INVESTIGATIVE NUCLEAR MEDICINE

Inverse Relationship Between Cardiac Accumulation of Meta-[^{131}I]Iodobenzylguanidine (I-131 MIBG) and Circulating Catecholamines in Suspected Pheochromocytoma

M. Nakajo, B. Shapiro, J. Glowniak, J. C. Sisson, and W. H. Beierwaltes

University of Michigan, Ann Arbor, Michigan

Heart intensity (HI) in the 24- and 48-hr images of meta-[^{131}I]iodobenzylguanidine (I-131 MIBG), a pheochromocytoma-seeking guanethidine analog, were compared with concentrations of plasma and urinary catecholamines and their metabolites in nonpheochromocytoma and pheochromocytoma patients. HI was inversely related to plasma concentrations and urinary excretion rates of the hormones. Plasma norepinephrine had the highest inverse correlation with HI ($r = -0.73$ at 24 hr, -0.63 at 48 hr), and urinary metanephrine the lowest ($r = -0.23$ at 24 hr, -0.28 at 48 hr). A similar relationship was observed in the intensity of salivary-gland visualization, but with less marked variations. HI was much higher in nonpheochromocytoma patients than in pheochromocytoma patients. HI in an I-131 MIBG image provides useful information in the diagnosis of pheochromocytoma, and may provide a tool for the study of the influence of catecholamines on the heart.

J Nucl Med 24: 1127–1134, 1983

Meta-[^{131}I]iodobenzylguanidine (I-131 MIBG) is a radiolabeled analog of guanethidine, an adrenergic blocking agent (*1*). A series of animal studies have established the affinity of radioiodinated MIBG for the adrenal medullae and the adrenergic nerves, suggesting its value as a diagnostic agent for pheochromocytoma in man (*1–3*). Clinical usefulness of I-131 MIBG has been verified by visualization of pheochromocytoma and adrenal medullary hyperplasia (*4,5*). Iodine 123 MIBG was also used to scintigraph the heart in man, presumably through its concentration in adrenergic nerves of the myocardium (*6*). MIBG is thought to share uptake and storage mechanisms with norepinephrine (*2*).

It was hypothesized that prevailing levels of catecholamines in plasma might influence I-131 MIBG uptake by the heart through a number of mechanisms including: tracer dilution, competition for uptake pathway, and down regulation of the uptake pathway. The uptake of I-131 MIBG by the salivary glands has been shown to depend on intact sympathetic innervation (*7*). Both the salivary glands and heart have abundant adrenergic innervation.

Our initial study on scintigraphic distribution of I-131 MIBG in the images of patients suspected of having pheochromocytomas revealed differences in intensity of the heart images. The cardiac intensity appeared inversely related to the catecholamine values in plasma and urine of the patients (*8*). This observation prompted us to carry out additional studies, including an examination of the influence of norepinephrine and epinephrine concentrations in plasma and the urinary excretion rates of catecholamines and their metabolites on cardiac I-131 MIBG uptake. We report an inverse relationship between heart intensity and hormonal concentrations in plasma and urine. The heart intensity was also related to the presence of pheochromocytoma as a cause of elevated catecholamine levels.

Received Apr. 11, 1983; revision accepted July 28, 1983.

For reprints contact: Dr. B. Shapiro, Div. of Nucl. Med., University of Michigan Hospitals, Ann Arbor, MI 48109.

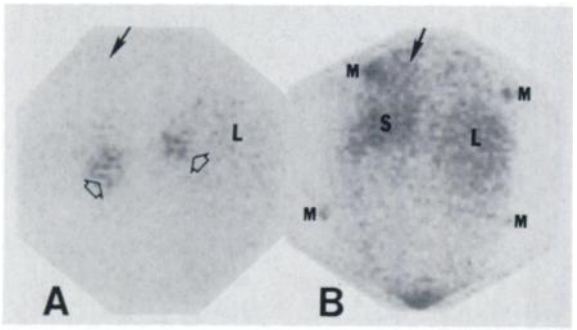

FIG. 1. Grades of cardiac uptake. Posterior chest/abdomen images 24 hr after injection of MIBG. A = Grade 0, B = Grade 1, C = Grade 2, D = Grade 3. Region of heart indicated by arrow; L = liver, S = spleen, M = surface markers.

MATERIALS AND METHODS

Patient population, image selection, and grading of heart intensity. We examined the I-131 MIBG posterior abdominal images from 168 patients (86 males, 82 females; ages 10 mo–78 yr) who were referred to the division of nuclear medicine between August 1980 and September 1982 for investigation of possible pheochromocytomas. In two cases images were repeated. The total number of pheochromocytoma patients was 29, providing seven benign intraadrenal tumors, seven benign extraadrenal, and 15 malignant metastatic tumors. The high proportion of cases with extra-adrenal and metastatic disease reflects the number of these difficult cases referred for study by I-131 MIBG scintigraphy, not the usual incidence of such lesions. Malignancy was defined as the presence of pheochromocytoma deposits in sites where chromaffin tissue does not normally occur. The methods of obtaining images were reported in detail previously (*4*). Briefly, images of the head, neck, thorax, and abdomen were obtained—using a wide-field-of-view gamma camera with a high-energy, parallel-hole collimator interfaced to a dedicated minicomputer—at 24, 48, and in some cases 72 hr after the injection of either 0.5 mCi I-131 MIBG, or 0.5 mCi/1.7 m^2, whichever was smaller. The "posterior images"—which included the regions of the lower lung to mid-abdomen, including the region of the heart—were examined. The numbers of images available were 102 at 24 hr and 148 at 48 hr.

Heart intensity was rated independently by three observers (MN, BS, and JG) by means of a semiquantitative grading system using the following scale: Grade 0 (no visible intensity), Grade 1 (visible intensity less than that of left lobe of liver), Grade 2 (same intensity as that of left lobe of liver), and Grade 3 (same intensity as that of right lobe of liver) (Fig. 1).

The intensity of salivary images was graded by means of the following scale: Grade 0 (no visible intensity), Grade 1 (faint intensity above head background), Grade 2 (moderate intensity, clearly greater than head background), and Grade 3 (prominent intensity).

The agreement in grading among the three observers was good. Of the cases studied, we chose (a) those in which three observers agreed, and (b) those in which two observers agreed, but the third observer differed by only one grade. The final grade of intensity assigned was that chosen by two or more of the three observers. The series on which further correlation studies were performed then contained 85 cases (83%) at 24 hr and 125 cases (84%) at 48 hr; 17 cases at 24 hr and 23 cases at 48 hr were excluded because of disagreement among observers. Most interobserver disagreement was due to varied appreciation of the high background activity in lower lung fields of some patients.

Exclusion of cases due to drug use. Four patients who were taking alpha-methyldopa, which influences urinary hormonal values (*9*), were excluded from the comparative study. We also excluded two patients who were taking tricyclic antidepressants, which might prevent the I-131 MIBG accumulation in the heart and salivary glands (*4*).

Biochemical selection and grading of hormonal values. After selecting the patients by imaging criteria as detailed above, we reviewed the plasma norepinephrine (NE) and epinephrine (E) concentrations and the urinary excretion rates of NE, E, normetanephrine (NM), metanephrine (M), and vanillyl mandelic acid (VMA) of these patients. Plasma levels of NE and E were determined by a radioenzymatic method (*10*). Rates of urinary excretion of catecholamines and their metabolites were determined from 12-hr overnight collections by the method of von Euler and Lishajko (*11*). Plasma for measurement of NE and E was obtained under resting and supine conditions through an indwelling venous catheter. The hormonal values for comparison with heart intensity were limited to those whose plasmas and urines were collected within 7 days of injection of I-131 MIBG. For most patients (>90%), collections of plasma and urine were made within 2 days before the tracer injection.

The hormonal values were arbitrarily scaled into four ranges based on the upper normal value (n) of each catecholamine or metabolite (plasma NE 500 pg/ml; E 100 pg/ml; urinary NE 60 μg/12 hr; E 15 μg/12 hr; NM 82.5 μg/12 hr; M 42.6 μg/12 hr; VMA 3.5 mg/12 hr): Range 1 (0 to n), Range 2 (n to 2n), Range 3 (2n to 3n), and Range 4 (>3n).

The final numbers of cases for comparative studies are shown in Table 1.

Methods of comparative studies. Comparison was made between the heart (and salivary gland) intensity and hormonal values. The number of cases in each grade corresponding to each hormonal range was obtained. Then the mean grade ± s.e.m. (standard error of mean) of heart intensity and incidence of heart nonvisualization (Grade 0) were calculated for each hormonal range. The linear correlation coefficient between heart (and salivary

TABLE 1. FINAL NUMBER OF PATIENTS FOR COMPARATIVE STUDIES WITH HEART INTENSITY AND NONVISUALIZATION RATE

Comparative items	Nonpheochromocytoma patients		Pheochromocytoma patients					
	24-hr image	48-hr image	24-hr image			48-hr image		
			A*	E†	M‡	A*	E†	M‡
Plasma NE and E	53	88	7	6	15(28)	7	6	15(28)
Urine NE and E	42	71	7	5	14(26)	6	6	14(26)
Urine NM and M	40	71	7	5	14(26)	6	6	14(26)
Urine VMA	41	71	7	5	14(26)	6	6	14(26)
Nonpheo compared with pheopatients	56	95	7	6	15(28)	7	7	15(29)

* Benign intraadrenal pheochromocytoma.
† Benign extraadrenal pheochromocytoma.
‡ Malignant metastatic pheochromocytoma.
( ) = Total number of pheochromocytoma patients.

gland) intensity and hormonal range was obtained and its significance calculated. Patients were considered to have pheochromocytoma when they had (a) histological proof, (b) I-131 MIBG scintigraphic images of tumor supported by appropriate biochemical data, and occasionally (c) when they exhibited strikingly abnormal biochemical values alone. In the last category, evidence of pheochromocytoma was also obtained by TCT, ultrasound, venous sampling, or angiography; this category included a patient in whom I-131 MIBG scintigraphy gave a false-negative result. All other patients were considered not to have pheochromocytomas.

The heart intensity and nonvisualization rates were compared between groups of nonpheochromocytoma and pheochromocytoma patients. The linear correlation coefficient of heart intensity with hormonal range was also calculated for pheochromocytoma and nonpheochromocytoma patients.

In addition, the specificity, sensitivity, and accuracy in the diagnosis of pheochromocytoma were compared between the scintigraphic and biochemical findings. The criteria for this were as follows: In the scintigraphic diagnosis, cases that showed no visible heart intensity (Grade 0) were considered positive for pheochromocytoma, and visible heart intensity (Grades 1–3) was considered negative for pheochromocytoma. Biochemically, the cases whose hormonal concentrations were in Range 1 were negative and those in Ranges 2–4 were positive for pheochromocytoma.

RESULTS

Comparison of heart intensity and nonvisualization rate with hormonal concentrations. Table 2 shows the relationship between heart intensity and nonvisualization rate at 24 hr, together with range of plasma and urine catecholamine concentrations. In general, mean heart intensity decreased, and nonvisualization rate increased, with rising hormonal values. There was no significant difference in this relationship between 24 hr and 48 hr, although a slight decrease in heart intensity and increase in nonvisualization rate was observed at 48 hr. The majority of pheochromocytoma patients clustered in Grade 0, whereas no pheochromocytoma patients were observed in Grade 3. The rank order of correlation between grade of heart intensity and range of hormonal concentrations estimated by the linear correlation coefficient was as follows: Plasma NE > urine NE ≤ urine VMA > plasma E > urine NM > urine E > urine M, at both 24 and 48 hr (Table 3). The correlation coefficient was higher at 24 hr than at 48 hr for all catecholamines or metabolites except urinary M, which had poorest correlation and no statistical significance at 24 hr.

Table 4 shows correlation coefficients between grade of heart intensity and range of hormonal concentrations when divided into nonpheochromocytoma and pheochromocytoma patients. Although correlation coefficients were much smaller than the values before division into two groups, negative correlation still existed in both groups at both 24 hr and 48 hr, except for urinary NM. However, the statistically significant correlations for nonpheochromocytoma patients were seen only for plasma NE and E at both 24 hr and 48 hr, and for urinary NE at 24 hr; in pheochromocytoma patients they were found for plasma E at 24 hr and plasma NE at 48 hr.

Table 5 shows correlation between grade of salivary-gland intensity and range of hormonal concentrations obtained, for comparison with the heart. In all hormonal categories, the correlation coefficient was much smaller for the salivary glands than for the heart. Statistically significant values were obtained in plasma NE, E, urinary NM, and VMA at 24 hr, and for plasma NE, urinary NE and VMA at 48 hr.

Comparison of heart intensity and nonvisualization rate

TABLE 2. RELATIONSHIP BETWEEN HEART INTENSITY AND NONVISUALIZATION RATE AT 24 hr, AND RANGE OF CONCENTRATIONS OF PLASMA AND URINARY CATECHOLAMINES AND THEIR METABOLITES

Catecholamine	Range of hormonal value	Grade of heart intensity 0	1	2	3	mean ± s.e.m.	Total no. of cases	Non visualization rate (%)
Plasma NE	I (0–500)	1(1)*	5	26(1)	6	2.0 ± 0.1	38(2)	3
(pg/ml)	II (501–1000)	5(3)	5	4(1)	0	0.9 ± 0.3	14(4)	56
	III (1001–1500)	3(2)	2	1	1	1.0 ± 0.4	7(2)	43
	IV (>1500)	20(18)	1(1)	1(1)	0	0.1 ± 0.1	22(20)	92
Plasma E	I (0–100)	9(6)	11(1)	30(3)	7	1.6 ± 0.1	57(10)	14
(pg/ml)	II (101–200)	7(6)	2	1	0	0.4 ± 0.2	10(6)	70
	III (201–300)	4(4)	0	0	0	0.0	4(4)	100
	IV (>300)	9(8)	0	1	0	0.2 ± 0.2	10(8)	90
Urine NE	I (0–60)	5(3)	8	22(1)	6	1.7 ± 0.1	41(4)	12
(μg/12 hr)	II (61–120)	6(4)	2(1)	2(1)	0	0.6 ± 0.3	10(6)	60
	III (121–180)	3(3)	1	1(1)	0	0.6 ± 0.4	5(4)	60
	IV (>180)	12(12)	0	0	0	0.0 ± 0.0	12(12)	100
Urine E	I (0–15)	14(11)	10(1)	22(2)	6	1.4 ± 0.1	52(14)	27
(μg/12 hr)	II (16–30)	3(2)	0	3(1)	0	1.0 ± 0.5	6(3)	50
	III (31–45)	2(2)	1	0	0	0.3	3(2)	67
	IV (>45)	7(7)	0	0	0	0.0 ± 0.0	7(7)	100
NM	I (0–82.5)	10(6)	9	21(2)	4	1.4 ± 0.1	44(8)	23
(μg/12 hr)	II (82.6–165.0)	4(4)	2(1)	2	1	1.0 ± 0.4	9(5)	50
	III (166–247.5)	3(3)	0	0	0	0.0	3(3)	100
	IV (>247.5)	9(9)	0	1(1)	0	0.2 ± 0.2	10(10)	90
M	I (0–42.5)	22(19)	11(1)	23(3)	5	1.2 ± 0.1	61(23)	36
(μg/12 hr)	II (42.6–85.0)	1	0	1	0	1.0	2	50
	III (85.1–127.5)	1(1)	0	0	0	0.0	1(1)	100
	IV (>127.5)	2(2)	0	0	0	0.0	2(2)	100
VMA	I (0–3.5)	5(3)	8	22(1)	4	1.6 ± 0.1	39(4)	17
(mg/12 hr)	II (3.6–7.0)	6(4)	2(1)	2(1)	1	0.8 ± 0.3	11(6)	55
	III (7.1–10.5)	2(2)	1	1(1)	0	0.8	4(3)	50
	IV (>10.5)	13(13)	0	0	0	0.0 ± 0.0	13(13)	100

* ( ) = Number of pheochromocytoma patients.

TABLE 3. CORRELATION BETWEEN GRADE OF HEART INTENSITY (x) AND RANGE OF HORMONAL CONCENTRATIONS (y)

Catecholamine or metabolite	Imaging time 24 hr N*	r†	Equation	p	48 hr N	r	Equation	p
Plasma NE	81	−0.73	y = −0.91x + 3.3	<0.001	116	−0.63	y = −0.75x + 2.9	<0.001
E	81	−0.56	y = −0.56x + 2.3	<0.001	116	−0.47	y = −0.45x + 2.1	<0.001
Urine NE	68	−0.63	y = −0.77x + 2.7	<0.001	97	−0.52	y = −0.53x + 2.2	<0.001
E	68	−0.44	y = −0.41x + 2.0	<0.001	97	−0.41	y = −0.38x + 1.9	<0.001
NM	66	−0.48	y = −0.51x + 2.3	<0.001	97	−0.45	y = −0.49x + 2.2	<0.001
M	66	−0.23	y = −0.13x + 1.3	>0.05	97	−0.28	y = −0.19x + 1.4	<0.01
VMA	67	−0.63	y = −0.73x + 2.7	<0.001	97	−0.50	y = −0.51x + 2.3	<0.001

* Number of cases.
† Correlation coefficient.

TABLE 4. CORRELATION BETWEEN GRADE OF HEART INTENSITY AND RANGE OF HORMONAL CONCENTRATIONS, FOR NONPHEOCHROMOCYTOMA AND PHEOCHROMOCYTOMA PATIENTS

Catecholamine or metabolite	Imaging time: 24 hr				48 hr			
	Nonpheo		Pheo		Nonpheo		Pheo	
	N*	r†	N	r	N	r	N	r
Plasma NE	53	−0.56‡	28	−0.35	88	−0.39‡	28	−0.41§
E	53	−0.27§	28	−0.43§	88	−0.26§	28	−0.33
Urine NE	42	−0.37¶	26	−0.33	71	−0.14	26	−0.37
E	42	−0.19	26	−0.15	71	−0.06	26	−0.20
NM	40	0.13	26	−0.19	71	0.02	26	−0.34
M	40	−0.19	26	−0.15	71	−0.09	26	−0.16
VMA	41	−0.26	26	−0.34	71	−0.09	26	−0.38

* Number of cases.
† Correlation coefficient.
‡ $p < 0.001$.
§ $p < 0.05$.
¶ $p < 0.02$.

between nonpheochromocytoma and pheochromocytoma patients. The nonvisualization rate was much lower in the nonpheochromocytoma patients (11% at 24 hr, 20% at 48 hr) than in pheochromocytoma patients (86% at 24 hr, 93% at 48 hr). The mean value of heart intensity was higher in the nonpheochromocytoma patients (1.7 at 24 hr, 1.5 at 48 hr) than in the pheochromocytoma patients (0.3 at 24 hr, 0.1 at 48 hr). This difference was statistically significant (Table 6). The two patients receiving tricyclic antidepressants showed inhibition of I-131 MIBG uptake by the heart and salivary glands; this reversed on withdrawal of the drug.

Table 7 shows the results of specificity, sensitivity, and accuracy of the scintigraphic (based on intensity of heart visualization) and biochemical diagnoses for the presence or absence of pheochromocytoma. Note that the scintigraphic diagnosis of elevated catecholamines (and pheochromocytoma) based on the heart intensity is accurate and comparable to that of urinary NE and VMA, although the specificity at 48 hr was relatively low (80%).

Figure 2 shows the change of heart intensity from Grade 0 to Grade 2 in a patient with bilateral pheochromocytomas before and after surgical resection.

DISCUSSION

Studies in dogs have shown that the peak heart concentration (% kg dose/g) of radiolabeled MIBG occurs 2 hr after the tracer injection (*2*). Thus the uptake of I-131 MIBG in the region of the heart, seen in images 24 hr or 48 hr after injection, represents activity in the myocardium (or nerve terminals therein). Most of this residual activity appears to be within specific NE storage

TABLE 5. CORRELATION BETWEEN GRADE OF SALIVARY-GLAND INTENSITY (x) AND RANGE OF HORMONAL CONCENTRATIONS (y)

Catecholamine or metabolite	Imaging time: 24 hr				48 hr			
	N*	r†	Equation	p	N	r	Equation	p
Plasma NE	83	−0.26	y = −0.41x + 3.0	<0.02	123	−0.26	y = −0.39x + 2.7	<0.01
E	83	−0.29	y = −0.36x + 2.3	<0.01	123	−0.06	y = −0.08x + 1.8	>0.05
Urine NE	71	−0.22	y = −0.26x + 2.1	>0.05	109	−0.27	y = −0.35x + 2.3	<0.01
E	71	−0.21	y = −0.21x + 1.8	>0.05	109	−0.05	y = −0.06x + 1.5	>0.05
NM	70	−0.24	y = −0.30x + 2.2	<0.05	108	−0.14	y = −0.18x + 1.9	>0.05
M	70	−0.05	y = −0.03x + 1.2	>0.05	108	+0.07	y = −0.06x + 1.1	>0.05
VMA	70	−0.26	y = −0.33x + 2.4	<0.05	101	−0.27	y = −0.34x + 2.3	<0.01

* Number of cases.
† Correlation coefficient.

TABLE 6. RELATIONSHIP OF HEART INTENSITY TO NONVISUALIZATION RATE, BETWEEN NONPHEOCHROMOCYTOMA AND PHEOCHROMOCYTOMA PATIENTS

Patients	Imaging time (hr)	Grade of heart intensity 0	1	2	3	Mean ± s.e.m.	Total no. of cases	Nonvisualization rate (%)
Nonpheo	24	6	13	29	8	1.7 ± 0.1*	56	11
patients	48	19	22	42	12	1.5 ± 0.1†	95	20
Pheo	24	24	1	3	0	0.3 ± 0.1*	28	86
patients	48	27	0	2	0	0.1 ± 0.1†	29	93

*,†*p <0.001 between the same symbol groups.

compartments because the nonspecific accumulation of guanethidine (a drug closely related to I-131 MIBG) decreases rapidly with time (*12,13*). Catecholamines are taken up by the heart into several compartments (*14*), the principal two of which are (a) those that are neuronal and are dependent on the "uptake 1" mechanism, inhibited by cocaine and desipramine, and (b) nonneuronal compartments that are dependent on the "uptake 2" mechanism (*15*). The latter mechanism may be inhibited by phenoxybenzamine, normetanephrine, and steroid hormones (*15*). The relative time courses of retention are such that at 24 hr the I-131 MIBG uptake observed is probably into the neuronal compartment. Furthermore, the patients receiving tricyclic antidepressants (related to desipramine), manifested nonvisualization of the heart that reversed following withdrawal of the drug. Among the pheochromocytoma patients there were those receiving phenoxybenzamine (which may inhibit uptake two) and those not receiving the drug, and in both groups there was frequently nonvisualization of the heart. The numbers of pheochromocytoma patients studied on various medications were: no medications: ten at 24 hr, nine at 48 hr; alpha blockade: six at 24 hr, seven at 48 hr; beta blockage: five at 24 hr, six at 48 hr; combined alpha and beta blockade: five at 24 hr, six at 48 hr; alpha-methyl paratyrosine: two at 24 hr, one at 48 hr. The present study shows an inverse relationship between (a) residual I-131 MIBG activity in the heart (and to a lesser extent in salivary glands) and (b) plasma and urinary catecholamines and their metabolites. Although this correlation became weaker when the population was divided into pheochromocytoma and nonpheochromocytoma patients, it is the catecholamine levels and excretion rates, rather than the presence of a pheochromocytoma per se, that correlate with this effect. Furthermore, since the tumor uptake of I-131 MIBG represents only 0.15% to 2.0% of the administered dose (*4*), it is not a result of sequestration of the tracer by the tumor. The plasma concentrations of NE and E, their urinary excretion rates, and the urinary excretion rates of their metabolites are each inversely related to cardiac I-131 MIBG uptake, but as none of the biochemical measurements is entirely independent of the others, their individual roles are difficult to separate.

Guanethidine inhibits the uptake of circulating radiolabeled NE by the rat heart in vivo and in vitro (*16,17*). Similarly, prior treatment with NE or E pre-

TABLE 7. COMPARISON OF SPECIFICITY, SENSITIVITY, AND ACCURACY OF THE FINDING OF ABSENT CARDIAC UPTAKE OF I-131 MIBG WITH A POSITIVE BIOCHEMICAL DIAGNOSIS (FOR EACH OF SEVEN MEASUREMENTS) OF PHEOCHROMOCYTOMA

Diagnostic methods	Imaging time (hr)	Diagnostic indices* Specificity†	Sensitivity‡	Accuracy§
Heart intensity	24	89	86	88
	48	80	93	83
Plasma NE	24	68	93	77
	48	68	96	75
Plasma E	24	89	64	80
	48	82	68	78
Urine NE	24	88	85	87
	48	89	88	89
Urine E	24	90	46	74
	48	92	58	82
Urine NM	24	90	69	82
	48	93	77	89
Urine M	24	95	12	62
	48	97	23	77
Urine VMA	24	85	85	85
	48	85	88	86

* Diagnostic criteria: 1. Heart intensity: Grade 0 = positive; grades 1–3 = negative. 2. Hormonal range: I = negative, II–IV = positive.

† $\frac{\text{True negative}}{\text{True negative + false positive}} \times 100\%$.

‡ $\frac{\text{True positive}}{\text{True positive + false negative}} \times 100\%$.

§ $\frac{\text{True negative + true positive}}{\text{Total number of cases}} \times 100\%$.

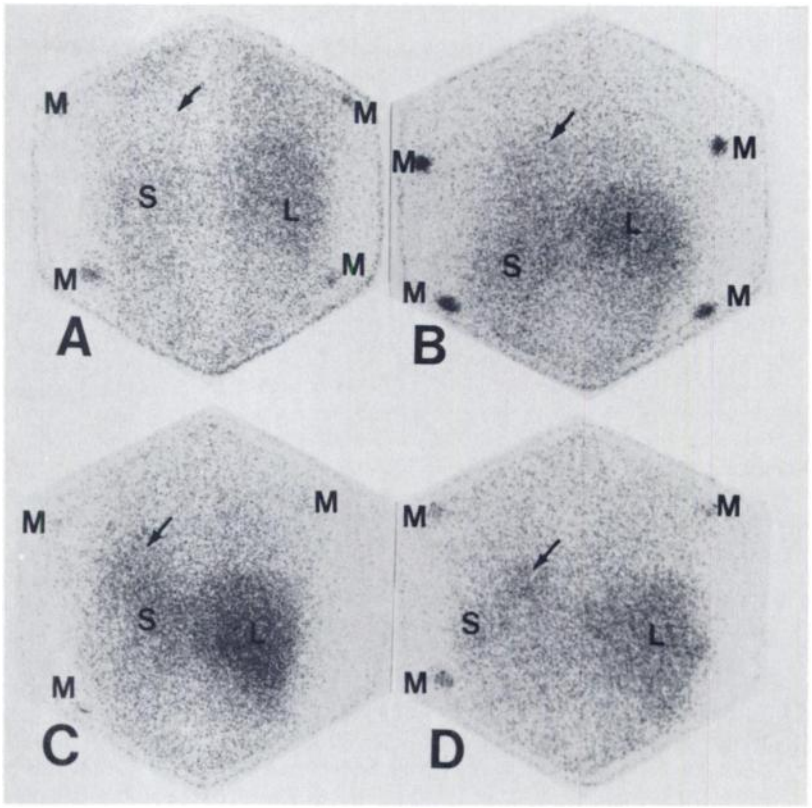

FIG. 2. Change of heart intensity in patient with bilateral pheochromocytomas. A: Heart was not seen before surgery (Grade 0). B: Grade 2 heart intensity was observed after surgery. Region of heart indicated by closed arrow. Bilateral pheochromocytomas indicated by open arrows; L = liver S = spleen M = surface markers.

vented the uptake of tracer doses of [^{3}H]guanethidine by the rat heart (*18*). Therefore, competitive uptake of I-131 MIBG, an analog of guanethidine, with circulating catecholamines in the heart, is a possible mechanism leading to the inverse relationship between the heart uptake and the plasma catecholamines presented by this study. But since nonpheochromocytoma patients show a decrease in heart intensity with increasing plasma and urinary catecholamine values, simple competition may not be the only explanation; rapidity of turnover of NE in neurons may also be important. The relationship of heart uptake to catecholamine metabolites then reflects increased synthesis, release, and metabolism that would be expected if there was increased sympathetic neuronal activity in a patient without pheochromocytoma. Normetanephrine, the metabolite of NE, which is also increased under greater neuronal activity, was probably not directly responsible for the effects, since NM has no effect in blocking guanethidine uptake in rat heart (*18*).

The intensity of heart uptake may be a helpful adjunct in the diagnosis of pheochromocytoma, as shown in the comparison with biochemical diagnosis. Table 6 shows that heart visualization is associated with normal or slightly elevated hormonal measurements, and makes the possibility of pheochromocytoma less likely [7% (4/54) at 24 hr, 3% (2/78) at 48 hr]. Nonvisualization of the heart suggests elevated hormonal measurements and makes the probability of pheochromocytoma more likely [80% (24/30) at 24 hr, 59% (27/46) at 48 hr]. In one patient in this series, I-131 MIBG imaging failed to locate an extra-adrenal pheochromocytoma. His heart failed to visualize at both 24 hr and 48 hr. As the above figures show, however, positive diagnosis of pheochromocytoma by nonvisualization of the heart is less accurate than the exclusion of pheochromocytoma by visualization of the heart, especially at 48 hr. Progressively less visualization is the expected consequence of the progressive normal release of the radioactivity from the heart.

Other causes of nonvisualization of the heart may be drugs that interfere with the uptake of I-131 MIBG in the heart, such as reserpine and tricyclic antidepressants (*2,4,19*). In a patient with severe adrenergic neuropathy who was not included in this study, the heart as well as the salivary glands were not seen at 48 hr despite low plasma catecholamine concentrations. Thus absence of I-131 MIBG uptake by the heart may result from several causes. In spite of this, however, I-131 MIBG imaging is a unique procedure in that the heart intensity enables us to estimate the state of circulating catecholamines through their influence on the heart, and to locate the pheochromocytoma itself when such a tumor is present (*4,5,8*).

Both the heart and salivary glands are richly innervated by sympathetic nerves. In this study, however, the heart intensity showed a more prominent negative correlation with circulating catecholamines than did the salivary glands. This difference may reflect differences in the handling of I-131 MIBG following uptake. The

salivary glands are known to deiodinate and excrete some of the I-131 of I-131 MIBG via the saliva (7), whereas loss from the heart, a continually active organ, is entirely through the circulation.

This study also suggests a future clinical use for radioiodinated MIBG or related agents in myocardial imaging and an in vivo means of investigating adrenergic influences on the heart.

ACKNOWLEDGMENTS

We thank Dr. T. Mangner and Holly Anderson-Davis for the manufacture of I-131 MIBG, the Phoenix Memorial Laboratory for the use of their radiochemistry facilities, and Ms. J. Boldt for the typing of the manuscript.

This work was supported by the following grants: DHEW #3M01 RR00042-22 S1 CLR, NIH #R01 AM 21477, NIAMDD #5P60 AM 20575, NCI #09015, and the Nuclear Medicine Research Fund. B.S. is the recipient of an NIH Clinical Associate Physician Award (DHEW #3M01 RR00042-22 S1 CLR).

REFERENCES

1. WIELAND DM, WU J-L, BROWN LE, et al: Radiolabeled adrenergic neuron-blocking agents: Adrenomedullary imaging with [^{131}I]iodobenzylguanidine. *J Nucl Med* 21:349-353, 1980
2. WIELAND DM, BROWN LE, ROGERS WL, et al: Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 22:22-31, 1981
3. WIELAND DM, BROWN LE, TOBES MC, et al: Imaging the primate adrenal medulla with [^{123}I] and [^{131}I] metaiodobenzylguanidine: Concise communication. *J Nucl Med* 22: 358-364, 1981
4. SISSON JC, FRAGER MS, VALK TW, et al: Scintigraphic localization of pheochromocytoma. *N Engl J Med* 305:12-17, 1981
5. VALK TW, FRAGER MS, GROSS MD, et al: Spectrum of pheochromocytoma in multiple endocrine neoplasia. A scintigraphic portrayal using ^{131}I-metaiodobenzylguanidine. *Ann Intern Med* 94:762-767, 1981
6. KLINE RC, SWANSON DP, WIELAND DM, et al: Myocardial imaging in man with I-123 meta-iodobenzylguanidine. *J Nucl Med* 22:129-132, 1981
7. NAKAJO M, SHAPIRO B, SISSON JC, et al: Salivary gland accumulation of ^{131}I-metaiodobenzylguanidine. *J Nucl Med:* in press
8. NAKAJO M, SHAPIRO B, COPP J, et al: The normal and abnormal distribution of the adrenomedullary imaging agent ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) in man: Evaluation by scintigraphy. *J Nucl Med:* in press
9. EVERED DC, TUNBRIDGE WG: Endocrine disorders. In *Textbook of Adverse Drug Reactions.* Davies DM, Ed. New York, Toronto, Oxford University Press, 1981, pp 301-313
10. PEULER JD, JOHNSON GA: Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci* 21:625-636, 1977
11. VON EULER US, LISHAJKO F: The estimation of catecholamines in urine. *Acta Physiol Scand* 45:122-132, 1959
12. CHANG CC, COSTA E, BRODIE BB: Interaction of guanethidine with adrenergic neurons. *J Pharmacol Exp Ther* 147:303-312, 1965
13. MAITRE L, STAEHELIN M: Guanethidine uptake and noradrenaline depletion in noradrenaline storage particles of rat heart. Naunyn-Schmiedeberg's *Arch Pharmacol* 266:399-400, 1970
14. LINDMAR R, LÖFFELHOLZ K: Neuronal and extraneuronal uptake and efflux of catecholamines in the isolated rabbit heart. Naunyn-Schmiedeberg's *Arch Pharmacol* 284:63-92, 1974
15. TRENDELENBURG U: The extraneuronal uptake and metabolism of catecholamines in the heart. In *The Mechanism of Neuronal and Extraneuronal Transport of Catecholamines.* DM Paton, ed. New York, Raven Press, 1976, pp 259-280
16. HERTTING G, AXELROD J, PATRICK RW: Actions of bretylium and guanethidine on the uptake and release of [^{3}H]-noradrenaline. *Br J Pharmacol Chemother* 18:161-166, 1962
17. IVERSEN LL: Inhibition of noradrenaline uptake by drugs. *J Pharm Pharmacol* 17:62-64, 1965
18. BRODIE BB, CHANG CC, COSTA E: On the mechanism of action of guanethidine and bretylium. *Br J Pharmacol Chemother* 25:171-178, 1965
19. MICHELL JR, OATES JA: Guanethidine and related agents. I. Mechanism of the selective blockade of adrenergic neurons and its antagonism by drugs. *J Pharmacol Exp Ther* 172: 100-107, 1970