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Cardiac Sympathetic Activity in the Asymmetrically Hypertrophied Septum in Patients with Hypertension or Hypertrophic Cardiomyopathy

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Summary

Background: In patients with essential hypertension (HT), proportional (symmetric) left ventricular hypertrophy (LVH) is common. In contrast, hypertrophic cardiomyopathy (HCM) is characterized by disproportional LVH and, in particular, asymmetric septal hypertrophy (ASH); however, some hypertensive patients also develop ASH. It has not been determined whether such cases represent a distinct type of hypertensive LVH or HCM combined with hypertension.

Hypothesis: The study was undertaken to evaluate sympathetic activity in the interventricular septum in patients with HT and ASH or in patients with HCM.

Methods: The patients were evaluated by I-123 meta-iodobenzylguanidine (MIBG) and thallium-201 (^{201}Tl) single-photon emission computed tomography (SPECT), respectively. They were divided into three groups: patients with essential HT and symmetric septal hypertrophy (Group A), patients with HT and ASH (Group B), and patients with HCM and ASH (Group C).

Results: Compared with the lateral wall, early uptake of MIBG in the septum was significantly higher in Group B than in Group A, but not significantly different between Groups A and C. Compared with the lateral wall, early uptake of ^{201}Tl in the septum did not differ among the three groups. No significant difference in the MIBG clearance in the lateral wall was seen among the three groups. By contrast, MIBG clearances in the septum and apex were significantly greater in Group C than in Groups A and B. There was an inverse correlation between systolic thickening and MIBG clearance in the septum.

Conclusion: These findings suggest that sympathetic activity in the septum differs between patients with HT and ASH and patients with HCM.

Key words: meta-iodobenzylguanidine, asymmetric septal hypertrophy, hypertension, hypertrophic cardiomyopathy

Introduction

In patients with essential hypertension (HT), proportional (symmetric) left ventricular hypertrophy (LVH) is common. In contrast, hypertrophic cardiomyopathy (HCM) is characterized by disproportional LVH and, in particular, asymmetric septal hypertrophy (ASH);[1, 2] however, some hypertensive patients also develop ASH.[3–5] It has not been determined whether such cases represent a distinct type of hypertensive LVH or HCM combined with hypertension.

While the etiology and pathophysiology responsible for ASH in patients with HCM are obscure, it has been hypothesized that abnormal sympathetic activity participates in the hypertrophy of the interventricular septum.[6–8] Using tracer-labeled epinephrine, Brush Jr. *et al.*[9] have found that neuronal uptake of norepinephrine was decreased in the heart with HCM. Moreover, a recent study using positron emission tomography (PET) has demonstrated that myocardial presynaptic and postsynaptic sympathetic function is decreased in patients with HCM.[10] Reduced presynaptic norepinephrine reuptake (uptake-1) may lead to an increased local epinephrine level,[10] and increased norepinephrine may cause hypertrophy of myocytes.[11] However, it has been uncertain whether norepinephrine movement (transfer, release, and reuptake) in the asymmetric hypertrophied septum differs from that in the symmetric hypertrophied septum.

I-123 meta-iodobenzylguanidine (MIBG) is an analogue of norepinephrine. It has the unique characteristic of sharing the

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same mechanisms of transfer, release, and reuptake as norepinephrine, and does not act as a transmitter to the postsynaptic receptor. Taking advantage of this unique characteristic, MIBG myocardial scintigraphy has been used to evaluate local myocardial sympathetic activity.[12, 13] The present study was performed to evaluate sympathetic activity in the interventricular septum in hypertensive patients with ASH and to investigate whether differences in sympathetic activity in the septum exist between patients with HT and ASH, patients with HT and symmetric septal hypertrophy, and patients with HCM and ASH.

Methods

Study Patients

The study included 8 patients with essential HT and evidence of symmetric septal hypertrophy (interventricular septal thickness/LV posterior wall thickness < 1.3; Group A), 8 patients with essential HT and evidence of ASH (interventricular septal thickness/LV posterior wall thickness ≥ 1.3 and an interventricular septal thickness ≥ 14 mm; Group B), and 12 patients with HCM and ASH (Group C). Hypertensive patients were included who satisfied either of the following criteria: (1) systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 95 mmHg while taking no medication, or (2) a history of at least 1 year of treatment with antihypertensive agents because of SBP ≥ 160 mmHg and/or DBP ≥ 95 mmHg. In Group C, two patients with HCM demonstrated LV outflow tract obstruction and 10 patients did not. All patients in Group B also had no LV outflow tract obstruction. Left ventricular outflow tract obstruction was defined as follows: (1) echocardiographic evidence of systolic anterior motion of the mitral valve and midsystolic closure of the aortic valve, (2) the presence of a pressure gradient (≥ 20 mmHg) in the outflow tract of the left ventricle at baseline, (3) a peak gradient ≥ 50 mmHg after provocative maneuvers (Valsalva maneuver, Brockenbrough-Braunwald phenomenon,[14] or dobutamine stress). All patients with HT (Groups A and B) and 9 patients with HCM (Group C) underwent coronary angiography because of electrocardiographic (ECG) abnormalities and chest pain, and had no evidence of significant coronary artery stenosis > 50%. Of the other three Group 3 patients who did not undergo coronary angiography, one demonstrated no stress-induced perfusion defect on exercise thallium scintigraphy and the other two had no ischemic ST-segment depression on stress electrocardiography. Patients with central nervous system disorders or diabetes mellitus were also excluded from the study.

Evaluation of Cardiac Sympathetic Nerve Activity

Patients were instructed to fast on the day of the radionuclide study and to continue the fast until the study was completed. No patient was taking reserpine or tricyclic antidepressants at the time of the study. An intravenous injection of 140 to 180 MBq of I-123 MIBG was given between 9:00 and 10:00 A.M., and the first and second single-photon emission computed tomographic (SPECT) studies were started about 20 min and 3 h, respectively, after injection. The SPECT system (Shimazu ZLC 7500-Scintipac 700, or Toshiba GCA 9300-GMS 550U, Tokyo, Japan) 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 a 360° arc in 6° increments with 30-s acquisitions for each view. After preprocessing the projection images with 9-point weighted smoothing, transaxial tomographic slices were reconstructed using the Shepp-Logan filtered back projection algorithm.

The thallium-201 (^{201}Tl) SPECT rest imaging study was performed within 1 week of the MIBG study. Data acquisition was started 15 min after the administration of 120 MBq of ^{201}Tl. The acquisition protocol and reconstruction method were the same as those for the MIBG study.

The method of SPECT data analysis has been previously described in detail.[13, 15] Rectangular regions of interest were placed over the septum, apex, LV lateral wall, lung, and mediastinum for both the I-123 MIBG and the ^{201}Tl transaxial images, and the SPECT count rate in a region of interest was measured. The clearance rate for MIBG was calculated as [(early uptake − delayed uptake) ÷ early uptake] from regions of interest on transaxial images. These analyses were performed for the septum, generally in the most hypertrophic region, and for the lateral LV wall.

Echocardiography

Standard cross-sectional echocardiographic studies, including long-axis, short-axis, and apical four-chamber views, were performed in all patients. The ultrasound system used was a Toshiba SSH-160A (Toshiba, Tokyo, Japan) or Aloka SSD-870 (Aloka, Tokyo, Japan). The end-diastolic thicknesses of the septum and posterior LV wall were measured at the level of the tip of the mitral valve. The ratio of the thickness of the septum to the posterior wall was calculated from these measurements. The end-systolic thickness of the septum was also measured at same level of the left ventricle. Systolic thickening of the septum was calculated as [(end-systolic septal thickness − end-diastolic septal thickness) ÷ end-diastolic septal thickness] and represents an index of systolic function for the interventricular septum.

Statistical Analysis

All data are expressed as mean ± 1 standard deviation. Comparison among the three groups was performed using a one-way analysis of variance (ANOVA). When statistically significant differences were noted, group comparisons were performed using Fisher's method. Categorical data were compared using chi-square analysis. Correlations were assessed by linear regression analysis and Pearson's correlation coefficient. Differences were considered statistically significant when $p < 0.05$.

TABLE I Baseline characteristics

	Group A (n = 8)	Group B (n = 8)	Group C (n = 12)
Gender			
Male (%)	6 (75.0)	7 (87.5)	10 (83.3)
Female (%)	2 (25)	1 (12.5)	2 (16.7)
Age (years)	56.3 ± 9.3	60.3 ± 5.5	61.8 ± 11.1
Chest pain (%)	4 (50)	1 (12.5)	6 (50)
LVOT obstruction (%)	0 (0)	0 (0)	2 (16.7)
NYHA class			
I (%)	4 (50)	4 (50)	8 (66.7)
II (%)	4 (50)	3 (37.5)	2 (16.7)
III (%)	0 (0)	1 (12.5)	2 (16.7)
IV (%)	0 (0)	0 (0)	0 (0)
SBP (mmHg)	168 ± 5	168 ± 6	120 ± 13[b, d]
DBP (mmHg)	99 ± 8	95 ± 8	71 ± 10[b, d]
HR (beats/min)	64.4 ± 5.1	63.1 ± 14.4	64.1 ± 11.5
Echocardiogram			
IVST (mm)	13.9 ± 2.6	19.5 ± 2.6[a]	20.4 ± 4.0[b]
PWT (mm)	12.8 ± 3.3	11.9 ± 1.4	11.7 ± 1.7
IVST/PWT	1.10 ± 0.07	1.65 ± 0.21[b]	1.76 ± 0.29[b]
%IVS (%)	31.1 ± 7.9	20.1 ± 8.2[a]	12.1 ± 4.0[b, c]
CAG	8	8	9
Coronary artery obstruction (≥ 50%) (%)	0 (0)	0 (0)	0 (0)

[a] $p < 0.005$, [b] $p < 0.001$ vs. Group A.
[c] $p < 0.05$, [d] $p < 0.001$ vs. Group B.
Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, LVOT = left ventricular outflow tract, NYHA = New York Heart Association functional class, IVST = interventricular septal thickness, PWT = left ventricular posterior wall thickness, %IVS = % systolic thickening of the septum, CAG = coronary angiogram.

Results

Age, Blood Pressure, Heart Rate, and Left Ventricular Wall Thickness

Baseline characteristics for the three groups are summarized in Table I. There were no significant differences in gender or age among the three groups. Systolic and diastolic blood pressures were higher in the hypertensive groups (Groups A and B) than in Group C, but no significant differences in blood pressure were noted between Groups A and B. No significant difference in heart rate among the three groups was observed. The interventricular septal thickness was significantly greater in Groups B and C than in Group A, but there was no significant difference in septal thickness between Groups B and C. No significant difference was seen in the LV posterior wall thickness between the three groups. Systolic thickening of the interventricular septum was significantly lower in Group B than in Group A, and significantly lower in Group C than in either Group A or Group B (Fig. 1).

Early Uptake and Clearance of Meta-Iodobenzylguanidine

The early uptakes of MIBG and ^{201}Tl (septal/lateral ratio) are summarized in Table II. The early uptake of MIBG was significantly greater in Group B than in Group A, while there was no significant difference in uptake between Groups A and C (Fig. 2). The early uptake of ^{201}Tl was not statistically different among the three groups. The MIBG clearance rates for the interventricular septum, LV lateral wall, and apex are summarized in Table II. There was no significant difference in the rate of MIBG clearance from the LV lateral wall among the three groups. By contrast, the rate of MIBG clearance from the interventricular septum was significantly greater in Group C than in Groups A and B (Fig. 3; Group A: 7.0 ± 5.3%/h,

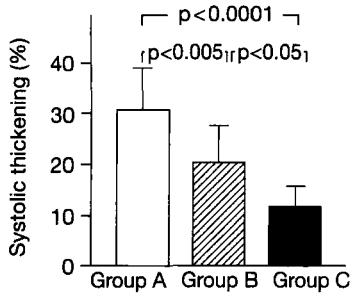

FIG. 1 Systolic thickening of the septum. Thickening was less in Group B than in Group A, and less in Group C than in Groups A or B.

TABLE II Myocardial scintigraphic data

	Group A	Group B	Group C
TI-E (S/L)	1.02 ± 0.16	1.09 ± 0.16	1.10 ± 0.11
MIBG-E (S/L)	1.00 ± 0.13	1.15 ± 0.16[a]	1.07 ± 0.13
MIBG-E/TI-E(S)	1.07 ± 0.43	0.95 ± 0.27	0.98 ± 0.31
MIBG-E/TI-E(L)	1.10 ± 0.46	0.90 ± 0.29	1.01 ± 0.32
MIBG-E/TI-E(Ap)	1.10 ± 0.54	0.86 ± 0.27	0.87 ± 0.31
MIBG clearance (S; %/h)	7.0 ± 5.3	12.2 ± 6.8	22.1 ± 12.7[b,c]
MIBG clearance (L; %/h)	11.5 ± 7.3	12.2 ± 9.4	16.8 ± 8.3
MIBG clearance (Ap; %/h)	10.0 ± 6.6	12.3 ± 10.3	21.3 ± 9.7[a,c]

[a] $p < 0.05$, [b] $p < 0.01$ vs. Group A.
[c] $p < 0.05$ vs. Group B.
Abbreviations: TI-E = TI-201 early uptake, MIBG-E = I-123 meta-iodobenzylguanidine early uptake, S = interventricular septum, L = lateral wall, Ap = apex.

Group B: 12.2 ± 9.4%/h, Group C: 22.1 ± 12.7%/h). In addition, MIBG clearance in the apex was significantly greater in Group C than in either Group A or B (Group A: 10.0 ± 6.6%/h, Group B; 12.3 ± 10.3%/h, Group C: 21.3 ± 9.7%/h).

Relationship between Systolic Thickening and Meta-Iodobenzylguanidine Clearance

Systolic thickening and MIBG clearance in the septum correlated inversely (Fig. 4); however, the interventricular septal thickness and MIBG clearance did not correlate (Fig. 5).

Discussion

Asymmetric septal hypertrophy is seen in many patients with HCM, and it is believed to be a characteristic finding of HCM;[1,2] however, ASH has been described in other conditions[16–18] including HT.[3–5] It is not clear whether this represents a distinct form of hypertensive LV hypertrophy or HCM combined with HT.[19] In some patients with HCM, myocardial concentration of norepinephrine is increased.[20] Norepinephrine induces myocardial hypertrophy[11] and may affect the ventricular septum differently from the right and left ventricular free walls. Thus, whether local cardiac sympathetic activity may influence the development of ASH is of great interest.

Meta-Iodobenzylguanidine Uptake in the Septum

Meta-iodobenzylguanidine is an analogue of norepinephrine, with similar rates of transfer, release, and reuptake as

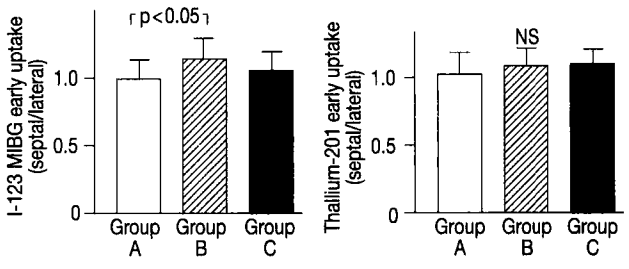

FIG. 2 Early uptake of I-123 meta-iodobenzylguanidine (MIBG) and thallium-201. The early MIBG uptake (septal uptake/lateral wall uptake ratio) is higher in Group B than in Group A. NS = not significant.

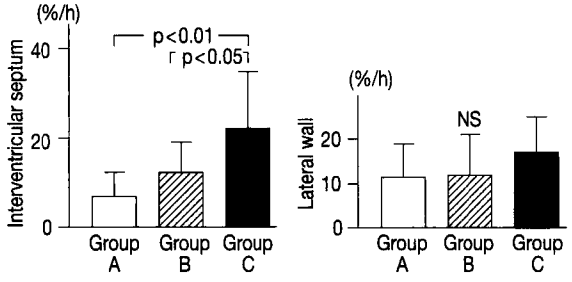

FIG. 3 Meta-iodobenzylguanidine (MIBG) clearance in the interventricular septum and left ventricular lateral wall. The MIBG clearance in the septum in Group C is greater than that in Groups A and B. There is no significant difference in MIBG clearance in the lateral wall in the three groups. NS = not significant.

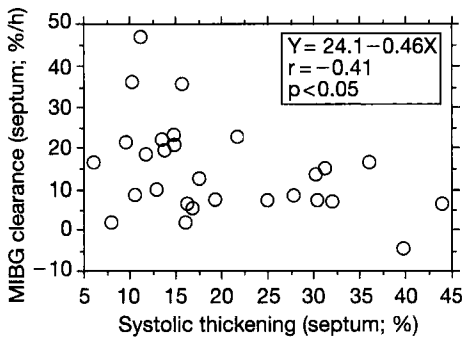

FIG. 4 Relationship between systolic thickening and meta-iodobenzylguanidine (MIBG) clearance in the septum.

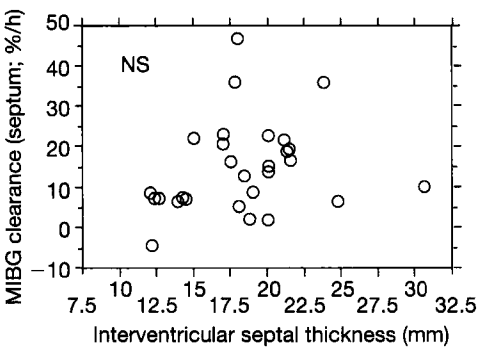

FIG. 5 Relationship between interventricular septal thickness and meta-iodobenzylguanidine (MIBG) clearance in the septum.

norepinephrine; however, MIBG does not act as a transmitter to the postsynaptic receptor. This unique characteristic of MIBG results in a different accumulation pattern on scintigraphy, and MIBG is used to evaluate presynaptic sympathetic activity in various cardiac diseases.[12, 13] The heart-to-background ratio has been used previously to quantitate MIBG uptake, and mediastinal activity has been used as a reference area.[13, 21] However, we evaluated the ratio of the early uptake in the septum and LV lateral wall because the mediastinal uptake and clearance may vary due to differential blood clearance and MIBG accumulation in adjacent organs.

In this study, Group B (hypertensive patients with ASH) had 15% greater early MIBG uptake than Group A (hypertensive patients without ASH). Although MIBG uptake varies with blood flow, myocardial blood flow did not differ among the three groups based on the early uptake of ^{201}Tl. These findings suggest that the asymmetrically hypertrophied septum in Group B may have an increased number of either sympathetic nerve endings or synaptic vesicles. However, because our SPECT system has a resolution of 15 mm full width at half maximum (FWHM), there may be no differences in MIBG uptake in the hypertrophied septum per unit volume between Groups A and B. In contrast, early MIBG uptake in Group C (patients with HCM and ASH), which had the same degree of interventricular septal thickening as Group B, was not different from that in Group A. Therefore, in hearts with HCM, MIBG uptake in the septum per unit volume may be decreased.

With respect to cardiac sympathetic function in the setting of HCM, it is believed that the number of cardiac sympathetic nerve endings decreases and neural norepinephrine uptake decreases.[9] In a study using PET, Lefroy *et al.*[22] demonstrated a reduction in the density of myocardial beta-adrenoceptors in patients with HCM. Moreover, a recent study using PET with 11C hydroxyephedrine demonstrated that myocardial presynaptic catecholamine reuptake was reduced.[10] This finding supports our result that, in Group C, MIBG uptake in the septum per unit volume may be decreased. Septal hypertrophy may occur despite decreased presynaptic sympathetic activity because of increased local norepinephrine level[10] or increased cardiac beta-adrenoceptor affinity for norepinephrine in hearts with HCM. In contrast, in the septum in patients with HT and ASH, MIBG uptake was not decreased. Presynaptic sympathetic activity in the hypertrophied septum in Group B may differ from that in Group C.

Meta-Iodobenzylguanidine Clearance in the Septum

There was no difference in MIBG clearance in the lateral wall among the three groups, while MIBG clearance in the septum was greater in the patients with HCM than in the other hypertensive groups. The MIBG clearance in control hearts in our institute is 9.6 ± 5.8%,[23] and that in Group A patients in this study showed about the control value. The mechanism of MIBG clearance is not well understood although it is thought that MIBG release from presynaptic vesicles or increased vesicular turnover may play a role. Increased MIBG clearance has been reported for a variety of cardiac diseases.[23] We have previously reported that MIBG clearance is greater in patients with HCM and worsening cardiac function.[15] Cellular disarray and interstitial fibrosis are found mainly in the hypertrophied septum in patients with HCM.[24] Because there was an inverse correlation between systolic thickening and MIBG clearance in the septum, we hypothesize that the higher MIBG clearance in patients with HCM reflects accelerated norepinephrine turnover in association with the histologic changes described above. Namely, in the septum of patients with HCM, the higher MIBG clearance may reflect a compensatory increase in sympathetic nerve activity in response to systolic dysfunction induced by severe myocyte disarray and interstitial fibrosis. This may be partly due to the shorter half-life of intracytoplasmic MIBG.[25] Regarding MIBG clearance in hypertensive hearts, Mitani *et al.*[26] reported that the myocardial washout rate for MIBG in hypertensive patients is greater than in normotensive patients. Moreover, Morimoto *et al.*[27] compared myocardial MIBG uptake in hypertensive patients before and after the institution of antihypertensive therapy, and found that the decrease in the washout ratio was significantly greater in patients with greater regression of cardiac hypertrophy. Their results demonstrate that sympathetic nervous function correlates with the degree of cardiac hypertrophy. However, in this study there was no correlation between septal thickness and MIBG clearance in the septum, as shown in Figure 5, and MIBG clearance and systolic thickening of the septum were different between Groups B and C despite the same septal thickness. It is suggested that septal presynaptic sympathetic function in Groups B and C is different, possibly due to histologic differences. However, the mechanism responsible for the greater degree of hypertrophy in the interventricular septum in hypertensive patients with ASH remains unclear.

Recently it has been found that HCM can be caused by mutations in the genes for cardiac beta-myosin heavy chain,[28, 29] cardiac troponin T,[30] cardiac troponin I,[31] alpha-tropomyosin,[30] and myosin-binding protein C.[32] Future studies may clarify whether HT with ASH represents a type of HT or HCM combined with HT. Moreover, evaluation of the presynaptic sympathoadrenergic system using positron emission tomography[10, 33] may be helpful in defining the relationship between ASH and sympathetic activity.

Study Limitation

In this study, norepinephrine turnover in the sympathetic nerve endings was assessed only with MIBG imaging. Postsynaptic function was not assessed nor were changes in MIBG clearance rates at different stages of cardiac hypertrophy. Future studies will be required to address these issues.

Conclusion

The accumulation and clearance of MIBG in the septum in patients with HT and ASH and patients with HCM were different in spite of equal septal thicknesses. These findings suggest that sympathetic nervous activity in the septum differs in the two groups.

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