Quantitation of Iodine-123 MIBG Uptake by Normal Adrenal Medulla in Hypertensive Patients

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Eighteen hypertensive patients with a clinical suspicion of pheochromocytoma and raised or borderline raised plasma catecholamine and urinary vanillyl mandelic acid (VMA) levels were studied by scintigraphy using ^{123}I-labeled metaiodobenzylguanidine (MIBG). None of these patients had any scintigraphic evidence of pheochromocytoma at the time of study or on subsequent clinical follow-up. A quantitative approach was taken to calculate the adrenal medullary uptake of [^{123}I]MIBG in these patients. Three different methods of quantitation were evaluated using data acquired from an anthropomorphic phantom and analysed by three independent observers. In the patient studies 34 out of 35 adrenal medullas were visualized with uptake in the range of 0.01–0.22% of the administered dose 22 hr postinjection which was calculated using the preferred quantitation method. This is an appropriate control group range for comparison with patients who have proven norepinephrine and epinephrine secreting tumors. A quantitative approach to [^{123}I]MIBG imaging provides an important tool for studying adrenomedullary pathophysiology.

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Metaiodobenzylguanidine (MIBG) has been used for imaging the adrenal medulla since 1980 (*1*). It is a physiological analog of norepinephrine and guanethidine. The uptake of this radiopharmaceutical is through two shared uptake systems, one sodium dependent; the other sodium independent (*2*). The efficacy of this radiopharmaceutical has been documented in cases of pheochromocytoma (*3*), neuroblastoma (*4,5*), carcinoid (*6*), nonfunctioning paraganglioma (*7*), adrenal metastases of choriocarcinoma, and metastatic carcinoma of the bronchus (*8*). These preliminary data indicate the necessity to have a quantitative measure of the normal adrenal medullary uptake, as in some cases uptake is low in this range of apudomas (*9*). We have used iodine-123 (^{123}I) labeled MIBG instead of ^{131}I-labeled MIBG for this purpose. Iodine-123 has a near optimum photon energy of 159 keV for imaging, combined with a short half-life of 13.2 hr, a lack of particulate radiation, and better radiation dosimetry per μCi administered. This allows the administration of up to 10 mCi of [^{123}I]MIBG, as this amount of activity gives a similar radiation dose as 0.5 mCi of [^{131}I]MIBG (*10*). Once a normal uptake range has been established, it will be helpful in differentiating patients with normal adrenals and those with adrenal medullary hyperplasia and/or small intra-adrenal pheochromocytomas.

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MATERIALS AND METHODS

Quantitation

The quantitation of activity in a small volume surrounded by a spatially inhomogeneous background activity is difficult and prone to errors. The size of the errors depends on several factors: the target-to-background count density ratio, the inhomogeneity of the background, and the total number of counts acquired in the image. In the example of the adrenal glands the uptake of [^{123}I]MIBG is low and the liver background activity is often comparable or higher. Frequently, particularly for the right adrenal, the edge of the liver is inconveniently placed across the gland in the images, presenting a highly inhomogeneous background. Clearly, an accurate reproducible background correction method is desirable. To examine the errors inherent in the quantitation process, an anthropomorphic phantom was constructed and three differ-

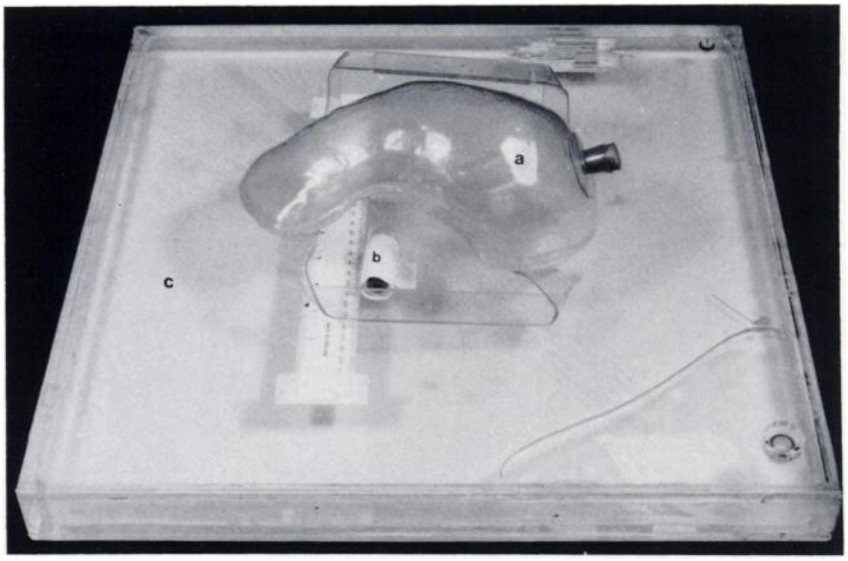

FIGURE 1
Adrenal phantom. a: Anthropomorphic liver; b: Simulated adrenal gland; c: Uniform background.

ent background correction algorithms were assessed by three independent observers.

The anthropomorphic phantom consisted of a vial containing ^{123}I to simulate an adrenal, attached to a flood phantom to simulate a uniform background component. In addition, an anthropomorphic liver phantom was included which could be moved across the flood phantom in steps of 1 cm. (Fig. 1). The activity levels in each part of the phantom were adjusted so that the ratio of peak counts in the "adrenal" to the "liver" to the "uniform background" was ~2:9:3. This simulated poor adrenal uptake and was, therefore, a worst case for quantitative accuracy. Four hundred thousand count images were acquired with the liver phantom positioned in such a way that its inferior border was: 0, 1, 2, 3, 4, 5, 6, and 11 cm superior to the center of the simulated adrenal gland. The 2 cm and 3 cm displacement images are shown in (Fig. 2).

Background Correction: Method 1

This is a standard method of background subtraction used in nuclear medicine. An irregular region of interest (ROI) was drawn around the adrenal manually and a 2-pixel-wide background region was created outside of this separated by 1 pixel. The background region was excluded from covering the liver and therefore did not necessarily completely surround the adrenal region. Correction was made in the usual way by normalizing the counts in the background region by the ratio of number of pixels in the two regions before subtracting them from the counts in the adrenal region.

Background Correction: Method 2

This is the Goris method of interpolative background correction using the weights of Watson (*11,12*). It is commonly applied to thallium cardiac images. A rectangular ROI is

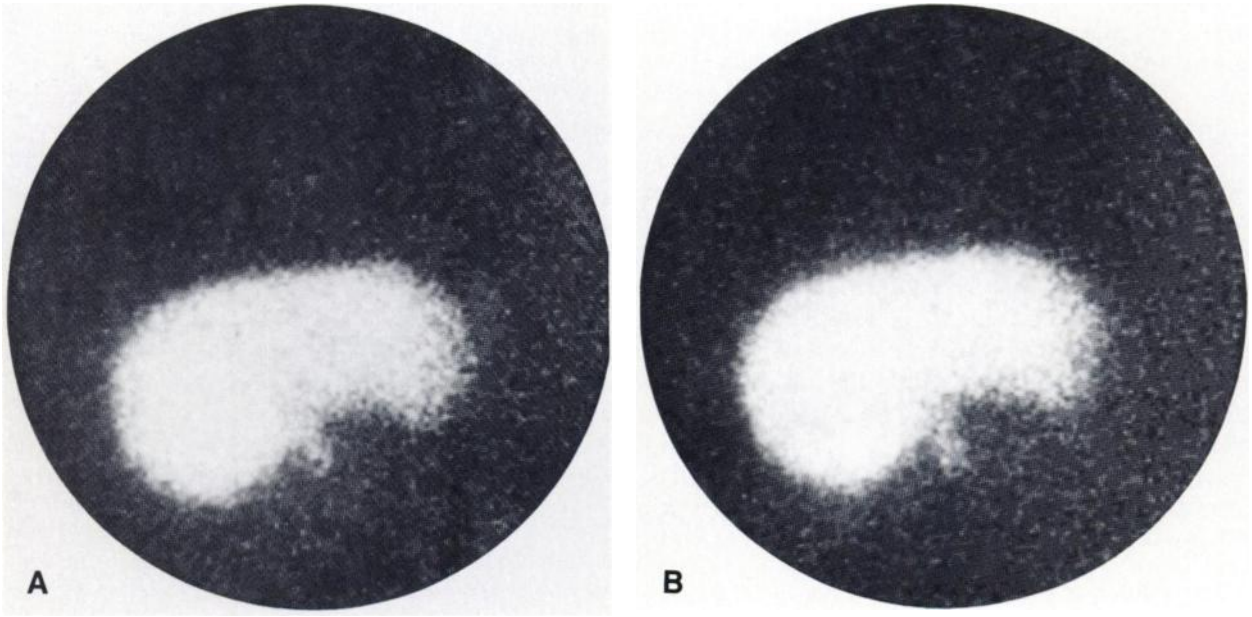

FIGURE 2
Phantom images for 400,000 counts. a: At 2 cm displacement; b: At 3 cm displacement.

drawn around the adrenal, expanded by three pixels, and the pixels at the edge are smoothed using a simple 9-point smooth. The background value of any pixel inside the expanded region is calculated as the weighted sum of the values of the four pixels at the edge having the same X or Y coordinates. Thus, a background interpolated image is formed; all pixels outside the expanded region retain their original values. The background interpolated image is then simply subtracted from the original image to give the background corrected result.

Background Correction: Method 3

This is an inverse square weighted interpolative method (*13*). An irregular ROI is drawn around the adrenal and expanded as per the Goris method. All the pixels at the edge (without being smoothed) contribute to the values of pixels within the expanded region. The weighting given to each edge pixel value is inversely proportional to the square of its distance from the pixel for which the background value is being calculated. A background interpolated image is created in a similar fashion to the previous method and subtracted in an identical manner to give the background corrected result.

The eight phantom images were analyzed by all three methods and by three independent observers. The results are shown graphically in (Fig. 3). Method 1 initially gives high values as the liver background is undersubtracted. As the liver displacement increases the values stabilize at a slightly low level and the interobserver variability decreases. The reason for the values being low is presumed to be due to a tendency for the observers to draw too small a region around the adrenal, resulting in an oversubtraction of the background. As these two sources of error are in opposite directions they tend to cancel out over part of the displacement range. The wide range of values found by the three observers makes accurate quantitation difficult.

Methods 2 and 3 both exhibit the tendency of simple interpolative schemes to overcorrect for inhomogeneities. In this context they spread the high counts in the liver too far into the expanded adrenal region, thus resulting in an oversubtraction of background. This underestimation will be greatest in cases of low adrenal uptake as simulated by the phantom, and so will not alter the normal range significantly. The low interobserver variability of Method 3 made it the preferred background subtraction method and it was used for analysis of all patient studies.

Patient Studies

Eighteen adult subjects were studied. They were all hypertensive and were selected on the basis of a high clinical suspicion for a pheochromocytoma, with raised or borderline raised biochemical levels of plasma catecholamines and/or 24-hr urinary vanillylmandelic acid (VMA) levels. The plasma concentrations of catecholamines were measured on samples obtained after an overnight fast, the patient having been in a supine and resting state for at least half an hour with an indwelling venous cannula in situ (*14*). The urinary VMA levels were determined on 12 hr overnight urine samples (*15*) and were expressed in μmol/24 hr. Prior to injection, a drug history was taken to rule out the possibility of reserpine, tricyclic antidepressant, and phenylpropanolamine usage as these drugs interfere with tracer uptake. The patients height and weight were recorded, and 400 mg of potassium perchlorate was given 30 min prior to study in order to block thyroid uptake of free iodine. Before each study the patient was asked to empty his/her bladder, as [^{123}I]MIBG is excreted largely in an unchanged form in the urine. MIBG was prepared as described by Wieland et al. (*1*). Iodine-123 produced by the ^{127}I(p,5n)^{123}Xe→^{123}I reaction (AERE, Harwell) was used. High purity of ^{123}I was achieved with no ^{124}I and <.02% of ^{125}I. The labeling was carried out with ^{123}I using a modified solid phase method in a closed system (*16*). The radiochemical yield was between 70–95% resulting in a specific activity of 1–5 mCi/mg. Free iodine was always <2%. The activity of the injection was measured in an ionization chamber before and after the injection, using the appropriate calibration factor. Between

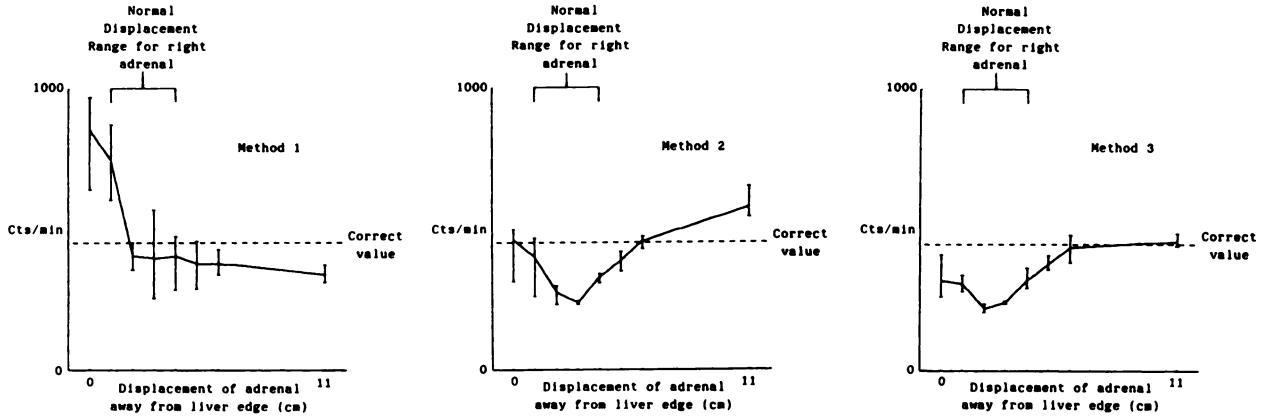

FIGURE 3

Comparison of background subtraction methods. (- - - -) Represents actual counts in adrenal phantom without background components; (——) Represents the means of the three observer values for each displacement. The error bars indicate the range of observer values.

I ← Maximum observer value

I ← Minimum observer value.

1.5–7 mCi of [^{123}I]MIBG was given intravenously over a period of 20–30 sec with the patient lying supine. Using a gamma camera* with a high resolution low-energy collimator and an on-line computer static images of 400,000 counts each were acquired for anterior abdomen, anterior chest, posterior abdomen, posterior chest and skull at 10 min, 4 hr and 22 hr.

Adrenal Uptake Measurement

This was carried out using only the posterior chest or posterior abdomen images at 22 hr as the adrenal medulla was not identifiable on the 10-min and 4-hr images. In cases where an adrenal could not be identified properly it was excluded from the study. Background correction was made using Method 3 described above. The background corrected values for uptake were modified to allow for attenuation by overlying tissue.

In ten patients the adrenal depth was measured using x-ray computed tomography (CT) data. In the other eight patients where this data was not available, the height and weight method was used to calculate kidney depth (*17*) and the adrenal depth was calculated from this value by adding 3.2 cm to allow for the mean difference between the depths of the two organs (*18*). Comparison of the two methods is given in Table 1. Depth correction factors were calculated from the attenuation curve for ^{123}I in perspex (Fig. 4). The background corrected adrenal counts were then multiplied by the appropriate factor. After a final correction for decay of the radionuclide the calculated values for adrenal uptake at 22 hr were expressed as a percentage of total injected dose.

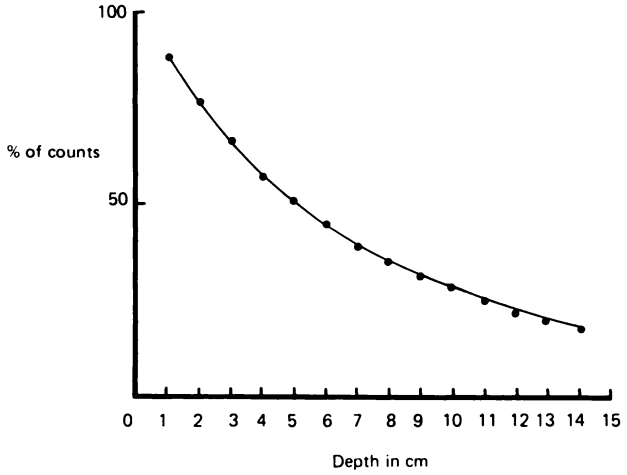

FIGURE 4
Attenuation factor for ^{123}I, measured in perspex.

RESULTS

Table 2 illustrates the clinical status of the patients and their biochemical values of plasma norepinephrine, epinephrine, and urinary VMA. In none of these hypertensive patients, was there any evidence for a pheochromocytoma at the time of study or on follow-up (mean time interval of sixteen months). In all cases except one both the adrenal medulla could be visualized at 22 hr (Fig. 5).

In Patient 1, the right adrenal medulla could not be defined clearly due to high liver background and this was excluded from the quantitative protocol. Patient 10 had her right adrenal resected due to previous surgery. The uptake for [^{123}I]MIBG by the adrenal medulla varied between 0.01% to 0.22% (median 0.11%) of the injected activity at 22 hr. The mean value ± s.d. for the left side was 0.08 ± 0.04% and on the right 0.06 ± 0.05%. In all subjects investigated there was no correlation found in the percentage uptake of [^{123}I]MIBG by the adrenal medulla and the biochemical levels of plasma catecholamines and/or urinary VMA. The clinical hypertensive status of these subjects did not show any correlation with the adrenal medullary uptake of [^{123}I]MIBG.

TABLE 1
Adrenal Depth Comparison

Patient no	Adrenal depth (cm) calculated through CT		Adrenal depth (cm) calculated through height and weight method		Difference in depth (cm)	
	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
1	14	12	12	12	2	0
2	14	14	12	12	2	2
3	9	9.5	9	9	0	0.5
4	11	10.5	10.5	10.5	0.5	0
5	13	12	11	11	2	1
6	11.5	10	10.5	10.5	1	−0.5
7	10.5	10	9	9	1.5	1
8	12	10.5	11	11	1	−0.5
9	13	11.5	11	11	2	0.5
10	10	Resected	8	Resected	2	Resected
				Mean values ± s.d.	1.4 ± 0.7	0.5 ± 0.8

TABLE 2
Biochemical Studies and [^{123}I]MIBG Uptake Measured at 22 hr in 18 Hypertensive Patients with No Adrenomedullary Abnormality

Patient no.	Plasma NE* pmol/ml	Plasma E† pmol/ml	Urinary VMA μmol/24 hr	^{123}I MIBG uptake expressed as % of injected dose LEFT	RIGHT
1	2.2	0.8	49	0.06	NI‡
2	0.8	1.0	15	0.06	0.05
3	2.0	0.1	35	0.10	0.02
4	12.6	1.1	10	0.06	0.02
5	—	—	32	0.22	0.06
6	—	—	78	0.04	0.02
7	2.2	0.7	122	0.08	0.08
8	—	—	79	0.08	0.01
9	0.8	1.5	84	0.13	0.13
10	1.9	0.2	35	0.05	Resected
11	2.2	0.1	30	0.07	0.01
12	—	—	78	0.05	0.02
13	—	—	44	0.08	0.17
14	2.9	0.2	39	0.08	0.04
15	1.7	0.1	36	0.08	0.17
16	1.0	0.7	28	0.05	0.02
17	3.6	0.8	24	0.12	0.10
18	0.8	1.0	41	0.03	0.04
Normal range	0.6–2	0.05–0.6	10–35	—	—
			Mean ± s.d.	0.08 ± 0.04	0.06 ± 0.05

* NE = Norepinephrine.
† E = Epinephrine.
‡ NI = Not identified clearly.

DISCUSSION

In patient studies high quality images were produced at 22 hr, when more than 4 mCi of [^{123}I]MIBG was injected and the adrenal medulla was always clearly visible in the posterior views. No correlation was found between the amount of activity injected and the % uptake of [^{123}I]MIBG by the adrenal medulla. When small amounts, 1.6 mCi or less, of [^{123}I]MIBG were administered, imaging times were increased and the image quality suffered due to patient discomfort and movement. This problem was particularly apparent for the right adrenal where there was a high background contribution from the underlying activity in the liver. A comparison of the adrenal depth, calculated by CT scan data and the height-weight formula gave a maximum discrepancy of 2 cm. This is to be expected because the estimated error of the CT technique is ~1 cm, and that of the height-weight formula somewhat higher. A 1-cm change in depth alters the calculated adrenal medullary uptake of [^{123}I]MIBG by ~11%. In this study an error of 2 cm would not alter the calculated range of percentage uptake in patients where the depth was calculated using the height-weight formula.

A wide range of normal adrenal medullary uptake of [^{123}I]MIBG was found in this study. The mean uptake of the left adrenal was 33% higher than for the right. This difference could be a result of oversubtraction of background for the case of the right adrenals, which are close to the edge of the liver. This would be in agreement with our phantom results. The upper limit of 0.22% in this study was found in Patient 5. In this patient the adrenals were identified clearly on CT and were of normal size and shape. This patient was labelled as essential hypertension on subsequent follow-up, as catecholamine levels over a period of 1 year have been within normal limits and no other stigmata for a clinical suspicion of pheochromocytoma could be found. In five patients where 48 hr images were acquired, the adrenal uptake was found to be lower than the 22 hr uptake. This would suggest that the 22 hr uptake is a reasonable measurement to take for interpatient comparisons.

In conclusion, the values for adrenal medullary uptake obtained in this study, form an appropriate control group range for comparison in patients with proven epinephrine or norepinephrine secreting tumors. This will also obviate the need for unnecessary further investigation in patients with borderline raised plasma norepinephrine, epinephrine or urinary VMA levels.

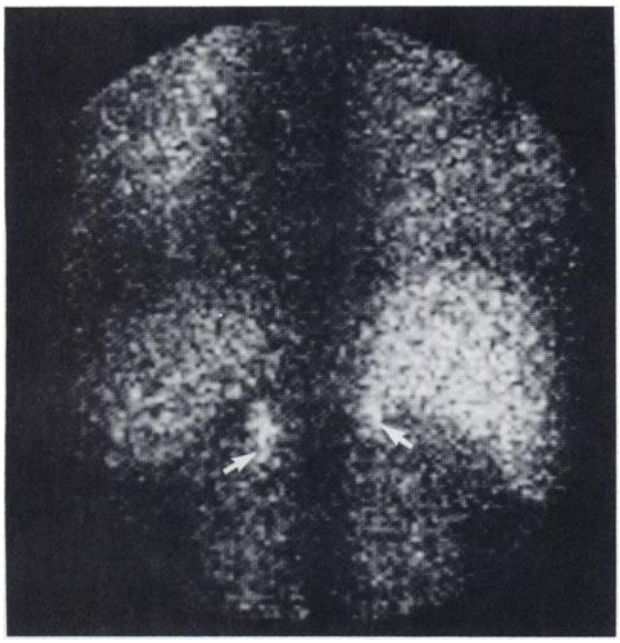

FIGURE 5
Posterior chest image, arrows indicate normal adrenal medulla 22 hr postinjection of [^{123}I]MIBG.

FOOTNOTE

*(Siemens ZLC). Searle-Siemens Medical Systems, Inc., Iselin, NJ.

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