Long term course and cardiac sympathetic nerve activity in patients with hypertrophic cardiomyopathy

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Abstract

***Objective*—To investigate the relation between regional myocardial sympathetic nerve activity and the electrocardiographic and cardiac functional changes in hypertrophic cardiomyopathy.**

***Design*—A retrospective study to compare the findings of myocardial scintigraphy with iodine-123 meta-iodobenzylguanidine (MIBG) and the serial electrocardiographic changes.**

***Setting*—Myocardial scintigraphy was performed with iodine-123 MIBG and thallium-201 and single photon emission computed tomography (SPECT) in the division of nuclear medicine of Kanazawa University Hospital. Both SPECT studies were performed within a week.**

***Patients*—22 patients with hypertrophic cardiomyopathy classified according to their serial electrocardiographic changes—namely, 15 patients with an increase in or the appearance of a negative T wave (group A) and seven patients with a conduction disturbance or a decrease in or disappearance of the negative T wave (group B). The mean follow up period was 45 (range 12–143) months.**

***Results*—Group B showed a high rate of decreased activity or defects in MIBG uptake compared with group A ($p < 0.005$). The areas of decreased activity or defects corresponded with the hypertrophied portion of the left ventricular wall. Although the early myocardial uptake (MIBG: thallium ratio) was similar in both groups, the mean (SD) MIBG clearance rate was significantly higher ($p < 0.05$) in group B (0·25 (0·17)) than in group A (0·10 (0·15)).**

***Conclusion*—Abnormalities of regional myocardial sympathetic nerve activity may be important in patients with hypertrophic cardiomyopathy and suspected progression of myocardial damage.**

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Accepted for publication 20 June 1991

The clinical course of hypertrophic cardiomyopathy varies considerably. Some patients remain symptom free for many years, whereas others die suddenly or develop congestive heart failure after a short time. Cases in which the disease progresses to a dilated cardiomyopathy, with left ventricular dilatation, left ventricular wall thinning, and left ventricular systolic impairment, have also been reported.[1–3] Electrocardiographic changes, particularly in T waves, occur in hypertrophic cardiomyopathy. We examined the relation between these T wave and functional changes, and reported that cardiac function was depressed in patients in whom a negative T wave decreased or disappeared.[4] It is not known how localised sympathetic nerve activity in the heart is involved in these changes.

Meta-iodobenzylguanidine (MIBG) is a guanetidine analogue known to produce effects similar to those of noradrenaline. For this reason scintigraphy with radiolabelled analogues shows promise as an aid in the study of the role of sympathetic nerve innervation in heart function.[5–7] In the present study we used MIBG to investigate the relation between sympathetic nerve activity in different myocardial regions and the electrocardiographic and cardiac functional changes that occur in hypertrophic cardiomyopathy.

Patients and methods

PATIENTS

We studied 22 patients with hypertrophic cardiomyopathy in whom electrocardiographic changes could be serially followed for more than 12 months. Hypertrophic cardiomyopathy was diagnosed in 20 of these patients by cardiac catheterisation with endomyocardial biopsy and in the remaining two patients by electrocardiographic and echocardiographic testing. As judged by left ventriculography, biventriculography, and echocardiography, hypertrophy, mainly of the interventricular septum, was present in 19 patients, hypertrophy of the apical portion in two patients, and global hypertrophy in one patient. The disease was non-obstructive in 20 and obstructive in two patients. The 22 patients were classified into two groups based on the serial electrocardiographic changes. Group A consisted of those who showed an unchanged T wave, positive T wave disappearance, or negative T wave deepening of more than 0·5 mV, during the study. Group B consisted of patients whose negative T wave decreased by more than 0·5 mV or those in whom the conduction system was disturbed. There were 15 patients (11 men and four women) in group A, and seven patients (four men and three women) in group B. In group A 12 patients were in New York Heart

York Heart Association class I and three were in class II. In group B four were in class II and three were in class III.

SCINTIGRAPHY

The patients were instructed to fast on the day of the radionuclide study and to continue the fast until the study ended. The patients received their usual medications, which included calcium channel blockers and antiarrhythmic agents. No patient was receiving reserpine or tricyclic antidepressants. All patients gave their informed consent to the protocol of MIBG imaging as part of a clinical trial.

An intravenous injection of 140–180 MBq (3·8–4·9 mCi) of ^{123}I-MIBG was given between 9.00 and 10.00 am and the first and second single photon emission computed tomography (SPECT) studies were started about 20 minutes and three hours thereafter. The SPECT system (Shimazu ZLC 7500-scintipac 700) consisted of a dual headed scintillation camera equipped with high resolution, low energy, parallel hole collimators. A total of 60 projection images were obtained over 360° in 6° increments with 30 seconds for each view. After preprocessing of the projection images with nine point weighted smoothing, transaxial tomographic slices were reconstructed by use of Shepp-Logan's filtered back projection algorithm. Neither a scatter correction nor an absorption correction was applied.

The thallium-201 SPECT study was performed within a week of the MIBG study with only a resting image obtained. Data acquisition was started 15 minutes after the administration of 120 MBq (3·2 mCi) thallium-201. The acquisition conditions and reconstruction method were the same as those of the MIBG study.

DATA ANALYSIS

The SPECT data were analysed as follows: rectangular regions of interest, usually 5 × 5 pixels in size, were placed over the septum, apex, lateral wall, lung, and mediastinum in both the ^{123}I-MIBG and ^{201}Tl transaxial images. To calculate the absolute uptake, an 8 ml vial containing 7·4 MBq (0·2 mCi) of either ^{123}I-MIBG or ^{201}Tl was placed in the centre of rotation in air and the SPECT count in the reconstructed image was measured. A cross calibration factor between the SPECT count and the amount of radioactivity was determined. The total injected dose in each patient was calculated by the difference between the radioactivities of the syringe before and after injection. The average SPECT count in a region of interest was divided by the total injected dose after conversion from MBq to counts by means of the cross calibration factor. For the delayed image the value was again corrected for the size and decay of the region of interest. To estimate the MIBG concentration per unit of blood flow the uptake ratio MIBG:thallium was calculated from the corrected uptake. The clearance rate of MIBG (washout rate) was calculated as (early uptake − delayed uptake) ÷ early uptake in each segment from the regions of interest on transaxial images. These analyses were performed on the septum, generally the most hypertrophic region, and on the apical portion.

Visual evaluation of the presence or absence of defects in the MIBG SPECT images was performed in the following way to minimise bias in interpretation. A group of cardiologists determined the most hypertrophic region from the ventriculographic and echocardiographic findings. Sites of MIBG defects were determined in the delayed MIBG images by two nuclear medicine experts who were unaware of the ventriculographic and echocardiographic findings. Finally the two sets of results were combined.

ECHOCARDIOGRAPHY

Cross sectional echocardiographic studies that comprised long axis, short axis, and apical four chamber views were performed within one week of the radionuclide studies in all patients. The hypertrophied sites were identified and the thickness of the septum and posterior wall of the left ventricle was measured.

STATISTICAL ANALYSIS

All data are expressed as mean (1 SD). The significance of the variance of the means was determined by Student's t test. The presence of MIBG defects was assessed by the χ^2 test. Differences were considered statistically significant at $p < 0{\cdot}05$.

Results

There was no significant age difference between the two groups (50·1 (11·4) for group A and 59·4 (7·3) for group B). Also the thickness of the left ventricular wall did not differ significantly between the two groups (interventricular septal thickness 16·3 (3·4) mm and 18·3 (2·0) mm, left ventricular posterior wall thickness 12·1 (3·0) mm and 10·7 (2·9) mm in groups A and B respectively).

ELECTROCARDIOGRAPHIC CHANGES AND MIBG DEFECTS

The table shows the serial electrocardiographic changes, hypertrophied sites, and MIBG defect sites. Mean follow up was 45 (range 12–143) months. In group A the electrocardiographic changes consisted of further deepening of the negative T wave in one patient and no change in the other 14. By contrast, in group B the negative T wave decreased in four patients including one patient in whom it disappeared. The results for the remaining three patients were complicated by conduction system disturbances consisting of atrial fibrillation, right bundle branch block, and sick sinus syndrome in one case each. Defects in MIBG uptake were found in only one of the 15 patients of group A but in six of the seven patients in group B ($p < 0{\cdot}005$), the one remaining patient in group B had a thallium scan defect in the hypertrophied interventricular septum. The MIBG defect sites were mostly at the sites of wall hypertrophy (table).

Electrocardiographic changes, sites of wall hypertrophy, and MIBG defects

Patient (age) sex	*ECG change*		*Hyper-trophy*	*MIBG defect*
Group A:				
1 (45) M	LVH NT	→ NT↑	AS	
2 (53) F	LVH	→ NC	ALL	
3 (63) M	LVH NT	→ NC	AS	
4 (69) M	LVH GNT	→ NC	AS,Ap	
5 (28) M	LVH NT	→ NT↑	Ap	
6 (54) M	LVH NT	→ NC	AS, Ap	
7 (44) M	LVH GNT	→ NC	AS	
8 (40) M	LVH NT	→ NT	AS, Ap	
9 (54) M	h-R NT	→ NC	S	
10 (67) F	LVH	→ NC	AS, Ap	A, Ap
11 (53) F	LVH	→ NC	AS	
12 (39) M	LVH NT	→ NC	Ap	
13 (48) M	LVH NT	→ NC	AS, Ap	
14 (56) F	LVH	→ NC	AS	
15 (38) M	LVH NT	→ NC	AS	
Group B:				
1 (69) M	LVH GNT	→ NT↓	AS, Ap	Ap
2 (57) F	LVH NT	→ Af	AS	
3 (66) M	LVH GNT	→ NT↓	AS, Ap	AS, Ap, I
4 (63) M	LVH GNT	→ NT↓	AS, Ap	AS, Ap, I
5 (58) F	LVH RBBB QS	→ NC	AS	S
6 (47) M	LVH GNT	→ NT↓	AS, Ap	Ap
7 (56) F	LVH SSS	→ NC	S, I	S, I

ECG, electrocardiogram; LVH, left ventricular hypertrophy; NT, negative T wave (less than −1·0 mV) in precordial leads; GNT, giant negative T wave (more than −1·0 mV) in precordial leads; NT↑ increased negative T wave; NT↓, decrease or disappearance of negative T wave; h-R, high R wave in right precordial leads; RBBB, right bundle branch block; QS, QS pattern in anterior precordial leads; SSS, sick sinus syndrome; Af, atrial fibrillation; NC, no change; ALL, global hypertrophy of left ventricle; AS, anteroseptal wall; A, anterior wall; S, interventricular septum; Ap, apex; I, inferior wall.

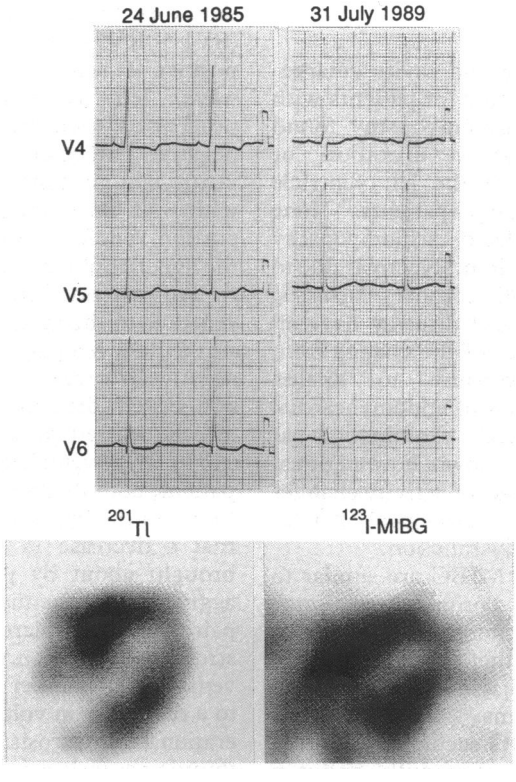

Figure 1 Electrocardiograms from a patient in group A showing slight T wave changes between the electrocardiograms. Increased accumulation, predominantly in the interventricular septum, was found on both the thallium image and MIBG image.

EXAMPLES OF ACTUAL CASES

Figure 1 shows the results for one patient in group A, a 53 year old woman. Only slight T wave changes occurred between the 1985 and 1989 electrocardiograms. On the thallium image increased accumulation occurred predominantly in the interventricular septum; increased accumulation at the same site on the MIBG image. Figure 2 shows the results for one patient in group B, a 66 year old man. A giant negative T wave of >1·0 mV was found on the 1977 electrocardiogram. This had disappeared on the 1989 electrocardiogram. On the thallium image increased accumulation was found predominantly in the apex whereas on the MIBG image defects were found from the apex to inferior wall and part of the anterior wall.

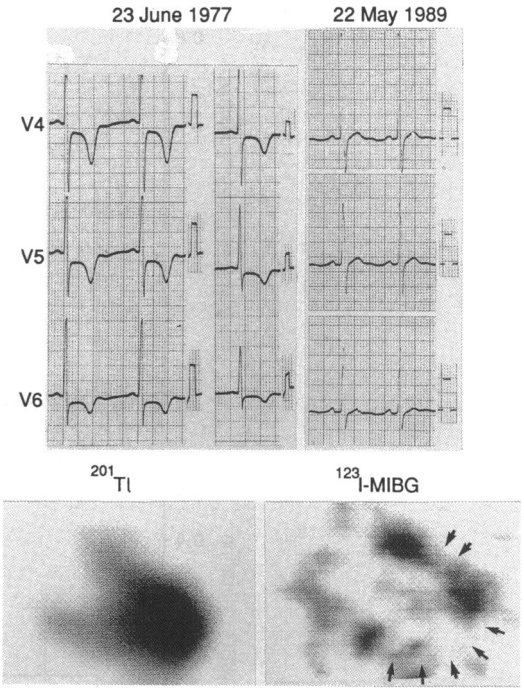

Figure 2 Electrocardiograms from a patient in group B showing that the giant negative T wave had disappeared from the second electrocardiogram. On the thallium image increased accumulation was found predominantly in the apex. On the MIBG image defects were found in the apex, inferior wall, and anterior wall (arrows).

EARLY UPTAKE AND CLEARANCE OF MIBG

There was no difference in early uptake (MIBG : thallium) between the two groups (0·57 (0·17) for group A and 0·58 (0·20) for group B). By contrast, MIBG clearance was significantly greater in group B (0·25 (0·17) *v* 0·10 (0·15)) (fig 3).

Discussion

Disproportionate hypertrophy of the left ventricle is a characteristic feature of hypertrophic cardiomyopathy, the clinical course of which is extremely variable. In 1979 Cate and Roelandt reported on two adult patients with hypertrophic obstructive cardiomyopathy who showed left ventricular dilatation.[1] Subsequently, there have been several reports of patients with hypertrophic cardiomyopathy undergoing transition to a dilated cardiomyopathy-like disease over a course of three to 17 years.[2 3 8] Spirito *et al* investigated 217 patients with hypertrophic cardiomyopathy and reported left ventricular systolic dysfunction in about 10%.[9] Also patients with a poor left ventricular ejection fraction also had left

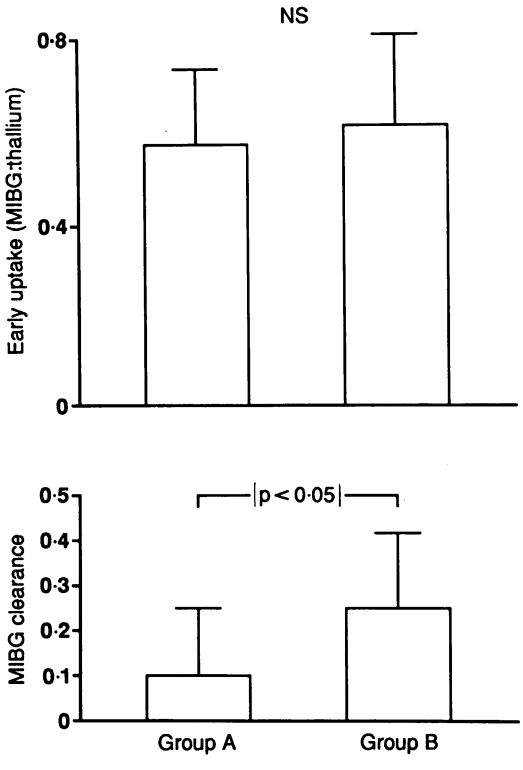

Figure 3 Early uptake and MIBG clearance in the two groups. There was no difference in early uptake between the two groups but clearance of MIBG was significantly greater in group B.

ventricular wall thinning and cavity enlargement. Nagata *et al* in a study of patients with familial hypertrophic cardiomyopathy found that older patients show dilatation or diminished contraction of the left ventricle more frequently than younger patients.[10] None the less, transition to dilated cardiomyopathy has been reported in children.[2] Necrosis due to narrowing of the small coronary arteries, progression of fibrosis, and disarray have all been implicated as causes of the change from hypertrophic cardiomyopathy to dilated cardiomyopathy in studies of endomyocardial biopsies and histological examination at necropsy.[3 11 12] It is not known how regional myocardial sympathetic nerve activity changes in association with these histological changes and myocardial systolic dysfunction.

Because the effects of MIBG are similar to those of noradrenaline, is a promising indicator of regional sympathetic nerve activity and is already used as a sympathetic nervous system imaging agent in the diagnosis of disorders such as pheochromocytoma.[13–15] Recently it has been reported that MIBG accumulates in the heart as well as the adrenal medulla, and it is attracting attention as a useful indicator of cardiac sympathetic nerve activity. Despite experimental evidence that catecholamines are involved in the aetiology of hypertrophic cardiomyopathy,[16] there have been few reports of sympathetic nerve imaging in this condition.

We used MIBG to evaluate the correlation between sympathetic nerve function in the heart and the pathophysiological changes that occur in hypertrophic cardiomyopathy. Transport of MIBG to the tissues is dependent on blood flow. In hypertrophic cardiomyopathy the small coronary arteries are narrowed,[17 18] and diminished coronary flow reserve[19 20] and perfusion abnormalities have been shown by thallium myocardial scintigraphy.[21 22] To correct for the influence of these blood flow abnormalities, MIBG uptake was expressed as a ratio to thallium uptake imaged under the same conditions. At the time of visual evaluation, we judged as abnormal only those sites that showed adequate thallium accumulation together with decreased MIBG accumulation or defects; we excluded patients that showed defects on the thallium image. Because at that time there were no established quantitative nuclear medicine techniques to correct for scatter and absorption such correction was not attempted. Thus correction factors were not a source of error when the uptake ratio MIBG: thallium was calculated.

The electrocardiographic course in 100 patients with hypertrophic cardiomyopathy was assessed by McKenna *et al*; follow up results showed increased voltage in most and reduced voltage in only four patients.[23] We previously reported in a study of patients with hypertrophic cardiomyopathy in whom left ventriculography was performed more than twice that T wave changes on the electrocardiograms more sensitively expressed the pathophysiological changes of hypertrophic cardiomyopathy than did the differences in voltage (SV1 + RV5).[4] In cases showing inversion of a positive T wave or increase of a negative T wave, left ventricular wall hypertrophy progressed. Conversely, in cases in which a negative T wave decreased or disappeared, left ventricular systolic function was depressed with wall thinning, particularly of the apical portion. A defect in MIBG uptake was found in the hypertrophied site in only one case in group A. This extended from the anterior of the left ventricle to the apical portion. By contrast, in six of the seven patients in group B in whom a negative T wave decreased or in whom conduction system disturbances were found, MIBG defects centred roughly on the site of hypertrophy in the ventricle and in the one remaining patient, both thallium and MIBG defects were found in the hypertrophied site. We speculate that a decrease in the negative T wave is brought about by primary changes such as aggravated ischaemia due to progressive impairment of the microcirculation and increased stress in association with dilatation of the left ventricular chamber. Secondary changes due to a reduction in voltage after myocyte degeneration and necrosis and left ventricular wall thinning as well as interventricular conduction disturbances may also play a part. A decrease in the negative T wave was found in four of the seven patients in group B, although this was accompanied by a decrease in the R wave in only two of these patients. This suggests that decreases in the negative T wave and R wave are not necessarily associated. Also, findings that suggested worsening of conduction disturbances, such as prolongation of the QRS interval, were not found in any patient. This suggests that this decrease in the negative T wave does not have a single cause, but is the

result of various factors such as myocyte degeneration and necrosis and aggravation of ischaemia leading to the development of myocardial interstitial fibrosis and changes in cardiac sympathetic nerve distribution—these are indicated by the MIBG defects. The possibility that primary abnormalities of the cardiac sympathetic nerves influence the myocytes and result in T wave changes, cannot however, be excluded.

To evaluate the MIBG uptake per unit of blood flow, the MIBG : thallium ratios from the regions of interest were examined. No difference in early uptake between the two groups was found, but MIBG clearance was greater in group B. Henderson *et al* studied 16 patients with congestive cardiomyopathy and reported that the distribution of MIBG activity within the myocardial images showed significantly greater heterogeneity in the congestive cardiomyopathy group than in the controls.[24] This is consistent with the results of our group B. It is thought that a major component of the myocardial retention of MIBG is sequestration within the noradrenaline storage vesicles of the adrenergic nerves.[5] Nakajo *et al* in a study of the rat heart reported that intravesicular accumulation was relatively uniform, with a plateau reached about four hours after intravenous injection, whereas extravesicular accumulation rapidly decreased from five minutes to six hours after injection.[25] They also studied MIBG movement, distinguishing between intravesicular and extravesicular sites. So there are two explanations why early uptake does not differ between the two groups though clearance is greater in group B. One possibility is that in group B there are few storage vesicles in the cardiac sympathetic nerve endings and so changes in extravesicular accumulation of MIBG play a major part, with a large MIBG clearance as a result. The second possibility is that in group B MIBG turnover is enhanced. According to the report of Glowniak *et al*, uptake of MIBG in the transplanted heart, amounts to less than 10% of the uptake in controls.[26] So an enhanced MIBG turnover seems more likely. Because cardiac function was more often depressed in group B than in group A we think that myocardial necrosis and scarring developed owing to increased disarray and fibrosis and this led to abnormalities of regional sympathetic nerve distribution. These abnormalities coupled with diminished systolic force enhance cardiac sympathetic nerve activity and noradrenaline turnover. Kawai *et al* reported that intramyocardial noradrenaline was reduced in dilated cardiomyopathy.[27] We believe that as with the disease progressed cardiac noradrenaline was further reduced leading to a reduction of MIBG uptake and that ischaemia due to narrowing of the intramyocardial small coronary arteries and increased fibrosis resulted in considerably depressed cardiac function and in thallium defects. Recently, reports that mutations in the cardiac myosin heavy chain genes are present in patients with familial hypertrophic cardiomyopathy[28 29] have been attracting attention. On the other hand, Weber *et al* reported that structural remodelling of collagen, which is the extracellular matrix of the myocardium occurs in left ventricular hypertrophy.[30]

How are these abnormalities related to the lack of sympathetic homogeneity found in the hearts of patients with hypertrophic cardiomyopathy? Clarification of this point awaits the results of future studies. Data on normal subjects would be of interest, but because this study was conducted as part of a clinical trial, it was limited to patients with hypertrophic cardiomyopathy. Patients in group B were studied for longer than patients in group A (72 (44) *v* 32 (16) months). Further studies are needed to determine whether these changes occur in patients with hypertrophic cardiomyopathy during a long follow up period and to determine the relations between these changes, progression of the disease process, and prognosis.

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