepressants or sympathomimetic cold or decongestant preparations).

Radiopharmaceutical Preparation

MIBG was radioiodinated by solid-phase exchange radioiodination by ammonium sulfate as described by Mangner et al. MIBG (2 mg) and ammonium sulfate (4 mg) were dissolved in 1 ml sterile water and mixed with 20 mCi NaI-123 solution. The reaction mixture was heated to dryness (140–150°C) in a magnetically stirred silicone bath. The dry reaction mixture was maintained at 145°C (140–150°C) under a stream of air introduced through a sterile filter assembly for the last 30 minutes. The reaction mixture was cooled to 90°C. One milliliter sterile water was added, and the previous heating step was repeated. The dry reaction mixture was then dissolved in 3 ml 13.5 mM acetate buffer (pH 4.5). The resulting solution was passed through a DEAE-cellulose (Sigma Chemical, St. Louis, Missouri) anion-exchange column (2 ml resin loosely packed in a 3-ml syringe) previously equilibrated with the same buffer. Then, the column was washed with another 3 ml acetate buffer. The product was filtered through a 0.22-μm sterile membrane filter into a collection vial containing 0.05 ml benzyl alcohol. Finally, the product was diluted with 4 ml sterile saline and tested for free iodine content by instant thin layer chromatography with the solvent mixture ethyl alcohol:ethyl acetate:concentrated ammonia (20:20:1). Usually, the free iodine content was less than 1%. The I-123 used in these syntheses was produced by Xe-123(p,2n)Cs-123 → Xe-123 → I-123 and contained less than 1% radionuclide impurities at the time of calibration (Atomic Energy of Canada Limited [AECL], Ottawa, Canada).

Protocol

On the day of the study, patients were allowed a light breakfast and then instructed to fast for 2–6 hours. All medications, including digitalis preparations, diuretics, and antiarrhythmic medications, were continued. Eighteen of 30 patients (eight patients with CM and 10 controls) had plasma catecholamine determinations performed immediately before imaging. Selection of patients to undergo catecholamine measurement was random and not based on clinical, personal, or other factors. In these patients, a heparin lock was inserted into a peripheral arm vein, and the patients were requested to lie quietly in the supine position for 30–40 minutes. Blood was aspirated into a 10-ml heparinized vacutainer from the heparin lock. The vacutainers were immediately immersed in an ice bath and centrifuged within 20 minutes. Centrifugation was performed for 20 minutes at 2–4°C and at 1,000 ± 100 g. The serum was immediately separated and frozen for transportation. Plasma catecholamine analysis was performed by Smith Kline Bio-Science Laboratories (Van Nuys, California) with high-pressure liquid chromatography (HPLC) with electrochemical detection. After the blood specimens were obtained, the imaging protocol was begun.

Imaging

One milliliter of Lugol’s solution was given by mouth 30–60 minutes before intravenous injection of 8–10 mCi I-123 MIBG. Patients were injected while upright when possible and ambulated for 5–10 minutes before imaging. Imaging was performed with a Technicare Omega 500 tomographic camera equipped

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with a high-resolution low-energy parallel hole collimator. Images were acquired into a dedicated nuclear medicine computer (Technicare 560, Solon, Ohio). Energy discrimination was provided by a 20% window centered on the 159-keV photopeak of 123I. Projection images were acquired for 20 seconds each at 3° increments over 180° circular orbits from 45° right anterior oblique to 45° left posterior oblique and were recorded at a digital resolution of 64 × 64. Imaging was begun approximately 15 minutes after the injection of MIBG (immediate study) and was repeated 85 minutes after the injection (delayed study). In a subset of patients in both groups (four patients with CM and four controls), imaging was also performed at 4 hours after the injection.

**Image Analysis**

Transaxial tomographic sections, including the entire cardiac volume, were reconstructed by filtered back projection (Technicare Omega 500S software system). The filter used during reconstruction was the product of a ramp and a Butterworth filter (cutoff, 0.34; order, 3.5). Corresponding vertical long-axis and short-axis sections were extracted from the reconstructed volume. The vertical long-axis image and select short-axis images representative of the apical and basal portions of the LV were subsequently analyzed for segmental I-123 MIBG activity and washout.

Image analysis consisted of the generation of regions of interest (ROI) by visual inspection, intended to divide the myocardium into anatomic divisions as depicted in Figure 1. The ROIs were placed to determine the average counts per voxel for each myocardial segment. Two investigators evaluated each image independently to ensure that reproducible values could be obtained. The method of ROI determination was simple and easily reproducible. Compared with myocardial activity, the I-123 MIBG activity in the lungs and liver of some patients was relatively intense. In these patients, the ROIs were placed to avoid contamination of myocardial activity by activity of pulmonary or hepatic origin. The vertical long-axis image consisted of a single midventricular slice 5.35 mm thick. From this image, four ROIs were constructed corresponding to the anterior, apical, inferior, and posterior segments. The apical and basal short-axis sections were also single short-axis slices, each approximately 5.35 mm thick. These images had anterior, septal, inferior (or posterior), and lateral ROI determinations (Figure 1). The average counts per voxel (counts/voxel) for all segments of each image were corrected for millicurie injected dose and for the display scale factor used during image reconstruction to avoid data overflow in the storage process. These "normalized" segmental activities were determined so that interindividual comparisons of myocardial uptake could be made. These normalized data made segment-to-segment, image-to-image, and patient-to-patient comparisons possible. No attempt was made to account for variations in attenuation or scatter secondary to varying body habitus among the different patients, and no correlation for count decay over time was attempted.

The average normalized left ventricular MIBG activity for each patient was determined. The intragroup variability for each image was defined as the difference in the maximum and minimum segmental counts divided by the maximum segmental counts expressed as a percentage. MIBG washout was defined as the percent change in activity within each segmental ROI from the acute to the delayed images and from acute to late images in patients in whom 4-hour imaging was performed. Thus, group comparisons of normalized ("absolute") MIBG distribution, heterogeneity of distribution (intragroup variability), and retention of MIBG (percent washout) were made for patients with cardiomyopathy and normals. In addition, ROIs were created over the activity distribution of the liver and the right upper lung in 13 patients with CM and 10 controls and the average I-123 MIBG counts/voxel for the liver and lung were calculated. With these data, comparisons were made of hepatic, pulmonary, and cardiac MIBG uptake between patients with CM and controls.

**Statistical Analysis**

Results are reported as the mean ± SD. Parametric analysis with Bartlett's test for equality of variances, the Student's *t* test, and Welch's approximation to the Student's *t* test was performed as indicated. *p* < 0.05 was considered statistically significant.

Interobserver reproducibility is presented as percent variability or the Pearson *r* value.

**Results**

**Plasma Catecholamines**

Eight of 16 patients with CM and 10 of 14 controls had plasma catecholamines measured. The mean plasma catecholamine concentration for the patients with CM was 226.5 ± 135.1 pg/ml compared with
229.0 ± 73.9 pg/ml for controls. Attempts to evaluate data by subgrouping the patients with CM into those with and without catecholamine data suggest that the patients with catecholamine values had slightly less abnormal MIBG images than those without. However, significant overlap between the groups clearly exists. The patients with CM were, therefore, analyzed as one group.

**Image Quality**

Initial attempts to perform comparisons between 15-minute and 4-hour images were abandoned in favor of 15–85-minute comparisons due to the poor image quality of the 4-hour images in the patients with CM. The degree of abnormality of these images was so severe that determination of endocardial and epicardial borders could not be made to allow ROI determination. Therefore, despite the fact that later images might have more accurately reflected intravascular accumulation of MIBG (as discussed below), complete data analysis was performed on intermediate (85-minute) images. These images had adequate resolution to allow reproducible quantification of MIBG distribution. All of the delayed and 4-hour images obtained from the controls were of adequate quality and good resolution. One control (excluded from data analysis) had inadvertently used an over-the-counter cold preparation 3 hours before imaging and, as has been previously reported, had almost no detectable myocardial MIBG uptake.

**Myocardial Concentration of MIBG**

At the time of acute (15-minute) imaging, there was no significant difference in myocardial MIBG concentration between the patients with CM and the controls. In the acute images from patients with CM, the average global LV MIBG activity was 117.0 ± 40.5 counts/voxel compared with 145.3 ± 36.8 counts/voxel in the controls (p = 0.06, NS). Segmental analysis of MIBG activity revealed a similar degree of difference independent of the region or section used. Statistical comparisons of the differences in activities between the patients with CM and controls for the apical and basal sections did achieve borderline statistical significance (Table 1).

The myocardial retention of MIBG activity from the time of acute to the delayed imaging in the patients with CM was significantly lower than in the controls (Figure 2). The net result of the reduced myocardial retention of MIBG was a marked difference in the concentration of MIBG between the patients with CM and controls at later imaging times (Figure 3). Data expressed as percent washout are presented in Table 2 and show statistically significant differences (p < 0.001) in washout independent of the tomographic section analyzed. In the subset of patients evaluated at the 4-hour imaging time, the degree of difference in washout appeared to be even greater, although the small number of patients evaluated precluded statistical comparisons.

### Table 1. Myocardial MIBG Concentrations

<table>
<thead>
<tr>
<th></th>
<th>15 min</th>
<th>85 min</th>
<th>4 hr</th>
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<tbody>
<tr>
<td><strong>Global</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td>117.0 ± 40.5</td>
<td>85.1 ± 35.4</td>
<td>51.8 ± 14.0</td>
</tr>
<tr>
<td>Controls</td>
<td>145.3 ± 36.8</td>
<td>140.2 ± 35.3</td>
<td>116.6 ± 35.6</td>
</tr>
<tr>
<td>p</td>
<td>0.06</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Vertical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td>114.7 ± 43.8</td>
<td>83.8 ± 37.2</td>
<td>54.5 ± 17.4</td>
</tr>
<tr>
<td>Controls</td>
<td>137.7 ± 54.0</td>
<td>138.6 ± 37.0</td>
<td>115.5 ± 32.2</td>
</tr>
<tr>
<td>p</td>
<td>0.2</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Apical</strong></td>
<td></td>
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</tr>
<tr>
<td>CM</td>
<td>120.1 ± 42.0</td>
<td>86.6 ± 37.4</td>
<td>44.8 ± 18.5</td>
</tr>
<tr>
<td>Controls</td>
<td>156.4 ± 42.5</td>
<td>142.8 ± 37.6</td>
<td>113.0 ± 34.7</td>
</tr>
<tr>
<td>p</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Basal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td>121.8 ± 38.0</td>
<td>89.9 ± 33.0</td>
<td>59.6 ± 10.7</td>
</tr>
<tr>
<td>Controls</td>
<td>148.9 ± 31.2</td>
<td>135.9 ± 32.7</td>
<td>120.8 ± 34.7</td>
</tr>
<tr>
<td>p</td>
<td>0.04</td>
<td>&lt;0.001</td>
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</tbody>
</table>

MIBG, metaiodobenzylguanidine; CM, patients with cardiomyopathy; global, average left ventricular MIBG activity over all 12 regions of interest; vertical, average MIBG activity from four regions of interest in vertical long-axis sections; apical, average MIBG activity from four regions of interest in apical short-axis sections; basal, average MIBG activity from four regions of interest in basal short-axis sections.

Compared with controls, the patients with CM demonstrated significantly greater intravenous heterogeneity of the myocardial MIBG activity (Figure 4). Statistically significant intravenous variability was present at the time of acute imaging and was even more pronounced by the time of delayed imaging (Table 3). This finding was apparent regardless of the tomographic section analyzed.

**Liver and Lung Uptake**

Comparison of MIBG concentrations in liver and lung tissues at the time of delayed imaging revealed no significant differences between the patients with CM and controls. The average MIBG activity in the liver was 210.9 ± 97.8 counts/voxel in the patients with CM and 202.5 ± 90.8 counts/voxel in the controls (p = 0.8, NS). Similar comparisons of lung activity in the patients with CM and controls demonstrated 102.0 ± 32.9 and 89.1 ± 27.1 counts/voxel, respectively (p = 0.3, NS).

**Interobserver Variability**

Interobserver variability determinations were made in a blinded manner by two independent observers. The interobserver correlation was represented by r = 0.90 (p < 0.001) with a regression line of y = 0.325 ± 0.88x.

**Consequences of MIBG Administration**

There were no adverse effects noted after intravenous injection of MIBG. Specifically, there were no changes in resting heart rates, respiratory rates,
or blood pressures. The administration of Lugol's solution resulted in near-complete suppression of thyroid uptake of radioactivity in all subjects.

**Discussion**

Abnormalities of myocardial sympathetic innervation in patients with dilated congestive CM have been appreciated for some time.\(^8\)\(^-\)\(^10\) Unfortunately, a noninvasive method to detect and characterize these abnormalities has not been described. Early studies with MIBG have suggested the potential of this radiopharmaceutical as a myocardial imaging agent with kinetic and distribution properties that might reflect the integrity of myocardial sympathetic innervation.\(^5\) Myocardial norepinephrine kinetics involve three major compartments: transport into the neuronal axoplasm, transport into the terminal storage vesicles, and transport in the extraneuronal myocardial tissues.\(^18\)\(^,\)\(^19\) MIBG has been found to share the same uptake and storage mechanisms as NE,\(^14\)\(^,\)\(^21\) although with dissimilar proportions of distribution in the various compartments. Specifically, in studies with rat myocardium, a greater proportion of MIBG appears to accumulate in extraneuronal tissues.\(^21\) Studies in humans confirm the predominantly extravascular accumulation of MIBG in the early hours after injection.\(^22\) The results of this study demonstrate that the myocardial distribution and washout of MIBG activity in controls differ significantly from the distribution and washout in patients with severe, nonischemic, dilated CM. Specifically, although the initial uptake of MIBG by CM myocardium does not appear to be dramatically different from uptake by normal myocardium, the retention of the MIBG within the myocardium is significantly different. In addition, the distribution of MIBG within the myocardium is significantly more "patchy" or heterogeneous in the patients with CM. The uptake of MIBG in organs other than the heart (specifically, liver and lung) is not significantly different in patients with CM and controls, reflecting the fact that disruption of sympathetic innervation in patients with CM may be localized to the myocardium.

**Plasma Catecholamines**

Analysis of the subset of patients with CM who had plasma catecholamine determinations revealed that this subgroup had less abnormality of MIBG uptake and distribution than the group as a whole, although there were individual patients in the group with MIBG abnormalities as severe as those found among the
Henderson et al 1-123 MIBG and Myocardial Adrenergic Derangement 1197

TABLE 2. Percent Washout of MIBG

<table>
<thead>
<tr>
<th></th>
<th>Vertical</th>
<th>Apical</th>
<th>Basal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM</td>
<td>0.28±0.12</td>
<td>0.29±0.13</td>
<td>0.27±0.12</td>
</tr>
<tr>
<td>Controls</td>
<td>0.06±0.08</td>
<td>0.08±0.08</td>
<td>0.08±0.07</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</table>

Percent washout from 15 minutes to 4 hours

<table>
<thead>
<tr>
<th></th>
<th>Vertical</th>
<th>Apical</th>
<th>Basal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM (n=14)</td>
<td>0.44±0.07</td>
<td>0.59±0.10</td>
<td>0.41±0.07</td>
</tr>
<tr>
<td>Controls (n=4)</td>
<td>0.12±0.15</td>
<td>0.16±0.12</td>
<td>0.16±0.14</td>
</tr>
</tbody>
</table>

MIBG, metaiodobenzylguanidine; CM, cardiomyopathy; vertical, percent washout of MIBG from acute to delayed imaging in the vertical long-axis sections; apical, percent washout of MIBG from acute to delayed imaging in the apical short-axis sections; basal, percent washout of MIBG from acute to delayed imaging in the basal short-axis sections.

patients with CM without plasma catecholamine determinations. It is possible that the remaining patients with CM had elevated plasma catecholamines. Thus, a potential role for competitive inhibition of MIBG uptake by elevated catecholamines cannot be fully assessed in this study, but the MIBG abnormalities we have identified are not solely the result of markedly elevated plasma catecholamine concentrations. Other investigators have also noted abnormalities of MIBG uptake with no correlation between plasma catecholamine levels and MIBG uptake.23

MIBG Uptake

Comparison of initial myocardial uptake of MIBG between patients with CM and controls demonstrated essentially no differences (Table 1). Increased extraction of MIBG by noncardiac tissues (i.e., lung and liver) was not demonstrated, and initial delivery of MIBG to the myocardium was apparently similar in the two groups. The initial similar concentrations argue that the marked disparity in concentration seen in late images is not explained by increased attenuation or scatter secondary to body habitus or the size of the ventricular blood pool and is not explained by different “input functions” or delivery of the radiolabel.

MIBG Washout

Patients with CM in this study demonstrated substantially reduced myocardial MIBG retention at the

FIGURE 4. Images of vertical long-axis (VERT), apical short-axis (ASA), and basal short-axis (BSA) sections from two of the cardiomyopathy (CM) patients depicting the patchy, heterogeneous pattern of MIBG distribution noted in the CM group. Images on the left had approximately 25% intraimage variability; images on the right had approximately 40% intraimage variability.
If there are fewer neurons to accumulate MIBG, it follows that a larger proportion of the MIBG would remain extraneuronal and, thus, demonstrate faster efflux from the myocardium.

Finally, in the Syrian hamster model of congestive CM, NE release and turnover appears to be accelerated.27 Faster washout of MIBG could, therefore, be attributable to increased release of MIBG from adrenergic neurons of patients with CM, which may function with accelerated NE release rates compared with controls.

### Intrame Image Heterogeneity

The MIBG images obtained from patients with CM demonstrated a more heterogeneous or patchy distribution of MIBG activity when compared with images from controls (Table 3). This abnormality was noted in the 15-minute, 85-minute, and 4-hour images. The degree of heterogeneity appeared to be greater with later imaging times, however. The enlarged cardiac blood pool may contribute to the heterogeneous appearance of the CM images but could not account for the apparent increase in heterogeneity from 15 to 85 minutes. As discussed previously, more of the MIBG should be intravesicular at 85 minutes than at 15 minutes. Focal attribution of adrenergic neurons could add to the inhomogeneity of MIBG in the CM images.13 Further, interstitial scar or fibrosis has been noted in necropsy specimens from patients with idiopathic CM.28 Any or all of these alterations may be involved in producing the intrame image heterogeneity that further distinguishes the CM MIBG images from the images obtained from controls.

This study of myocardial imaging with I-123 MIBG in controls and patients with CM represents an attempt to noninvasively characterize the abnormalities of myocardial adrenergic innervation occurring in patients with severe congestive CM. The principle findings in this study (reduced myocardial retention of MIBG and more patchy or heterogeneous distribution of MIBG activity) may be explained based on current understanding of the sympathetic nervous system in patients with CM and the mechanisms of MIBG uptake by the heart.

Although we have no information regarding the prognostic value of myocardial MIBG imaging in patients with CM, the potential for using MIBG as a prognostic indicator should be investigated. Cohn et al29 were able to correlate plasma catecholamine levels with the risk of death, but the severity of myocardial adrenergic dysfunction has not been directly linked to the risk of morbidity or mortality in patients with CM.

In conclusion, this study with myocardial scintigraphy with I-123 MIBG demonstrates that images from patients with congestive CM differ significantly from images obtained from controls. The major areas of difference are that there is faster washout of MIBG from the myocardium of patients with CM and that patients with CM have more

### TABLE 3. Percent Intrame Image Variability in MIBG Distribution

<table>
<thead>
<tr>
<th>Time after MIBG administration</th>
<th>Vertical</th>
<th>Apical</th>
<th>Basal</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>CM</td>
<td>Controls</td>
<td>$p$</td>
</tr>
<tr>
<td>0.38 ± 0.16</td>
<td>0.24 ± 0.10</td>
<td>0.007</td>
<td></td>
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<tr>
<td>0.47 ± 0.15</td>
<td>0.22 ± 0.09</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>0.39 ± 0.12</td>
<td>0.26 ± 0.13</td>
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<td></td>
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<tr>
<td>85 min</td>
<td>CM</td>
<td>Controls</td>
<td>$p$</td>
</tr>
<tr>
<td>0.26 ± 0.09</td>
<td>0.15 ± 0.08</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>0.33 ± 0.16</td>
<td>0.16 ± 0.07</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>0.34 ± 0.23</td>
<td>0.19 ± 0.09</td>
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</tr>
<tr>
<td>4 hour</td>
<td>CM</td>
<td>Controls</td>
<td>$p$</td>
</tr>
<tr>
<td>0.31 ± 0.14</td>
<td>0.23 ± 0.07</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>0.43 ± 0.18</td>
<td>0.21 ± 0.05</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>0.45 ± 0.27</td>
<td>0.22 ± 0.06</td>
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MIBG, metaiodobenzylguanidine; CM, cardiomyopathy; vertical, maximum percent variation among the four regions of interest in the vertical long-axis sections; apical, maximum percent variation among the four regions of interest in the apical short-axis sections; basal, maximum percent variation among the four regions of interest in the basal short-axis sections.

The 4-hour washout is reflect to be even more dramatic at later imaging times based on the subset of patients imaged at 4 hours.

Possible explanations of the increased MIBG washout are evident based on current understanding of NE and MIBG kinetics in normal and failing hearts. Although MIBG and NE share common uptake and storage mechanisms,14-21 a larger proportion of MIBG appears to remain in extraneuronal tissues with approximately 20% of the MIBG appearing intravesicularly at 1 hour after administration and a plateau of 50% of the MIBG intravesicularly at 4 hours after administration.21 Our imaging times of 85 minutes and 4 hours reflect the differences in myocardial retention of MIBG between patients with CM and controls at a time when between 20% and 50% of the myocardial MIBG would be expected to be inside the neuronal vesicle in the normal heart. An additional uncertain amount of myocardial MIBG would be inside the neuronal axoplasm but outside the storage vesicles. If, in fact, the energy-requiring processes of MIBG transfer across the neuronal membrane into the axoplasm and from the axoplasm into the storage vesicle are perturbed in patients with CM, an even larger percentage of MIBG may remain extraneuronal at 85 minutes or 4 hours in those patients. Experimental studies suggest that NE efflux from extravesicular sites is more rapid than from intraneuronal sites and that MIBG is also more firmly bound inside NE storage vesicles than outside.21-24,26 Therefore, a larger proportion of extraneuronal MIBG in the patients with CM might account for the appearance of more rapid washout of MIBG in this group.

Another possible explanation for a larger extraneuronal accumulation of MIBG in the patients with CM is the finding that cardiomyopathic myocardium tends to have a reduced number of sympathetic neurons.11

time of delayed imaging (Table 2). This finding appears to be even more dramatic at later imaging times based on the subset of patients imaged at 4 hours.
heterogeneous or patchy uptake of MIBG. Thus, this approach provides a relatively noninvasive scintigraphic means to evaluate the severity of alterations in adrenergic innervation in the hearts of patients with dilated CM. The ability of myocardial scintigraphy with MIBG to stratify patients with LV dysfunction according to severity of disease and risk for future serious complications of CM remain to be determined.

References

KEY WORDS • myocardial adrenergic derangement • I-123 metaiodobenzylguanidine • cardiomyopathy • norepinephrine
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