Rapid Clearance of Iodine-131 MIBG from the Heart and Liver of Patients with Adrenergic Dysfunction and Pheochromocytoma

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Iodine-131 MIBG, a radiolabeled adrenergic neuron-blocking agent, decreased rapidly from the heart and liver of patients with adrenergic dysfunction (n = 3) and pheochromocytoma (n = 2) when compared with eight controls. The 4-hr activity expressed as percentages (mean ± s.d.) of the 20-min counts were as follows: 80 ± 3.0% in the controls compared with 60 ± 7.6% in the patients over the heart ($p < 0.01$) and 79 ± 3.2% in the controls compared with 51 ± 17% in the patients over the liver ($p < 0.02$). However, there was no significant difference in the rate of [^{131}I]MIBG decrease in these organs between controls and patients in the intervals subsequent to 4 hr ($p > 0.05$). These findings suggest that adrenergic neuronal uptake of [^{131}I]MIBG in these organs is smaller in the patients than in the controls. Measurements of time-activity relationships of radioiodinated MIBG may be useful for assessment of adrenergic function of these organs and thus of generalized disorders of adrenergic innervation.

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Iodine-131 meta-iodobenzylguanidine ([^{131}I]MIBG) is a radioiodinated analog of guanethidine, an adrenergic blocking agent (*1*). The affinity of [^{131}I]MIBG for the adrenal medullae has proven useful in the scintigraphic localization of pheochromocytoma (*2*,*3*) and the assessment of adrenal medullary hyperplasia (*4*). It has been suggested that radioiodinated MIBG may be taken up and stored in adrenergic neurons by the same mechanism as that for norepinephrine (NE) (*5*). It has also been shown that the efflux of NE from the isolated rabbit heart differs between neuronal and extraneuronal compartments (*6*); the efflux of NE is more rapid from the extraneuronal compartments than from the adrenergic neuronal compartments. The efflux of guanethidine (an analog of MIBG) from the extravesicular compartments is also rapid in the rat heart (*7*). Therefore MIBG would have similar effluxes to NE and guanethidine in vivo. This hypothesis prompted us to carry out the present study.

We report here rapid clearance of [^{131}I]MIBG activity from the heart and liver of patients with adrenergic dysfunction and pheochromocytoma when compared with that of controls. This finding suggests that MIBG has different compartments in efflux as well as NE and guanethidine and measurements of time activity provide a method for assessment of adrenergic function by using radioiodinated MIBG.

MATERIALS AND METHODS

Subjects

The control group consisted of four male volunteers and four patients without evidence of pheochromocytoma and adrenergic dysfunction. The volunteers, ages

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TABLE 1
Clinical Data of Patients with Adrenergic Dysfunction

Item		Patient no. 1	2	3
Age/sex		59/M	62/M	55/M
Diagnosis		Multiple system atrophy	Shy-Drager's syndrome	Shy-Drager's syndrome
Orthostatic hypotension*		Yes (30/2)	Yes (100/35)	Yes (50/40)
Urinary and fecal incontinence		Yes	Yes	Yes
Sexual impotence		Yes	Yes	Yes
Sweating disturbance		No	Yes	Yes
Pupil disturbance		Yes	Yes	Yes
Duration of above symptoms and signs		1 yr	3 yr	4 yr
Liver function†		ZTT 15.8 Ku.U (4–12) TTT 8.3 Ku.U (<5)	CHE 0.63 ΔPH (0.8–1.1)	Normal
EKG		Normal	LVH	Normal
Circulation time† (arm to tongue; dehydrocholic acid) (10–16 sec)		18 sec	25 sec	16 sec
Hormonal values	Plasma NE (pg/ml)	204	161	135
	Plasma E (pg/ml)	13	60	43
	Urine NE (g/24 hr)	118	70	50
	Urine E (g/24 hr)	6.2	8.9	4.9
	Urine VMA (mg/24 hr)	5.8	8.4	8.6

* (upper/lower): Different value (mm Hg) in systolic (upper) and diasystolic (lower) blood pressure between supine and sitting positions.
† ( ): Normal range.

25–36 yr, were normal by history, physical examination, electrocardiogram (EKG) and liver function tests except for slight elevation of γ-gamma glutamyl transpeptidase in two of them. The other four patients, three males and one female, ages 27–66 yr, underwent [^{131}I]MIBG imaging in the course of diagnostic workup; two with essential hypertension, one with lung cancer, and one with mediastinal neurinoma. The latter two patients were normal by EKG and liver function tests. However, EKG showed left ventricular hypertrophy (LVH) in two with essential hypertension and one of them had slightly elevated values of serum transaminases. In these subjects, concentrations of plasma NE and epinephrine (E) in supine position and/or excretion rates of urine catecholamines and vanillylmandelic acid (VMA) were all within normal limits or slightly elevated; plasma NE: 134–354 pg/ml, plasma E: 20–123 pg/ml, urine NE: 36–70 μg/24 hr, urine E: 8–16 μg/24 hr and urine VMA: 4.1–7.3 mg/24 hr.

The adrenergic dysfunction group consisted of a male patient with multiple system atrophy (*8*) and two with Shy-Drager's syndrome (*9*). The clinical data of these patients are summarized in Table 1; they had symptoms and signs suggesting autonomic dysfunction including orthostatic hypotension, urinary and fecal incontinence, sexual impotence and/or sweating disturbance. Concentrations of plasma NE and E in supine position and excretion rates of urine catecholamines and VMA were all within normal limits or slightly elevated. However, plasma NE failed to increase on standing or sitting in two with Shy-Drager's syndrome, while it increased 1.5 times on standing when compared with the supine values in a patient with multiple system atrophy.

We used a pharmacological interventional test of the cardiovascular autonomic function as an assessment of the autonomic function in these patients (*10*). In this test, the following parameters can be estimated by responses of pulse rate or blood pressure during successive intravenous infusions of parasympathetic blocker atropine, beta-receptor stimulant isoproterenol with atropine, beta-receptor blocker propranolol with atropine, alpha-stimulant phenylephrine and alpha-receptor blocker phentolamine; parasympathetic tone, beta-sympathetic tone, beta-sensitivity, beta-secretion, alpha-sympathetic tone, alpha-sensitivity, and alpha-secretion. The results of this test are shown in Table 2. They show hypersensitivity of alpha-receptor and decrease of catecholamine secretion onto alpha-receptor sites in Patient 1, and decrease of parasympathetic tone, severe hypersensitivity of alpha- and beta-receptors, and decrease of catecholamine secretion onto both receptor

TABLE 2
Results of Pharmacological Interventional Test of Cardiovascular Autonomic Function in Patients with Adrenergic Dysfunction

Parameter*	Patient no. 1	2	3
Parasympathetic tone (36–59 beats/min)	54	7	28
Beta-sympathetic tone (19–28 beats/min)	27	5	20
Beta-sensitivity (1500–3000 beats/μg/kg/min isoproterenol)	2,500	6,250	8,500
Beta-secretion (0.006–0.012 μg/kg/min isoproterenol)	0.0108	0.0008	0.0024
Alpha-sympathetic tone (8–14 mmHg)	16	30	40
Alpha-sensitivity (10–40 mmHg/μg/kg/min phenylephrine)	60	550	110
Alpha-secretion (0.4–1.0 μg/kg/min phenylephrine)	0.27	0.055	0.36

* ( ): Normal range.

sites suggesting denervation hypersensitivity.

Two patients were proven hormonally and histologically to have pheochromocytoma; a 59-yr-old male with a right intra-adrenal pheochromocytoma 8 cm in diam and a 54-yr-old female with an extra-adrenal pheochromocytoma 4 cm in diam which located at the paraaortic region inferior to the right kidney. These tumors concentrated [^{131}I]MIBG. The preoperative hormonal values of these patients were, respectively, as follows: plasma NE: 1,300 pg/ml and 5,350 pg/ml, plasma E: 986 pg/ml and 126 pg/ml, urine NE: 426 μg/24 hr and 232 μg/24 hr, urine E: 395 μg/24 hr and 17 μg/24 hr, and urine VMA: 28 mg/24 hr and 14.5 mg/24 hr. EKG showed LVH in both of them and slight elevation of lactate dehydrogenase was shown in one of them by liver function tests.

In this study, plasma levels of NE and E were determined by liquid-chromatographic methods (*11*). Rates of urinary excretion of catecholamines and VMA were determined by a method using high-speed ion exchange column chromatography (*12*). Their normal ranges are as follows: plasma NE: 40–350 pg/ml, plasma E: <120 pg/ml in supine position, urine NE: 10–90 μg/24 hr, urine E: <12 μg/24 hr, and urine VMA: 2–12 mg/24 hr.

Imaging methods

Iodine-131 MIBG was prepared according to the method of Wieland et al. (*1*). The average specific activity was 1.9 μCi/μg (0.6–3.9 μCi/μg). The radiochemical purity was greater than 95% as determined by thin layer chromatography (silica gel support, acetate/ethanol (1:1), Rf [^{131}I]MIBG = 0.07, Rf [^{131}I]iodide = 0.75).

The subjects received 0.4–0.7 mCi (average dose: 0.5 mCi/subject) of [^{131}I]MIBG i.v. No side effects were observed during or after its injection. Potassium iodide 300 mg a day was given orally to block uptake of ^{131}I by the thyroid glands on the day before its injection and for 6 days afterwards. Serial anterior chest images which included the heart and liver were obtained using a gamma camera equipped with a medium-energy, multiparallel-hole collimator. Subjects were positioned reproducibly utilizing marks of the collimator and skin. A 30% window was used, centered at 364 keV. All data were recorded by a nuclear medicine minicomputer for display and semiquantitative analysis. Fourteen-minute images were acquired sequentially on a 64 × 64 computer matrix at 20, 50, and 125 min and 4, 24, and 48 hr after the tracer injection.

Data processing

After nine points smoothing, rectangular regions of interest (ROIs) were set over the heart, liver, and upper lung fields to obtain the time-activity relationships as functions of time. The size of the ROI was determined as maximum as possible over each organ or region in the 20-min image with the smallest organs. It was 49 pixels for the heart and each of the upper lung fields, and 165 pixels for the liver, respectively, as shown in Fig. 1. The ROI over the liver of a patient with a right intra-adrenal pheochromocytoma was set in the hepatic portions which were free from the influence of activity originated from the tumor.

The initial 20-min counts of ROIs over the heart and liver were normalized by average administered dose (0.5 mCi) and body weight (57 kg) to compare the activity of these organs between control, adrenergic dysfunction, and pheochromocytoma groups: The normalized ROI counts = ROI counts × 0.5 mCI × body weight (kg)/administered dose (mCi) × 57 kg. The [^{131}I]MIBG time-activity of each organ was expressed as a percentage of the 20-min ROI counts because of difficulty of absolute quantitation. The rate of [^{131}I]MIBG decrease of the heart and liver was calculated between neighboring acquisition times as follows: $(x - y) \times 100\%/xt$, where x is the activity of the earlier acquisition time, y is the activity of the later acquisition time, and t is the time interval (hr) between these neighboring acquisition times.

Statistical analyses were performed using unpaired t-test or linear regression and correlation with t-test.

RESULTS

Table 3 shows the 20-min normalized ROI counts over the heart and liver. There was little difference in the mean value over the heart between control, adrenergic

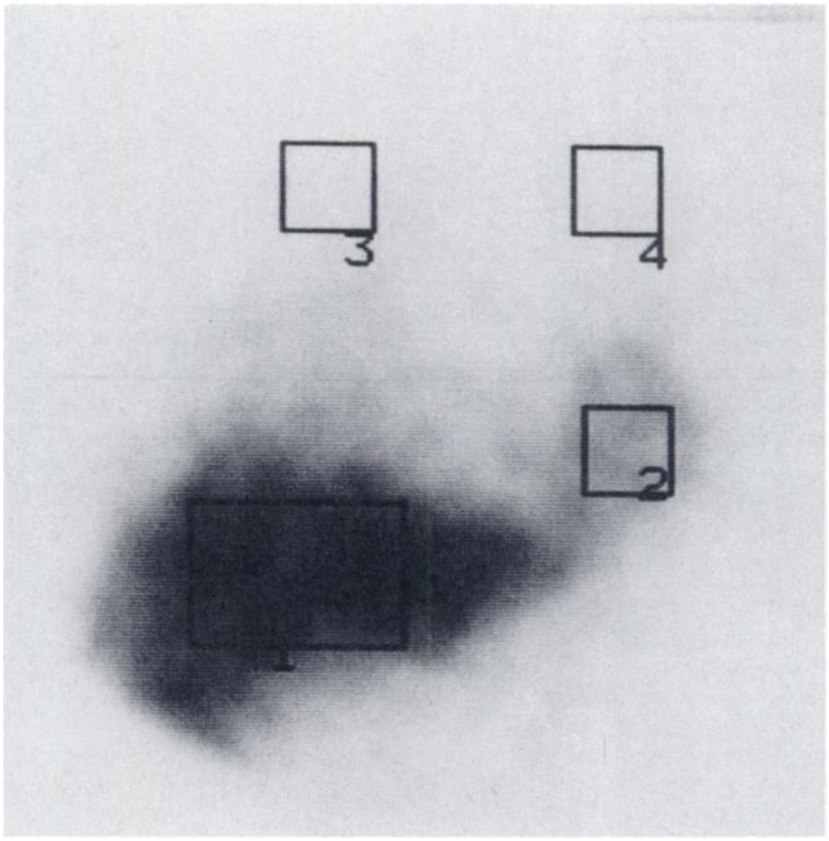

FIGURE 1
ROIs over liver (1), heart (2), and upper lung fields (3 and 4) in [^{131}I]MIBG anterior chest digital image

dysfunction, and pheochromocytoma groups, whereas the value over the liver was higher in the latter two groups by about 110% than in the control group.

Table 4 shows the time activity and rate of [^{131}I]MIGB decrease over the heart and liver. In both organs, the adrenergic dysfunction and pheochromocytoma groups showed more rapid clearance in the period of 4 hr after the tracer injection than the control group. The largest difference in activity was observed at 4 hr between the former two and control groups. The mean 4-hr activity over the heart was 80% in the control group, 57% in the adrenergic dysfunction group, and 65% in the pheochromocytoma group. Over the liver, it was 79%, 43%, and 63%, respectively. These differences in activity at 4 hr over the heart and liver between control and the latter two groups were statistically significant ($p < 0.01$ over the heart and $p < 0.02$ in the liver). The largest difference in the rate of [^{131}I]MIBG decrease was observed from 125 min to 4 hr over both organs; over the heart, the mean rate was 7.3%/hr in the control group, 17%/hr in the adrenergic dysfunction group and 14%/hr in the pheochromocytoma group. Over the liver, it was 7.9%/hr, 22%/hr, and 15%/hr, respectively. These differences in the rate of [^{131}I]MIBG decrease between control and the latter two groups were statistically significant ($p < 0.05$ over both organs). However, no significant differences in the rate were observed between control and the latter two groups in the intervals subsequent to 4 hr ($p > 0.05$ over both organs).

TABLE 3
Mean 20-min Normalized ROI Counts over Heart and Liver*

Group	N	Heart	Liver
Control	8	11,506 (9,225–12,761)†	57,362 (50,798–63,157)
Adrenergic dysfunction	3	10,920 (8,084–12,398)	64,806 (60,241–70,076)
Pheochromocytoma	2	11,186 (10,386–11,986)	62,493 (58,251–66,734)

* Counts/57 kg of body weight/0.5 mCi administered dose.
† ( ): Range.

Figure 2 shows the activity changes of the heart and liver from 20 min to 4 hr observed in images of a control and a patient with Shy-Drager's syndrome. The abrupt change of activity in the heart and liver is evident in the latter patient.

Figure 3 shows the heart-to- and liver-to-lung ratios as functions of time. In both organs, the ratio increased from 20 to 125 min in the control group, whereas such increase in ratio was slight in the pheochromocytoma group and lacking in the heart or the ratio decreased in the liver in adrenergic dysfunction group. The major differences in the ratio between the heart and liver are:

TABLE 4

Iodine-131 MIBG Time Activity and Rate of Decrease Between Neighboring Acquisition Times in Heart and Liver of Subjects in Control, Adrenergic Dysfunction (AD), and Pheochromocytoma (PHEO) Group*

			[^{131}I]MIBG time activity and rate of decrease between neighboring acquisition times (%/hr)									
Organ	Group	N	%/hr	50 min	%/hr	125 min	%/hr	4 hr	%/hr	24 hr	%/hr	48 hr
Heart	Control	8	−1.0 ± 7.8 (−14 − 6.0)	101 ± 3.9 (97 − 107)	5.4 ± 4.2 (0.8 − 14)	94 ± 6.5 (81 − 102)	7.3 ± 2.7 (3.9 − 11)	80 ± 3.0 (75 − 84)	2.6 ± 0.2 (2.2 − 3.0)	39 ± 4.6 (33 − 46)	1.8 ± 0.4 (1.3 − 2.4)	22 ± 2.7 (18 − 25)
	AD	3	6.7 (6,24,−10)	97 (97,88,105)	8.5 (10,12,4)	87 (85,75,100)	17 (12,13,27)	57 (65,56,49)	2.5 (2.7,3.1,1.5)	28 (30,21,34)	2.1 (2.4,2.8,1.1)	15 (13,7,25)
	PHEO	2	12 (14,10)	94 (93,95)	4.6 (0.9,8.4)	89 (92,85)	14 (14,14)	65 (68,62)	2.4 (2.7,2.1)	34 (32,36)	1.7 (1.4,2.0)	20 (21,19)
	AD + PHEO	5	8.8 ± 12	96 ± 6.2	7.0 ± 4.5	87 ± 9.3	16 ± 6.0†	60 ± 7.6‡	2.4 ± 0.6	31 ± 5.8§	1.9 ± 0.7	17 ± 7.1
Liver	Control	8	−3.3 ± 9.7 (−24 − 6.0)	102 ± 4.9 (97 − 112)	6.7 ± 2.7 (3.0 − 11)	93 ± 5.7 (86 − 101)	7.9 ± 3.2 (1.6 − 11)	79 ± 3.2 (71 − 94)	2.9 ± 0.2 (2.6 − 3.3)	33 ± 3.2 (29 − 39)	1.9 ± 0.4 (1.5 − 2.7)	18 ± 4.0 (12 − 25)
	AD	3	15 (14,4,28)	92 (93,98,86)	17 (11,18,22)	73 (80,76,62)	22 (15,19,33)	43 (57,48,23)	2.6 (2.8,3.2,1.7)	19 (25,17,15)	2.0 (2.3,2.7,0.8)	10 (11,6,12)
	PHEO	2	3.0 (6,0)	99 (97,100)	8.5 (5.0,12)	88 (91,85)	15 (13,17)	63 (68,58)	2.4 (2.7,2.2)	32 (31,33)	1.8 (1.5,2.0)	19 (20,17)
	AD + PHEO	5	10 ± 11†	95 ± 5.5†	14 ± 6.7	79 ± 11§	19 ± 7.8†	51 ± 17§	2.5 ± 0.6	24 ± 8.1	1.9 ± 0.7	13 ± 5.5

* All values of time-activity and decreasing rate are expressed as mean ± s.d. percentage of 20-min counts and mean ± s.d. decreasing rate, respectively; numbers in parentheses give range or individual value which corresponds to that of Patients 1, 2, and 3 in adrenergic dysfunction group and intra-adrenal and extra-adrenal pheochromocytoma patients in order.

† $p < 0.05$.

‡ $p < 0.01$.

§ $p < 0.02$ compared with control group.

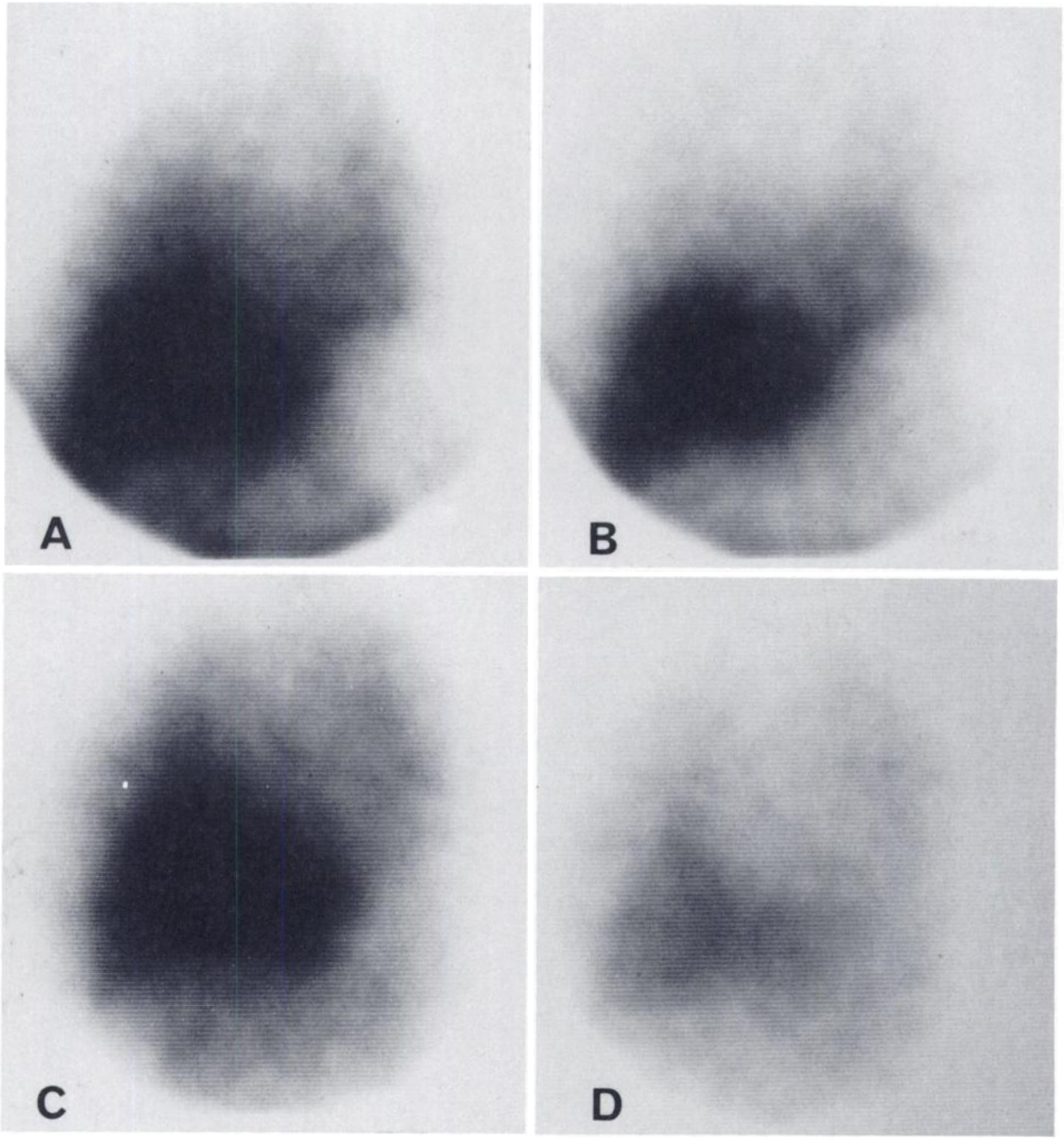

FIGURE 2
[^{131}I]MIBG images of anterior chest in normal control (A and B) and Patient 2 with Shy-Drager's syndrome (C and D), acquired for 14 min. A and C; 20-min images, and B and D; 4-hr images. Abrupt decrease in activity of heart and liver is demonstrated in patient with Shy-Drager's syndrome when compared with that of normal control

1. All groups showed almost the same 20-min ratio in the heart, whereas in the liver, the ratio was higher in the adrenergic dysfunction and pheochromocytoma groups than in the control group.
2. In general, decrease in the ratio is more rapid in the liver than in the heart after 125 min in all groups.

DISCUSSION

Meta-iodobenzlguanidine is thought to share the same uptake, storage, and release mechanisms as NE in adrenergic nerve terminals; however, it is not metabolized by catechol-*o*-methyl transferase and monoamine oxidase and thus can be viewed as a "nonmetabolizable" NE (*5*). The evidences for adrenergic neuronal uptake of radioiodinated MIBG were demonstrated by the previous animal and human studies: Reserpine pretreatment caused a 30% decrease in the canine myocardial concentration of [^{125}I]MIBG at 2 hr after i.v. injection of the tracer (*5*). Reserpine is thought to block

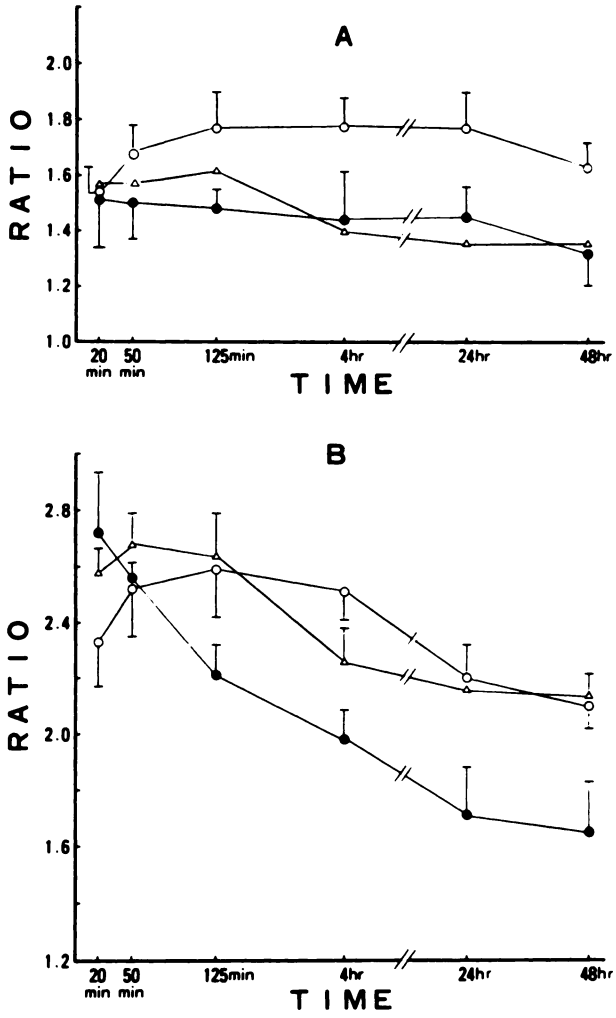

FIGURE 3
Heart-to-lung ratios (A) and liver-to-lung ratios (B) for [^{131}I]MIBG as functions of time in control (○), adrenergic dysfunction (●), and pheochromocytoma (△) groups, derived from ROIs in digital images. Bars show s.e.m. Marks with no bars are due to s.e.m. too small to be shown

selectively the vesicular uptake of NE in adrenergic neurons (*13*). Iodine-131 MIBG heart intensity in the 24- and 48-hr posterior images was inversely related to plasma concentrations of catecholamines suggesting competitive uptake of [^{131}I]MIBG by the heart with circulating catecholamines as a major cause for the inverse relationship (*14*). The 24-hr or later images (*15*) revealed that [^{131}I]MIBG salivary gland accumulation was reversely blocked by administration of tricyclic antidepressants known to inhibit the neuronal uptake of NE and guanethidine (*16*), was markedly diminished by the ipsilateral salivary glands in a patient with Horner's syndrome and was bilaterally diminished in a patient with severe idiopathic sympathetic neuropathy. The heart and salivary glands are both richly innervated by the sympathetic nerves (*17*,*18*). However the time course to determine such imaging findings has remained to be elucidated.

The rapid clearance of [^{131}I]MIBG from the heart and liver in the patients with adrenergic dysfunction and pheochromocytoma observed in this study should be related to the property of MIBG. After i.v. injection of this tracer, it will enter several compartments with different effluxes of the organs as observed in the study of catecholamines in the isolated rabbit heart (*6*). They can be classified into adrenergic neuronal compartments such as the axoplasm and vesicles and extraneuronal compartments including vascular space and nonneuronal tissues. Therefore the time activity of [^{131}I]MIBG in organs can be viewed as the sum of adrenergic neuronal and extraneuronal accumulation.

Although the adrenergic neuronal and extraneuronal fate of radioiodinated MIBG after its i.v. injection has not been fully or directly studied as a function of time, it would be similar to that of NE and guanethidine (an analog of MIBG). In the heart, the efflux of NE located extraneuronally is more rapid than that of NE located in the neurons (*6*,*19*,*20*). The intravesicular accumulation of guanethidine in the rat heart is relatively constant, while its accumulation in the other compartments decreased rapidly for a period of 2 to 5 hr (*7*). Such property of NE and guanethidine provides a hypothesis to the phenomenon observed in this study that the major factor to result in the different clearance of activity from the heart and liver is the difference in relative amount of [^{131}I]MIBG neuronal to extraneuronal accumulation in these organs between controls and patients with adrenergic dysfunction and pheochromocytoma at the early period after i.v. injection of the tracer.

This point of view is supported by the following:

1. The rapidity of circulation is probably not the cause of the rapid clearance observed in the patients with adrenergic dysfunction because they had normal or rather prolonged circulation times. It also does not appear to be related to abnormalities of the heart and liver as evaluated by routine function tests and to specific activity of [^{131}I]MIBG (Table 5).

2. The decreasing patterns of [^{131}I]MIBG in the hearts of the subjects in the control, and adrenergic dysfunction or pheochromocytoma groups from 2 to 4 hr are analogous with those of guanethidine in the hearts of the control rats and the rats pretreated with reserpine, respectively (*7*).

3. The clearance of [^{131}I]MIBG is more rapid in Patients 2 and 3 than Patient 1. Much more severe abnormality of the adrenergic nerve terminals is suggested in Patients 2 and 3 than in Patient 1 by the clinical symptoms and signs, the pharmacological interventional test and postural response of plasma NE (Tables 1 and 2).

4. There was no significant difference in the rate of [^{131}I]MIBG decrease over the heart and liver between control, and adrenergic dysfunction and pheochromocytoma groups in the intervals subsequent to 4 hr. This

TABLE 5
Relation Between Routine Function Tests or Specific Activity of [^{131}I]MIBG and 4-hr Activity (%) of [^{131}I]MIBG

Item	Organ	No. of patients		4-hr activity (mean ± s.d.)		p
		Normal	Abnormal	Normal	Abnormal	
Liver function tests	Heart	7	6*	73 ± 13	71 ± 10	
	Liver			69 ± 23	68 ± 14	
EKG	Heart	8	5*	76 ± 12	68 ± 9	>0.05
	Liver			70 ± 22	65 ± 12	
Blood pressure†	Heart	8	5	76 ± 12	68 ± 9	
	Liver			70 ± 22	65 ± 12	
		No. of patients		Equation	r	
Specific activity‡	Heart	13		y = −0.015x + 3.1	−0.15	
	Liver			y = −0.010x + 2.6	−0.15	

* Having at least one abnormal finding in liver function tests or EKG.
† Normal = normotensive; abnormal = hypertensive in supine position.
‡ x = 4-hr activity, y = specific activity of [^{131}I]MIBG (μCi/μg) and r = correlation coefficient.

suggests that the slow efflux from the neuronal compartments is a major determinant for the clearance in these intervals.

5. The heart-to- and liver-to-lung ratios as functions of time (Fig. 3) showed differences between groups: The increase in ratio in both organs in the control group from 20 to 125 min is consistent with that obtained in the normal volunteers reported by Kline et al. (*21*). This indicates that certain compartment(s) in which [^{131}I]MIBG accumulates actively retains against the lung activity. Guanethidine studies (*7*,*22*) suggest that this is due mainly to active accumulation process or retention in the NE storage vesicles. However, this increase is lacking in the adrenergic dysfunction group or slight in the pheochromocytoma group.

The heart-to-lung ratio as a function of time also suggests that nonvisualization of the heart in the 24- or 48-hr images of the patients with high levels of circulating catecholamines produced by pheochromocytoma reported previously (*14*) is already determined around 4 hr after the injection of the tracer because the ratio is constant thereafter. Slight increase in the ratio from 20 to 125 min in the patients with pheochromocytoma appears to be consistent with the concept that competitive uptake of [^{131}I]MIBG with circulating catecholamines is a major possible mechanism leading to nonvisualization of the heart in pheochromocytoma patients. However, the rapidity of circulation may result in the rapid decrease in ratio from 125 min to 4 hr in both organs.

Although the liver is innervated by the sympathetic nerves (*23*), it is a major site for blood-pool and catecholamine degradation. More rapid decrease in the ratio of the liver compared with the heart suggests that the liver is different in compartment(s) or relative amount between compartments from the heart. Higher 20-min counts and liver-to-lung ratios and more rapid decrease in the ratio of patients with adrenergic dysfunction suggest that blood pool as an extraneuronal compartment may be larger than in the controls. Generalized adrenergic dysfunction would change the liver blood pool (*24*,*25*).

Thus, the rapid clearance of [^{131}I]MIBG from the heart and liver of the patients with adrenergic dysfunction and pheochromocytoma can be interpreted as follows. In the patients with adrenergic dysfunction, the heart and liver have smaller amounts of intact functioning adrenergic neurons to take up and store [^{131}I]MIBG than in the controls. In the patients with pheochromocytoma, high levels of circulating catecholamines compete with [^{131}I]MIBG in entering adrenergic neurons. Such conditions result in a relatively larger amount of extraneuronal compartments with rapid effluxes in the heart and liver of these patients when compared with that of the controls. This difference in the relative amount of extraneuronal and neuronal compartments is a major factor to result in the rapid clearance of [^{131}I]MIBG from the heart and liver of the patients from 20 min to 4 hr after the injection of the tracer. Most of the activity in the extraneuronal compartments will be washed out by 4 hr. Thereafter the rate of decrease is mainly governed by the neuronal efflux to make no significant difference in it between groups. However, further experimental studies using MIBG itself are required to prove more directly the validity of this interpretation.

In spite of use of semiquantitative methodology, the present study suggests that serial measurement of time activity of radioiodinated MIBG in certain organs may

be useful in the assessment of their adrenergic function and thus a generalized adrenergic neuropathy. In addition, it implies the appropriate time (4 hr or later after injection of radioiodinated MIBG) for imaging to quantify its neuronal accumulation in the myocardium (*21*).

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