Myocardial Uptake of Metaiodobenzylguanidine in Patients with Left Ventricular Hypertrophy Secondary to Valvular Aortic Stenosis

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The time course of myocardial uptake of metaiodobenzylguanidine ([¹²³I]MIBG) was studied in 26 patients: seven control subjects (Group 1) and 13 patients with left ventricular hypertrophy secondary to valvular aortic stenosis. Seven of these had received no treatment (Group 2) and six were receiving amiodarone or digoxin (Group 3); six heart transplant recipients were investigated for extra neuronal myocardial uptake of [¹²³I]MIBG (Group 4). The index of myocardial [¹²³I]MIBG uptake was lower in Groups 2 and 3 than in Group 1 (Group 2: 1.42 ± 0.07, p < 0.001; Group 3: amiodarone, 1.30 ± 0.10, p < 0.05; digoxin, 1.22 ± 0.06, p < 0.01; Group I: 1.83 ± 0.18) and lower in Group 3 than in Group 2. Patients of Group 4 showed a much lower mean index of myocardial [¹²³I]MIBG uptake than the control group (1.07 ± 0.08, p < 0.001). In conclusion:

- 1. Patients with left ventricular hypertrophy secondary to valvular aortic stenosis were found to have lower myocardial [¹²³I]MIBG activity and rapid washout than the control subjects.
- Amiodarone and digoxin partially inhibited myocardial [¹²³] MIBG uptake.
- 3. Extra neuronal myocardial uptake of [¹²³I]MIBG in humans only accounts for 13% of the total cardiac activity.

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Deveral clinical findings have suggested the involvement of sympathetic nervous system abnormalities in left ventricular hypertrophy, including microvascular spasm (1,2), a reduction in coronary reserve even when the coronaries are normal (3), increased ventricular arrhythmia and sudden death.

A technique for measuring neuronal uptake of norepinephrine in man was previously described (4,5) to investigate sympathetic nervous system modifications, especially neuronal accumulation of norepinephrine. By this technique, a decrease in neuronal uptake of tritiated norepinephrine was demonstrated in hypertrophic cardiomyopathy patients (6). However, current clinical applications with this technique are unlikely since it requires selective cardiac catheterization and the use of tritiated norepinephrine. To overcome this problem, subjects may be given ¹²³I-labeled metaiodobenzylguanidine (MIBG), an analog of norepinephrine (7). Uptake of this compound involves the same cell transport systems as those used by norepinephrine (uptake-one system, uptake-two system and vesicular uptake). On the other hand, MIBG is not metabolized and does not affect adrenergic membrane receptors. Changes in cardiac [¹²³I]MIBG uptake can be analyzed over time by external imaging with labeled ¹²³I and a standard gamma camera (8-10). The present study was aimed at investigating the time course of myocardial [¹²³I] MIBG activity in patients with left ventricular hypertrophy secondary to valvular aortic stenosis compared to that of control subjects and heart transplant recipients.

MATERIALS AND METHODS

Patients

Twenty-six patients were studied after informed consent was obtained. They were divided into four groups according to the following criteria:

Group 1: Seven control subjects (four men, three women, mean age 30 ± 15 yr) who showed no clinical signs of cardiac pathology.

Group 2: (Table 1) Seven patients with valvular aortic stenosis (four men, three women, mean age 62 ± 16 yr) who were without treatment (n = 4) or were receiving furosemide or heparin (n = 3), drugs which have no effect on myocardial [¹²³I]MIBG uptake (11,12). The coronarography showed coronary stenosis to be less than 20% in six of these patients, with 50% stenosis of the left anterior descending artery observed in the last patient.

Group 3: (Table 1) Six patients with valvular aortic stenosis (one man, five women, mean age 70.5 \pm 9 yr) who were receiving treatment with drugs known to affect myocardial uptake of tritiated norepinephrine or [¹²³I]MIBG. Three of these patients (three women, mean age 70 \pm 12 yr) were receiving amiodarone to prevent relapse of auricular fibrillation and paroxysmal tachyarrhythmia and the other three (two women, one man, mean age 71 \pm 7.5 yr) were receiving digoxin for class II (NYHA) cardiac heart failure (n = 2) or to reduce

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TABLE 1										
Hemodynamic Data for Patients with Left Ventricular Hypertrophy Secondary to Valvular Aortic Stenosis										

					Hemodynamic data		Doppler echocardiograph data					
Patients	Sex	Age	Weight (Kg)	AR	Syst press grad (mmHg)	LVEF	Septum (mm)	P Post (mm)	Grad mean (mmHg)	Grad max (mmHg)	[¹²³ I]MIBG uptake index	Treatment mg/wk
Group 2												
1	Μ	64	73		100	0.75	20	15	57	110	1.30	—
2	F	67	72	_	NA	0.77	15	15	74	107	1.38	FH
3	Μ	77	60	_	NA	0.85	13	10	39	68	1.45	
4	М	77	68	AR	60	0.63	_		41	65	1.43	н
5	F	30	54	AR	NA	0.64	12	12	62	125	1.38	
6	F	65	65		70	0.71	14	_	50	79	1.54	_
7	М	53	77	AR	100	0.39	15	13	55	90	1.44	FH
Mean ±	s.d.	62 ± 16	67 ± 8		82.5 ± 20.6	0.68 ± 0.15	14.8 ± 2.8	13 ± 2	54 ± 12	92 ± 22.7	1.42 ± 0.07	
Group 3 (with Amiodarone)												Amiodarone
1	F	60	78	AR	65	0.26	12	11	40	65	1.19	1400
2	F	83	50	—	NA	NA	14	12	60	90	1.34	800
3	F	68	67	AR	110	0.79	17	14	70	110	1.38	100
Mean ±	s.d.	70 ± 12	65 ± 14	ł			14.3 ± 2.5	12.3 ± 1.5	57 ± 15	88 ± 22	1.30* ± 0.10	
Group 4 (with digoxin)												digoxin
4	F	75	58		NA	0.77	21	15	106	156	1.28	1
5	F	75	70		75	0.80	15	_	70	110	1.17	1.25
6	м	62	55	_	NA	0.56	12	12	56	100	1.22	1.50
Mean ±	s.d.	71 ± 7.5	61 ± 8			0.71 ± 0.13	16 ± 4.5	13.5 ± 2	77 ± 26	122 ± 30	$1.22^{\dagger} \pm 0.06$	

* p < 0.05 for nontreated patients.

 † p < 0.01 for nontreated patients.

AR = aortic regurgitation, LVEF = left ventricular ejection fraction, F = furosemide, H = heparin, NA = not available.

the heart rate (n = 1). Coronary angiography was normal in all of these patients.

Group 4: Six heart transplant recipients (six men, mean age 43 ± 10 yr) were studied to compare extra neuronal cardiac uptake of [¹²³I]MIBG with neuronal cardiac uptake. Radioisotopic exploration was performed 15 ± 10 mo after cardiac transplantation surgery. There were no clinical signs of rejection and no pericardial effusion for any of these patients on the date of the examination. They were being treated with cyclosporine, azathioprine and corticosteroids.

Myocardial [123]MIBG Scintigraphy

Iodine-123-MIBG was obtained commercially (CIS Bio International, France). A capsule of potassium perchlorate (40 mg) was given orally 2 hr before intravenous injection of [123]MIBG and 6 hr after to block thyroidal uptake of ¹²³I. This treatment was continued for two days thereafter (two capsules daily). Each subject was given 148 MBq (4.0 mCi) [123I]MIBG via the antecubital vein. Cardiac images were acquired in a 45° left anterior oblique projection using a standard-field gamma camera equipped with a medium-energy parallel-hole collimator. A 20% window was used centered at 159 keV. All data were recorded by a nuclear medicine computer for display and semiquantitative analysis. Imaging was performed 0.3 hr and 1 hr postinjection in 18 patients (seven control subjects, six heart transplant recipients and the five nontreated valvular aortic stenosis patients) and 4 hr postinjection in all patients. Each image represents the cardiac activity detected over 4 min.

Data Processing

To evaluate the myocardial uptake of $[^{123}I]MIBG$, two regions of interest (ROI) were drawn manually on the 45° left anterior

oblique image. The first (ROI 1) delineated the myocardium and the second (ROI 2) delineated the mediastinal region, excluding the large vessels at the base and the lungs. The myocardial uptake index for [¹²³I]MIBG was then calculated by the following formula:

Uptake Index =
$$\frac{(activity in ROI 1/pixels in ROI 1)}{(activity in ROI 2/pixels in ROI 2)}$$
. Eq.1

This myocardial uptake index for [123 I]MIBG was calculated from scintigrams obtained at 0.3 hr, 1 hr and 4 hr postinjection. Intra- and between-operator reproducibility of the above calculation was assessed. Calculation of the myocardial uptake index for [123 I]MIBG in 10 patients by two separate operators showed a mean difference of 0.016, with a standard deviation of 0.041 (ns). The same calculation repeated twice by one operator showed a mean difference of 0.043, with a standard deviation of 0.077 (ns).

Statistical Analysis

Data are expressed as mean \pm s.d. for each patient group. The Mann-Whitney test was used for between-group comparisons. A p value of < 0.05 was statistically significant.

RESULTS

Control Subjects

The mean index of myocardial [¹²³I]MIBG uptake was 1.90 ± 0.30 at 20 min postinjection. At 1 hr postinjection, this index was 1.86 ± 0.30 (ns) with a subsequent mean decrease of 0.5%/hr from 1 hr postinjection, reaching 1.83 \pm 0.18 (ns) at 4 hr postinjection.

Nontreated Patients with Left Ventricular Hypertrophy Secondary to Valvular Aortic Stenosis (Table 1)

The mean index of myocardial [¹²³I]MIBG uptake was lower than that of the control subjects at 20 min postinjection (1.55 \pm 0.18, p < 0.05). At 1 hr postinjection, this difference was still observed (1.53 \pm 0.12, p < 0.05), with a subsequent mean decrease of 2.3%/hr until 4 hr postinjection (1.42 \pm 0.07, p < 0.001).

There was no significant correlation between the index of myocardial [¹²³I]MIBG uptake at 4 hr postinjection and the left ventricular mass calculated from echocardiographic data as described by Devereux (13) (r = 0.37, ns).

Patients with Left Ventricular Hypertrophy Secondary to Valvular Aortic Stenosis Treated with Amiodarone (n = 3) or Digoxin (n = 3) (Table 1)

The mean index of myocardial [123 I]MIBG uptake at 4 hr postinjection was significantly lower than that in the nontreated patients with the same pathology (respectively 1.30 ± 0.10, p < 0.05 and 1.22 ± 0.06, p < 0.01 for the amiodarone- and digoxin-treated patients versus 1.42 ± 0.07 for the nontreated group).

Heart Transplant Recipients

The mean index of myocardial [123 I]MIBG uptake at 20 min postinjection was markedly lower than that of the control subjects (1.12 ± 0.09 versus 1.90 ± 0.30, p < 0.001). This difference was maintained at 1 hr and 4 hr postinjection (1.11 ± 0.10 versus 1.86 ± 0.30, p < 0.001) and 1.07 ± 0.08 versus 1.83 ± 0.18, p < 0.001). There was a mean decrease of 1.2%/hr from 1 hr to 4 hr postinjection.

DISCUSSION

Iodine-123-labeled metaiodobenzylguanidine is considered to be a nonmetabolizable analog of norepinephrine (14) which can be used to evaluate the functional condition of sympathetic innervation in the myocardium through external detection of cardiac activity (9). Following intravenous injection, [123I]MIBG present in the synaptic gap is taken up by the sympathetic nerve endings (neuronal uptake) and by the myocardial cells (extra neuronal uptake) (14-16). Both neuronal and extra neuronal cardiac activity are thus detected. The relative proportions of these two types of cardiac activity has yet to be defined. After cardiac transplantation, extra neuronal myocardial ¹²³I]MIBG uptake is quite low (17) or null (18) in man, whereas this uptake accounts for as much as 31% of total cardiac activity in the rat (14) and 61% in the dog (19). We decided to measure myocardial [123I]MIBG uptake in six heart transplant recipients since very few transplant patients have undergone myocardial imaging with [¹²³I] MIBG (eight patients to date). The index of myocardial ¹²³I]MIBG uptake was very low in these patients. Since calculation of this index is dependent on mediastinal activity, we compared the mean activity per pixel in the mediastinal ROI of heart transplant patients with that of the control subjects. No differences in mediastinal activity were noted (281 ± 87 cps versus 300 ± 49 cps in the control subjects). This could not be explained by a greater attenuation of radioactivity in heart transplant recipients due to pericardial effusion since these patients did not show this clinical sign on the date of echocardiographic and scintigraphic imaging. Moreover, the very low mean index of myocardial [¹²³I]MIBG uptake at 20 min postinjection (1.12) is evidence of low extra neuronal [¹²³I]MIBG cardiac activity in man. Extra neuronal cardiac uptake of [¹²³I]MIBG was only 13% of total cardiac uptake in the control group (1.12–1.00/1.90–1.00). The index of myocardial uptake of [¹²³I]MIBG thus essentially provides an estimate of neuronal [¹²³I]MIBG activity.

In patients with left ventricular hypertrophy secondary to valvular aortic stenosis, the index of myocardial [¹²³I] MIBG uptake was less than that of the control subjects at all measurement times, and washout of cardiac radioactivity was faster from 1 hr to 4 hr postinjection.

In these patients, the low myocardial uptake of [¹²³I] MIBG observed at 4 hr postinjection was evidence of a low myocardial concentration of norepinephrine since, in man, the myocardial uptake index 4 to 6 hr after intravenous injection is significantly correlated with the myocardial norepinephrine concentration (20).

To explain the presence of a small myocardial [¹²³I] MIBG pool with rapid turnover in these patients, two hypotheses can be proposed:

- 1. The sympathetic nervous system is hyperstimulated in patients with left ventricular hypertrophy, as reported in the rat after banding the abdominal aorta (21), and in Syrian hamsters with left ventricular hypertrophy without cardiac insufficiency (2,22).
- 2. In human patients with left ventricular hypertrophy secondary to aortic stenosis, cellular ATP is depleted even when the coronaries are normal (23). A cellular energy deficit can result in a reduction in the activity of the different norepinephrine transporters (24). This is shown by a reduction in norepinephrine storage and an increase in its neuronal release. In these patients, since [123I]MIBG uses the same cell transporters (14), neuronal uptake and storage of ¹²³I]MIBG was therefore reduced. This could explain the rapid washout of cardiac [¹²³I]MIBG, since the extravesicular compartment empties faster than the vesicular compartment (25). Moreover, a reduction in neuronal uptake of tritiated norepinephrine has been previously demonstrated (6) in cases of primary hypertrophic cardiomyopathy in man.

In the patients with left ventricular hypertrophy secondary to valvular aortic stenosis treated with amiodarone or digoxin (Group 3), the index of myocardial [¹²³I]MIBG uptake was lower than that of the nontreated patients with the same pathology (Group 2). The mechanism of action of amiodarone on [¹²³I]MIBG or norepinephrine metabolism has yet to be defined.

However, pharmacological studies in animals have shown that ouabain inhibits neuronal uptake of tritiated norepinephrine (26-32) and increases neuronal release of norepinephrine (31,32). The very low myocardial uptake of [¹²³I]MIBG observed in the digoxin-treated patients was thus due to the action of digoxin on the [¹²³I]MIBG cell transport mechanisms.

In conclusion, the present results demonstrate that:

- In patients with left ventricular hypertrophy secondary to valvular aortic stenosis, we observed low neuronal cardiac uptake of [¹²³I]MIBG relative to the control subjects, with a rapid washout of this drug.
- 2. Amiodarone and digoxin partially inhibited myocardial uptake of [¹²³I]MIBG.
- 3. In man, extra neuronal myocardial [¹²³I]MIBG uptake only accounts for a minor part of the total myocardial uptake.

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