Scintigraphic Assessment of MIBG Uptake in Globally Denervated Human and Canine Hearts—Implications for Clinical Studies

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To further characterize the behavior of metaiodobenzylguanidine (MIBG) in the myocardium and to test the hypothesis that the denervated heart would show normal early uptake on MIBG due to non-neuronal localization, we examined the early and late distribution of ^{123}I-labeled MIBG in normal and globally denervated canine and human hearts. Canine hearts were denervated by intravenous injections of 6-hydroxydopamine, while patients were studied a mean of 4.3 mo following cardiac transplantation. Results in denervated hearts were compared to normal controls. Normal hearts showed prominent MIBG uptake on initial 5-min and 3-hr delayed images. Globally denervated canine hearts showed prominent uptake on initial images and absence of localization on delayed images, indicating complete washout of non-neuronally bound radionuclide. The transplanted human hearts showed no localization of MIBG on either early or delayed images. These results suggest that the non-neuronal uptake mechanism (uptake 2) is not significant in human myocardium. This finding has significant implications for interpreting the myocardial behavior of MIBG in various pathologic situations such as *dilated* cardiomyopathy.

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Numerous experimental studies have shown that radiolabeled norepinephrine is taken up by neuronal and nonneuronal sites in the heart (*1*). The rate of efflux of norepinephrine is more rapid from nonneuronal sites than from neuronal sites (*2*). Recent studies have shown that radioiodinated metaiodobenzylguanidine (MIBG) is taken up by myocardial sympathetic nerves, and behaves in a manner that is qualitatively similar to norepinephrine, although quantitative differences do exist (*3–5*). MIBG uptake has been evaluated in the myocardium of patients with adrenergic dysfunction (*6–10*), and the results have been interpreted based on findings in experimental preparations. Nonneuronal localization of MIBG has been assumed to occur in human myocardium, however, no studies have been done in humans to test this hypothesis. To further characterize the behavior of MIBG in the myocardium, we examined the early and late distribution of MIBG in normal and globally denervated human hearts and compared the results to the findings in normal and globally denervated canine hearts.

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METHODS

Preparation of MIBG

Unlabeled MIBG was obtained from the University of Michigan (D. Wieland) and radioiodinated by solid-phase ammonium sulfate exchange as previously described (*5*).

Dog Studies

Study Population. Studies were performed on 15 conditioned adult mongrel dogs that weighed 8–20 kg. Six dogs underwent imaging with ^{133}I-MIBG during the baseline state. Two of these six dogs, and an additional nine dogs were imaged 1 wk after the administration of 6 hydroxydopamine. Seven of these nine dogs were reimaged after receiving chronic immunosuppression for 1 wk following the initial post-6-hydroxydopamine study (see below). Six-hydroxydopamine causes a chemical sympathectomy (*11*).

Imaging Protocol. The animals were anesthetized with pentobarbital, intubated, and ventilated with a Harvard respirator. Four to six millicuries (150–225 MBq) of [^{123}I]MIBG were injected intravenously, followed by the acquisition of 5-min planar images in the anterior, 40° and 70° left anterior oblique projections obtained 5 min after injection. A Siemens LEM portable gamma camera, fitted with a 20° slant-hole collimator and interfaced to an IBM PC-XT based portable computer acquisition system (Harpootlian Associates, Los Altos, CA) was used. The energy window was set at the 159 keV photopeak of ^{123}I. Three hours after injection of MIBG, the planar images were repeated.

Following imaging at baseline, four animals were killed with an injection of saturated potassium chloride, and the hearts were rapidly excised, biopsied and analyzed for norepinephrine content. The remaining 11 animals were treated with 6-hydroxydopamine (see below).

Hydroxydopamine Treatment. The dogs were treated accord-

ing to the method of Burks et al. (*12*). The animals were injected intravenously with 4 mg/kg of phentolamine followed by 1 mg/kg of propranolol. The dogs were then injected with 50 mg/kg of 6-hydroxydopamine, and allowed to recover. One week following 6-hydroxydopamine treatment, the animals were imaged as outlined above, then four were killed for analysis of tissue norepinephrine content. Seven were subsequently treated with immunosuppression to assess its possible effects on MIBG localization in dogs denervated by 6-hydroxydopamine.

Immunosuppression Treatment. Following the imaging studies done 1 wk after 6-hydroxydopamine treatment, seven dogs were treated orally with cyclosporin (100 mg BID) and prednisone (5 mg BID) for 1 wk. Three of the seven also received azathioprine (25 mg BID). The cyclosporin dose that was used has been previously reported to provide therapeutic effects in dogs (*13*). The doses of prednisone and azathioprine were chosen to approximate patient doses. Following immunosuppressive therapy, the animals were imaged as outlined above, and five were killed for analysis of tissue norepinephrine content.

Norepinephrine Content Analysis. Biopsy samples were weighed, and stored in 2 ml of 0.1 N perchloric acid at −70 C, until analyzed. Just prior to analysis, the tissue was homogenized in a polytron, and the supernatant was analyzed by high-pressure liquid chromotography (HPLC) (SmithKline Bio-Science Laboratories, Van Nuys, CA). Norepinephrine content values were compared between normal (n = 4) and treated (n = 9) dogs using an unpaired t-test.

Human Studies

Patient Population. Imaging with [^{123}I]MIBG was performed in five normal paid volunteers and 10 patients following cardiac transplantation as part of a research protocol approved by the Committee on Human Research. The normal volunteers had a mean age of 28 yr (range 25–32), were in good health and were not taking any medication. The patients were studied a mean of 4.4 ± 0.6 mo after cardiac transplantation. All patients were male, with a mean age of 49 ± 10.7 yr. The mean left ventricular ejection fraction (LVEF) was 55.6% ± 10.6% by radionuclide angiography. There was no evidence of ischemia on exercise thallium scintigraphy and the coronary arteries were normal at angiography, which were done as part of the clinical evaluation. Nine of ten patients showed no evidence of rejection at the time of MIBG imaging, while one patient showed moderate rejection on biopsy. Biopsies and other studies were obtained within 3 wk of the MIBG studies. Patients were taking the following medications: cyclosporin, azathioprine, prednisone, ranitidine, verapamil (2), nifedipine (2), and diltiazem (4).

Imaging Protocol. The normals were imaged in a manner similar to the dog protocol. Six to eight millicuries (225–300 MBq) of [^{123}I]MIBG were injected intravenously and 5-min planar images were acquired in three projections at 5 min and 3 hr after injection.

The first transplant patient was imaged in a similar manner. However, the 5-min image showed no myocardial localization of MIBG compared to background. The remaining nine patients underwent serial dynamic imaging at 30-sec intervals commencing just prior to injection of MIBG, and continuing for 15 min. In addition 5-min static images were taken at 5, 10, and 15 min, and 3 hr after injection.

Image Quantitation. To quantitate the degree of myocardial and lung uptake of MIBG, ratios of myocardial-to-mediastinal and lung-to-mediastinal uptake were measured. Myocardial-to-mediastinal uptake has been used by others to quantitate MIBG uptake (*9*).

To define the region of the heart in the transplant patients, regions of interest (ROIs) were drawn loosely around the blood-pool image of the left ventricle from the initial flow study and used to define the left ventricle on the 15-min image, after the blood pool had cleared. Care was taken to exclude lung or liver from these regions.

ROIs were also placed over the left lung and the mediastinum. Counts per pixel were measured for each region (heart, lung, mediastinum). Heart-to-mediastinum and lung-to-mediastinum ratios were computed for normals and patients. Values between normals and patients were compared using an unpaired t-test.

RESULTS

Dog Studies

The early and 3-hr delayed images showed good myocardial localization in all dogs studied at baseline (Fig. 1). The findings were different after treatment with 6-hydroxydopamine. While the initial images again showed good myocardial localization, the delayed images failed to show any evidence of myocardial localization (Fig. 1). Tissue norepinephrine content in the normal dogs was 935 ± 248 ng/gm, as opposed to 57 ± 76 ng/gm in dogs treated with 6-hydroxy dopamine ($p < 0.01$). This decrease in tissue norepinephrine is consistent with denervation. The image findings and tissue norepinephrine contents were similar in denervated dogs that were treated with immunosuppression (Fig. 2). The initial uptake of MIBG was not diminished by immunosuppression. Also, the large degree of washout between the early and delayed images again occurred.

Human Studies

All of the normals showed good myocardial localization of MIBG on the early images (Fig. 3) and on the delayed images (Fig. 4). None of the transplanted hearts however,

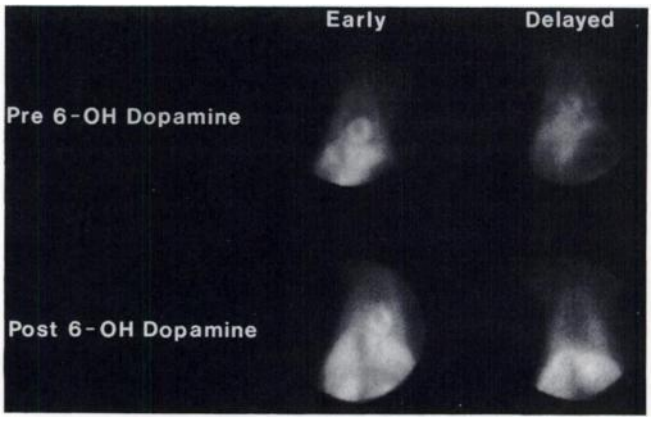

FIGURE 1. Shown are early and delayed MIBG images in a dog studied at baseline (above) and 1 wk after 6-hydroxydopamine treatment (below). There is prominent myocardial localization on both the early and delayed images at baseline. The post-6-hydroxydopamine images show prominent myocardial localization on the early images, whereas the delayed images show absence of myocardial localization.

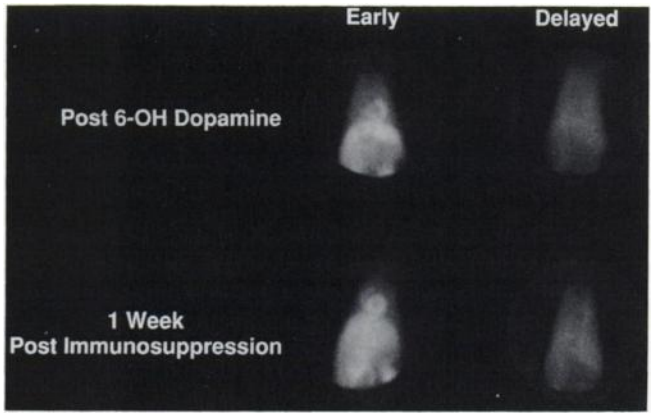

FIGURE 2. Early and delayed images in a dog studied 1 wk after 6-hydroxydopamine treatment (above) and 1 wk following subsequent immunosuppressive therapy (below). As noted in Figure 1, the post-6-hydroxydopamine image shows prominent myocardial uptake on the early image and major washout of MIBG on the delayed image. In the same dog studied 1 wk after cyclosporin, prednisone and azathioprine, the initial uptake of MIBG remains prominent. The delayed image again shows a major degree of washout of MIBG. The minor residual of MIBG on the delayed image may be consistent with an element of partial reinnervation. These images show no evidence of reduced initial uptake in the presence of immunosuppression therapy.

showed localization of MIBG on either the early or delayed images (Figs. 3 and 4). The salivary glands were included in the field of view in four patients. In each, salivary gland uptake was present (Fig. 3), indicating uptake of MIBG in an organ outside of the heart that is not denervated. The heart-to-mediastinal ratio was significantly greater in the normals in comparison to transplant patients (1.8 ± 0.08 versus 1.19 ± 0.09, $p < 0.0001$). Prominent pulmonary uptake was occasionally seen in the patients after transplantation (Figs. 3 and 4). However, there was no significant difference in the lung-to-mediastinal ratio between normals and patients (1.4 ± 0.13 versus 1.6 ± 0.21, $p = 0.27$).

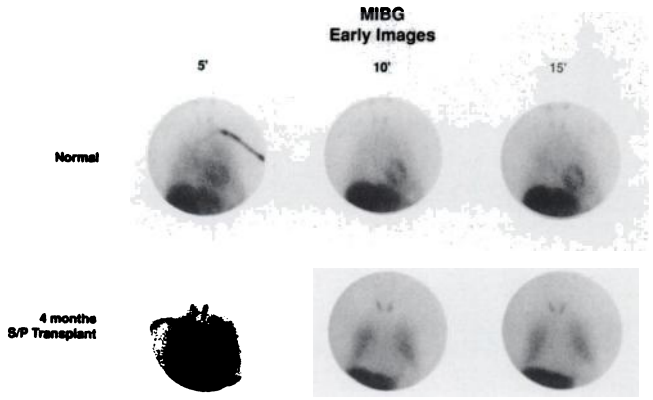

FIGURE 3. Five-minute static images taken at 5, 10, and 15 min after injection in a normal control (above) and a patient studied 4 mo after cardiac transplantation. After blood-pool clearance, there is absence of myocardial localization in the transplanted heart.

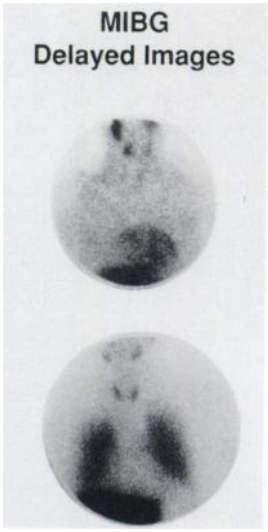

FIGURE 4. Three-hour delayed images are shown for a normal control and a patient with cardiac transplantation. There is persistence of myocardial activity in the normal heart, whereas the transplanted heart continues to show absence of MIBG uptake.

DISCUSSION

The ability of sympathetic nerve endings to take up exogenously administered catecholamines is well established. Axelrod (*14*) and Whitby (*15*) showed rapid accumulation of 3H-norepinephrine and 3H-epinephrine in heart, spleen and other peripheral tissues in cats and mice. Many subsequent reports have confirmed the existence of a high affinity, neuronal uptake mechanism, confined to postganglionic sympathetic nerves (uptake 1), and a low affinity, high capacity extraneuronal uptake mechanism (uptake 2) (*1*). Tracer amounts of injected radiolabeled catecholamines are largely distributed to neuronal sites, however, even at low concentrations, extraneuronal uptake has been shown to occur (*2*). Neuronally-bound catecholamines are generally retained for long periods of time, whereas, in the case of norepinephrine, the extraneuronal material is rapidly metabolized, and not retained (*2*).

Previous studies have demonstrated the affinity of radioiodinated MIBG, an analog of guanethidine, for the adrenal medullae and adrenergic nerves (*16*). Myocardial localization has been demonstrated with MIBG in several animal species and in man (*3*). MIBG is thought to share similar uptake and storage mechanisms as norepinephrine (*17*), but it is not metabolized by monoamine oxidase or catechol-o-methyl transferase (*3*). An additional uptake mechanism, involving passive neuronal uptake has been hypothesized for MIBG (see below).

Reserpine, which blocks the vesicular uptake of norepinephrine in adrenergic neurons, caused a marked decrease in canine myocardial concentration of MIBG (*16*). Nakajo et al. (*18*) found an inverse relationship between the accumulation of [^{131}I]MIBG in the heart and the plasma concentration of catecholamines, suggesting competitive uptake of MIBG by the heart and circulating catecholamines. Salivary gland uptake of MIBG was blocked by the administration of tricyclic antidepressants which are

known to inhibit neuronal uptake of norephinephrine (*19*).

Norepinephrine, guanethidine and MIBG are distributed to neuronal and non-neuronal compartments in the heart (*17*). Assessment of the neuronal distribution is facilitated by the fact that efflux from the nonneuronal compartment is more rapid than from the neuronal compartment. By 3 to 4 hr after injection of MIBG, the images obtained are thought to largely represent the neuronally bound radionuclide (*20*).

Sisson et al. (*4*) have hypothesized the presence of a passive type of neuronal uptake, unrelated to transport by the amine uptake pump. This conclusion was reached after experiments to assess the uptake of [^{125}I]MIBG in rat hearts showed a 69% reduction in MIBG uptake in 6-hydroxydopamine (neuron depleted) hearts (versus 88% for 3H-norepinephrine), as compared to a 50% reduction (versus 94% for 3H-norepinephrine) in hearts treated with desipramine (a potent uptake one inhibitor). They deduced that the difference (about 20%) between 6-hydroxydopamine and desipramine represented [^{125}I]MIBG that entered the neuronal sites by a route other than uptake one. The observations made by Sisson et al. (*4*) could also be explained by differing affinities of the uptake mechanism for MIBG and norepinephrine without invoking a unique uptake mechanism for MIBG. A recent study compared the uptake of MIBG versus norepinephrine in human SK-N-SH neuroblastoma cells, which have been shown to possess a "pure" uptake one mechanism (*21*). Iodine-125-MIBG was found to have a higher apparent affinity for uptake one than did 3H-norepinephrine. Although not yet demonstrated in peripheral sympathetic neurons, it is possible that higher doses of desipramine may be required to cause a comparable block of the neuronal uptake of MIBG compared to norepinephrine. The higher residual uptake of MIBG after desipramine may relate to incomplete blockage of the uptake one system.

A diffusion pathway has been described in adrenal medulla cells as a high-capacity, sodium-independent non-energy requiring process. This pathway has been shown to increase MIBG uptake in adrenal medulla cells; however, this occurs only at very high concentrations of MIBG that are not reached in vivo to the adrenals (*22*).

Further studies by Sisson et al. have shown that the rates of disappearance of MIBG show physiologic responses to interventions that either increase sympathetic nerve activity, i.e., feeding (*4*), yohimbine (*23*); or decrease sympathetic nerve activity, i.e., clonidine (*23*). Whether or not the diffusion pathway is active, the dominant responses of neuronally localized MIBG appear to reflect the functional activity of the adrenergic nerves in the heart (*23*).

Our results in globally denervated dog hearts are consistent with the results obtained in other species. The early localization of MIBG was normal, and probably represented non-neuronal localization. The efflux from the heart was near complete during the three hour interval, indicating an absence of neuronal retention. Low levels of cardiac norepinephrine confirm that these hearts were denervated.

The findings in the cardiac transplant patients were surprising. It was assumed that the denervated human heart would behave similarly to the denervated dog heart. However, there was no myocardial localization of MIBG on either the early or delayed images. The possibility was considered that the immunosuppressive therapy used to treat the patients after transplantation may be the cause of the absence of cardiac uptake. We found no effect of immunosuppression on the initial uptake of MIBG in denervated dog hearts. Hence, immunosuppression is not a likely explanation for the findings in the patients. Also, there is not likely to be any effect of the antihypertensive medications that some of the patients were taking. The findings were the same whether or not the patients were taking antihypertensives.

The possibility must be considered that high-circulating catecholamines may have caused the absence of cardiac uptake of MIBG as has been described in patients with pheochromocytoma (*18*). Plasma catecholamines were not measured in this study; however, other studies have shown normalization of serum catecholamine levels in patients after transplantation (*24*). Hence, there is no reason to believe that plasma catecholamines were elevated in our patients. Schofer et al. (*9*) found that the increased plasma catecholamine levels in patients with heart failure did not significantly influence myocardial MIBG uptake.

Our findings suggest that the non-neuronal uptake mechanism is not significant in human hearts. Other studies have suggested that the uptake 2 mechanism is not significant in humans. Probably the most compelling evidence comes from the work of Carr et al. (*25*). They found significant uptake of ^{125}I-O-iodobenzyltrimethylammonium iodide (RIBA), a radioiodinated analog of bretylium, by the myocardium of the intact rat and dog. Localization of RIBA occurs by the uptake 2 mechanism (*25*). Interestingly, however, no myocardial uptake of RIBA was observed in the hearts of primates or humans.

Esler et al. (*26*) found that the selective extraneuronal norepinephrine uptake blocker, cortisol, had no effect in normal subjects on the plasma clearance of tritiated norepinephrine. Thus, they could not demonstrate the existence of extraneuronal uptake of norepinephrine in humans. Glowniak et al. (*27*) reported absence of MIBG uptake in four patients after cardiac transplantation; however, the imaging was done 1 hr after injection, which did not allow assessment of the initial distribution of MIBG.

We have further evidence to support the view that nonneuronal uptake is not significant in humans. We have assessed MIBG uptake in two patients that underwent regional sympathetic denervation (left stellectomy for long QT syndrome). Both patients showed a comparable decrease in MIBG uptake in the posterior left ventricle on the early and delayed MIBG images. Neither patient took

corticosteroid or antihypertensive therapy. We have also studied MIBG uptake and washout in dog hearts that were regionally denervated by either left or right stellectomy, or epicardial phenol application (*28*). As in the globally denervated dog hearts, the early images were homogeneous, whereas the late images showed regional defects in MIBG localization due to greater washout in the denerevated region. These findings in human and canine hearts, regionally denervated by similar surgical techniques, parallel our findings in globally denervated human and canine hearts, and add further support to our conclusions.

Lung Uptake

Although the transplant patients showed a trend towards increased lung uptake, there was no significant difference in lung-to-mediastinal ratios between patients and normals. The lungs do extract catecholamines from the circulation (*29*) and have been shown to extract MBIG (*30*). Glowniak et al. (*27*) also found a trend towards increased lung uptake in transplanted patients and suggested that the mechanism may relate to increased pulmonary artery pressure or persistent effects of prior elevations in pressure on pulmonary endothelial cells in the transplanted patients.

Implications for MIBG studies in Human Myocardium

Studies of MIBG distribution and kinetics have recently been reported in patients with dilated cardiomyopathy (*8,9*). Henderson et al. (*8*) studied 16 patients with severe dilated cardiomyopathy and 14 healthy volunteers. Tomographic images were obtained 15 min (initial), and 85 min (delayed) after injection of [^{123}I]MIBG. There were no significant differences in MIBG concentrations on the initial images between the hearts of patients with dilated cardiomyopathy and controls. Myocardial retention of MIBG was significantly reduced in the patients with cardiomyopathy on the delayed images, however. These results are similar to our findings in denervated dog hearts and could be interpreted as indicating denervation with enhanced washout of nonneuronal MIBG. This mechanism was also proposed by Nakajo et al. to explain the normal initial uptake but enhanced washout of MIBG from the hearts of three patients with autonomic insufficiency (Shy Drager Syndrome in two, multiple system atrophy in one) (*6*).

Our results in the transplanted human hearts, however, would suggest that the initial normal distribution of MIBG in patients with cardiomyopathy is consistent with the presence of intact sympathetic nerves and not with denervation. Numerous studies have shown decreased myocardial content of norepinephrine in experimental animals (*31*) and patients with heart failure (*32*). Although the cause of the norepinephrine depletion may relate to denervation and decreased number of sympathetic nerve endings (*31*), a number of other factors are also possible etiologies, including impaired neuronal uptake (*31,32*), decreased synthesis of norepinephrine (*33*) or excessive release of norepinephrine (*34*).

It is not inconceivable that patients with congestive heart failure can show decreased myocardial norepinephrine contents, but preserved capacity to take up labeled catecholamines by myocardial sympathetic nerves. The synthesis of norepinephrine and the uptake process involve different mechanisms (*35*). Eighty percent of the myocardial norepinephrine content is synthesized within the heart itself and not recaptured (*35*). In experimental studies by Tyce et al., where dog hearts were surgically denervated, the ability to take up 3H-norepinephrine recovered while the tissue levels of norepinephrine remained at markedly reduced levels (*36*).

Whether the failing human heart is denervated or not remains controversial. Our findings in the transplanted human heart suggest that the denervated human heart does not take up MIBG. This observation may help sort out some of the mechanisms related to abnormalities in the sympathetic nervous system in heart failure.

The enhanced washout of MIBG described by Henderson would be most consistent with increased sympathetic nerve activity, resulting in enhanced release of MIBG. Increased spillover of norepinephrine from the heart has been demonstrated in patients with congestive heart failure, consistent with increased sympathetic nerve activity (*34,37*). The cause of increased spillover of norepinephrine was thought due to increased sympathetic discharge, as opposed to impaired neuronal uptake due to the fact that the extraction fraction of tritiated norepinephrine was normal (*37*). Increased release of norepinephrine from the heart to plasma has also been reported in essential hypertension, and cirrhosis (*38*).

An alternative explanation for the findings of normal initial uptake and rapid washout of MIBG observed by Henderson et al. is that the MIBG was localized by passive diffusion into the neurons, according to the mechanism proposed by Sisson et al. (*4*). The presence of neuronal uptake by passive diffusion still implies the presence of intact neurons however. This is not inconsistent with our suggestions. As noted earlier, MIBG localized to sympathetic nerves predominantly shows physiologic responses to stimuli that either increase or decrease sympathetic nerve activity. It is difficult to envision neurons that are intact morphologically, but have no ability to take up catecholamines by the uptake one mechanism, in the absence of active inhibition of the uptake pump. As previously noted, the uptake one property appears to be one of the most sensitive indicators of functioning sympathetic nerves and appears to be a more robust property than is the synthesis of norepinephrine (*36*).

Others have reported reduced neuronal uptake and release of norepinephrine in patients with congestive heart failure, and have suggested that the myocardial sympathetic nerves are not activated in heart failure (*39*). Our observations in transplanted human hearts, and the observations of Henderson et al., favor the view that neuronal uptake is preserved, and that neuronal release is enhanced.

Further studies are needed to resolve these conflicting views.

It is difficult to attribute the finding of enhanced washout of MIBG in the patients with autonomic insufficiency studied by Nakajo et al. to increased nerve activity (*6*). The peripheral sympathetic nervous system, however, is relatively intact in this disorder, and the deficit is thought to be due to a lack of activation by the central nervous system (*40*). This suggests that the initial normal localization of MIBG in the patients studied by Nakajo represented neuronal localization. The mechanism leading to rapid washout of MIBG remains to be explained.

Optimum Time of MIBG Imaging in Patients

It would appear that to evaluate the dynamic behavior of myocardial sympathetic nerve activity, early and delayed images of MIBG distribution are necessary. In situations where the goal is the detection of regionally denervated myocardium, as has been reported after myocardial infarction (*10*), early imaging after injection of MIBG alone may suffice. Due to the absence of non-neuronal uptake in human myocardium, it would be expected that the denervated regions will not accumulate MIBG. Imaging immediately after injection may facilitate simultaneous comparisons of myocardial perfusion using dual-isotope acquisition techniques (*5*).

CONCLUSION

We have demonstrated a significant species difference in the myocardial localization of MIBG. As opposed to the clearly established extraneuronal uptake in the hearts of some animals species, there appears to be insignificant extraneuronal uptake in the human heart. This finding has significant implications for the interpretation of the behavior of MIBG in various pathologic situations in human myocardium.

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FIRST IMPRESSIONS

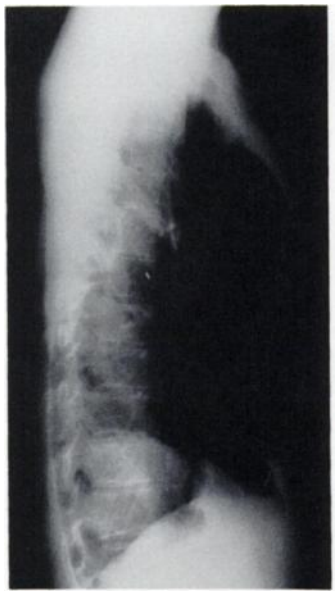

Figure 1

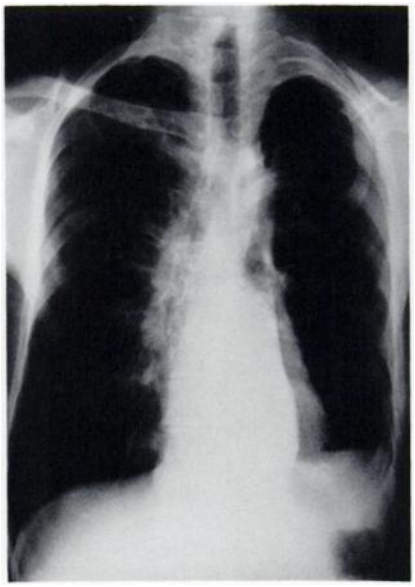

Figure 2

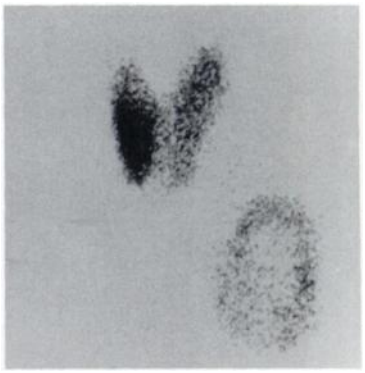

Figure 3

PURPOSE
This 46-yr-old man had had an esophageal resection at age 10 mo for atresta. The missing left clavicle, distorted diaphragm and surgical clips are residual evidence of the surgery. The pertechnetate scan (Fig. 3) reveals uptake in the stomach and asymmetric activity in the thyroid.

TRACER
^{99m}Tc-RBCs

ROUTE OF ADMINISTRATION
Intravenously

TIME AFTER INJECTION
5, 10, 15, 30, 60, 140, 180 min and 9 hr postinjection

INSTRUMENTATION
Gamma camera (Elscint)

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