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Marked Expression of Plasma Brain Natriuretic Peptide Is a Special Feature of Hypertrophic Obstructive Cardiomyopathy

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Objectives. **We examined whether plasma brain natriuretic peptide levels are abnormally elevated in hypertrophic obstructive cardiomyopathy compared with other cardiac diseases.**

Background. **We previously reported that plasma brain and atrial natriuretic peptide levels were elevated in hypertrophic cardiomyopathy.**

Methods. **We compared plasma concentrations of brain and atrial natriuretic peptide and hemodynamic and echocardiographic data in 50 patients with hypertrophic obstructive cardiomyopathy (n = 15, mean [±SD] intraventricular pressure gradient 37 ± 16 mm Hg), hypertrophic nonobstructive cardiomyopathy (n = 15), aortic stenosis (n = 10, mean pressure gradient 41 ± 18 mm Hg) and hypertensive heart disease (n = 10, mean systolic/diastolic blood pressure 203 ± 16/108 ± 11 mm Hg, respectively) and 10 normal subjects.**

Results. **Plasma brain natriuretic peptide levels were higher in the hypertrophic obstructive cardiomyopathy group (397.1 ± 167.8 pg/ml*) than in the hypertrophic nonobstructive cardiomyopathy (60.0 ± 48.1 pg/ml*†), hypertensive heart disease (53.9 ± 31.4 pg/ml*†), aortic stenosis (75.4 ± 54.3 pg/ml*†) and normal groups (9.8 ± 6.4 pg/ml† [*$p < 0.05$ vs. normal group, †$p < 0.05$ vs. hypertrophic obstructive cardiomyopathy group]). Although plasma atrial natriuretic peptide levels were higher in the hypertrophic obstructive cardiomyopathy group than the other patient groups, the brain/atrial natriuretic peptide ratio in the hypertrophic obstructive cardiomyopathy group was higher (4.5 ± 2.3) than those in the other three patient groups (1.1 to 1.4) and the normal group (0.7 ± 0.5). Left ventricular end-diastolic pressure and left ventricular end-diastolic volume index were similar among the four patient groups. The interventricular septal thickness and the ratio of interventricular septal thickness to left ventricular posterior wall thickness were similar between the hypertrophic obstructive and nonobstructive cardiomyopathy groups.**

Conclusions. **Abnormal elevations of plasma brain natriuretic peptide levels are difficult to explain on the basis of hemodynamic and echocardiographic data and are a special feature of hypertrophic obstructive cardiomyopathy.**

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Hypertrophic cardiomyopathy is a cardiac disease of unknown origin that has inappropriate (i.e., unrelated to any pressure or volume overload) myocardial hypertrophy, predominantly involving the interventricular septum of a nondilated left ventricle, with ventricular hyperdynamic systolic function and ventricular diastolic dysfunction. In some patients with hypertrophic cardiomyopathy, an intraventricular dynamic pressure gradient is observed that divides the left ventricle into a high pressure apical region and a low pressure subaortic region. These patients have been classified as having hypertrophic obstructive cardiomyopathy, which accounts for only 7% to 30% of hypertrophic cardiomyopathy cases in the Japanese population (1); but 80% to 90% of those in European and American populations (2). The transformation of obstructive into nonobstructive or of nonobstructive into obstructive is observed in only 5% of patients with hypertrophic cardiomyopathy (3).

Brain natriuretic peptide, originally isolated from the mammalian brain (4), is a novel natriuretic peptide with striking structural and biologic similarities to atrial natriuretic peptide (5). Brain natriuretic peptide has been recently found in human cardiac tissue and plasma (6,7). In the human heart, brain natriuretic peptide is synthesized primarily by the ventricles (8), and its expression in the ventricles is greatly accelerated in ventricular overload and hypertrophy, causing congestive heart failure (5,8–10). However, we previously reported (11) that plasma atrial and brain natriuretic peptide levels are elevated in patients with hypertrophic cardiomyop-

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athy with normal systolic function as well as in those with congestive heart failure. In ventricular myocytes of tissue obtained from endomyocardial biopsy, positive atrial natriuretic peptide immunoreactivity was found both in patients with hypertrophic obstructive cardiomyopathy and in those with hypertrophic nonobstructive cardiomyopathy (12), but positive brain natriuretic peptide immunoreactivity was seen only in patients with hypertrophic obstructive cardiomyopathy (11). These findings suggest that the presence of the obstruction in hypertrophic cardiomyopathy may contribute to the accelerated synthesis and secretion of ventricular brain natriuretic peptide. However, it is unknown whether any difference in plasma levels of brain natriuretic peptide between hypertrophic obstructive and hypertrophic nonobstructive cardiomyopathy is present. Also, the correlations between plasma brain natriuretic peptide levels and hemodynamic or echocardiographic data has not been studied in patients with hypertrophic obstructive cardiomyopathy.

Therefore, the present study was designed to assess 1) whether plasma concentrations of brain natriuretic peptide in hypertrophic obstructive cardiomyopathy are higher than those in hypertrophic nonobstructive cardiomyopathy, aortic stenosis as a representative disease of left ventricular high pressure and hypertensive heart disease with concentric hypertrophy of the left ventricle due to pressure overload; and 2) whether abnormal elevation of plasma brain natriuretic peptide levels in hypertrophic obstructive cardiomyopathy is related to hemodynamic or echocardiographic data.

Methods

Subjects. The study included 50 patients with hypertrophic obstructive cardiomyopathy (n = 15), hypertrophic nonobstructive cardiomyopathy (n = 15), aortic stenosis (n = 10) and hypertensive heart disease (n = 10) who were evaluated clinically by both cardiac catheterization and echocardiography (Table 1). The mean ages of the patients with aortic stenosis and hypertensive heart disease were matched with those of patients with hypertrophic obstructive and nonobstructive cardiomyopathy. All patients had normal sinus rhythm without critical ectopic premature contractions as evaluated by 24-h Holter electrocardiographic (ECG) monitoring and coronary arteries without significant stenosis and normal left ventricular ejection fraction at cardiac catheterization. Except for those with aortic stenosis, the patients had no evidence of critical aortic or mitral regurgitation or stenosis by both cardiac catheterization and echocardiography. The patients with aortic stenosis had no critical mitral regurgitation or stenosis. All patients were in New York Heart Association functional class I or II (mainly first degree for each patient group). There were no differences in degree among the four patient groups. There were no significant differences in drugs used between the hypertrophic obstructive and nonobstructive cardiomyopathy groups.

The diagnosis of hypertrophic cardiomyopathy was made according to the definition and classification proposed by the

Table 1. Patient Profiles and Cardiac Catheterization Data

Group	No. of Pts	Age (yr)	Gender (M/F)	NYHA (I/II)	SBP (mm Hg)	DBP (mm Hg)	LVEDP (mm Hg)	PAWP (mm Hg)	PAP (mm Hg)	CI (ml/m²)	HR (beats/min)	IVSth (mm)	LVPWth (mm)	IVSth/ LVPWth	LVEDVI (ml/m²)
Normal	10	56 ± 17	8/2		122 ± 12	67 ± 9	5 ± 2*	3 ± 2*	17 ± 3*	3.2 ± 0.3	72 ± 11	9 ± 1*	9 ± 1*	1.0 ± 0.1*	72 ± 9
HOCM	15	57 ± 16	10/5	11/4	133 ± 23	70 ± 10	14 ± 4†‡	9 ± 2†‡	26 ± 3†‡	2.9 ± 0.5	71 ± 14	20 ± 4†‡	13 ± 2†‡	1.6 ± 0.4†‡	67 ± 8
HNCM	15	56 ± 14	10/5	12/3	130 ± 25	70 ± 11	15 ± 3†‡	9 ± 3†‡	25 ± 5†‡	3.2 ± 0.5	71 ± 12	17 ± 3†‡	12 ± 1†‡	1.5 ± 0.2†‡	64 ± 8
HHD	10	59 ± 8	7/3	9/1	203 ± 16*†‡	108 ± 11*†‡	8 ± 3*†‡	5 ± 2*†‡	18 ± 3*	3.5 ± 0.4	74 ± 8	14 ± 2*†‡	13 ± 2†‡	1.1 ± 0.1*	72 ± 7
AS	10	59 ± 10	6/4	6/4	122 ± 12	65 ± 8	13 ± 2†‡	8 ± 4†‡	19 ± 4*	3.2 ± 0.3	75 ± 11	13 ± 1*†‡	12 ± 1†‡	1.1 ± 0.1*	73 ± 13

*$p < 0.05$ versus hypertrophic obstructive cardiomyopathy. †$p < 0.05$ versus normal subjects. Data presented are mean value ± SD or number of patients (Pts). AS = aortic stenosis; CI = cardiac index; DBP = diastolic blood pressure; HHD = hypertensive heart disease; HNCM = hypertrophic nonobstructive cardiomyopathy; HR = heart rate; IVSth = intraventricular septal thickness; LVEDP = left ventricular end-diastolic pressure; LVPWth = left ventricular posterior wall thickness; NYHA = New York Heart Association functional class; PAP = systolic pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; SBP = systolic blood pressure.

World Health Organization/International Society and Federation of Cardiology Task Force (13). Thirty patients with hypertrophic cardiomyopathy had asymmetric ventricular septal hypertrophy evaluated by two-dimensional echocardiography and biventriculography performed during cardiac catheterization. In the present study, the patients with hypertrophic cardiomyopathy with a left intraventricular pressure gradient >16 mm Hg were classified as having hypertrophic obstructive cardiomyopathy (14). Fifteen of the patients with hypertrophic cardiomyopathy had a significant systolic intraventricular pressure gradient >16 mm Hg at rest or after provocation by amyl nitrite and revealed intraventricular acceleration flow images from the site of stenosis to the left ventricular outflow tract during systole in color images on Doppler echocardiography (15). The minimal and maximal intraventricular pressure gradients in patients with hypertrophic obstructive cardiomyopathy were 18 and 70 mm Hg, respectively. The other 15 patients with hypertrophic cardiomyopathy showed no sign of an intraventricular pressure gradient (within physiologic range) by either cardiac catheterization or echocardiography; they were classified as having hypertrophic nonobstructive cardiomyopathy.

In patients with hypertrophic obstructive cardiomyopathy, the diagnosis of both midventricular and subaortic obstruction was made on the basis of typical angiographic and echocardiographic features: The former is characterized by an hourglass appearance of the left ventricle with midventricular obstruction and an apical chamber (3 of 15 cases), whereas the latter is characterized by an obstruction at the site of the left ventricular outflow tract (12 of 15 cases) (16).

Ten patients with hypertensive heart disease had high systemic systolic (maximal) blood pressure and diastolic (minimal) blood pressure at rest (significantly >180 and 90 mm Hg, respectively) despite medication for hypertension for at least 2 years. The mean systolic and diastolic blood pressures were 203 ± 16 and 108 ± 11 mm Hg, respectively (Table 1). All patients with hypertensive heart disease had left ventricular concentric hypertrophy on two-dimensional echocardiography and left ventriculography during cardiac catheterization. The mean interventricular septal and left ventricular posterior wall thicknesses among patients with hypertensive heart disease are shown in Table 1.

In 10 patients with aortic stenosis, the minimal and maximal pressure gradients through the aortic valve were 20 and 75 mm Hg, respectively (Table 1).

The control group included 10 normal patients with clinically suspected cardiac disease because of atypical chest pain or minimal ECG changes but no specific or critical abnormalities on echocardiography and cardiac catheterization. Their mean ages matched those of the other patient groups. All normal control subjects received no medication.

All subjects gave written informed consent to participate in the study, which was approved by the local ethics committee on human research (Gifu University).

Plasma sampling. Drugs were stopped, and patients fasted overnight. After a 19-gauge butterfly needle connected to a three-way stopcock was inserted into the antecubital vein, all subjects assumed a supine position with eyes closed for at least 30 min before blood sampling. Peripheral venous blood samples were taken slowly through the three-way stopcock and transferred to chilled disposable tubes containing 2-natrium-ethylenediaminetetraacetic acid (1.5 mg/ml) and aprotinin (50 μl/ml) for brain and atrial natriuretic peptide assay. The blood samples were placed immediately on ice and promptly centrifuged at 4°C, and aliquots of plasma were immediately stored at −80°C until the assay.

In eight hypertrophic obstructive cardiomyopathy and five hypertrophic nonobstructive cardiomyopathy group patients, second plasma sampling to measure reproducibility of plasma atrial and brain natriuretic peptide levels was performed 2 weeks after the first plasma sampling.

Measurement of brain and atrial natriuretic peptide plasma levels. Plasma brain natriuretic peptide concentrations were measured with a specific immunoradiometric assay for human brain natriuretic peptide (17). This assay system uses two monoclonal antibodies against alpha-human brain natriuretic peptide, one recognizing a carboxy terminal sequence and the other the ring structure of human brain natriuretic peptide, and measures human brain natriuretic peptide by sandwiching it between the two antibodies without extraction of plasma. The minimal detectable quantity of human brain natriuretic peptide was 2 pg/ml. The intraassay and interassay coefficients of variation were 5.3% and 5.9%, respectively, and recovery rates of 10 to 300 pg/ml of human brain natriuretic peptide added to plasma were 105.7 ± 5.4%. The correlation between the plasma level of human brain natriuretic peptide measured by this method and that by the extraction method was highly significant (range 0 to 1,500 pg/ml, $r = 0.98$, $p < 0.001$). The cross-reactivity for alpha-human atrial natriuretic peptide was <0.001% on a molar basis.

Plasma atrial natriuretic peptide concentrations were measured with a specific immunoradiometric assay for alpha-human atrial natriuretic peptide (Shionoria ANP kit, Shionogi, Japan), as reported previously by Hama et al. (18). This assay is performed in the same manner as that for brain natriuretic peptide. The minimal detectable quantity of alpha-human atrial natriuretic peptide was 5 pg/ml. The intraassay and interassay coefficients of variation were 4.7% and 5.8%, respectively, and recovery rates of 20 to 600 pg/ml of alpha-human atrial natriuretic peptide added to plasma were 99.2 ± 3.0%. The correlation between the plasma level of alpha-human atrial natriuretic peptide measured by this method and that by the extraction method was highly significant (range 20 to 1,500 pg/ml, $r = 0.97$, $p < 0.001$). The cross-reactivity with human brain natriuretic peptide was <0.001% on a molar basis.

Cardiac catheterization. Cardiac catheterization was performed within 2 weeks before or after blood sampling. All patients and normal control subjects underwent both right and left heart catheterization according to standard techniques.

During measurement of intraventricular pressures in pa-

tients with hypertrophic obstructive cardiomyopathy, care was taken to exclude the possibility of a pressure difference being artifactually produced by entrapment of the left ventricular catheter in areas of the ventricle that became obliterated during systole. Criteria used to exclude the possibility of catheter entrapment included verification that the catheter tip was freely mobile in a blood-filled area of the left ventricular cavity (i.e., blood could be withdrawn from the catheter throughout the cardiac cycle), and left ventricular systolic pressure was not prolonged (i.e., it declined at or before the dicrotic notch of the systemic arterial pressure contour) (3).

Echocardiography. Echocardiography (HP 77020AC, Hewlett-Packard Co.) was performed twice at intervals of >1 week (mean interval 22 ± 18 days, range 7 to 60) for comparison of pressure gradients, which was done by a single operator (M.T.) according to established methodology. The first echocardiographic study was performed within 1 week before or after blood sampling. Interventricular septal thickness, left ventricular posterior wall thickness, left ventricular end-diastolic dimension, intraventricular flow velocity in patients with hypertrophic obstructive cardiomyopathy, and aortic flow velocity in those with aortic stenosis, were measured according to standard procedures. Interventricular septal thickness was measured at the mitral leaflet tips as the reference standard. However, thickness at the midventricular level was used for patients with midventricular obstruction because maximal septal thickness is usually at the midventricular level. The pressure gradient was measured using the modified Bernoulli equation ($\Delta P = 4V^2$, where ΔP = pressure gradient; and V = peak velocity) from continuous wave Doppler echocardiograms (19).

Statistical analysis. Plasma levels of brain and atrial natriuretic peptide and hemodynamic and echocardiographic variables were compared among the patient groups and the control group using one-way analysis of variance, and if significant, a modified unpaired *t* test was performed to assess which group was significantly different. Correlations of plasma levels of brain and atrial natriuretic peptide with hemodynamic and echocardiographic variables were examined using simple linear regression analysis by the least-squares method, and differences between regression lines were tested by analysis of covariance using brain or atrial natriuretic peptide as a dependent variable and a hemodynamic or echocardiographic variable as an independent variable. Results are expressed as mean value ± SD. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics. Table 1 shows the clinical profiles and cardiac catheterization data for the patient groups and control subjects. There were no significant differences in age or gender among the five groups. Left ventricular end-diastolic and pulmonary artery wedge pressures were similar among hypertrophic obstructive cardiomyopathy, hypertrophic nonobstructive cardiomyopathy, and aortic stenosis groups. Pulmonary artery pressure was similar between hypertrophic obstructive and nonobstructive cardiomyopathy groups. Cardiac index and heart rate showed no significant difference among patient groups and normal subjects.

The left intraventricular pressure gradient in patients with hypertrophic obstructive cardiomyopathy was similar to that through the aortic valve in patients with aortic stenosis. The difference between initial and second left intraventricular pressure gradients measured ~3 weeks after the first echocardiographic study in the hypertrophic obstructive cardiomyopathy group was very small (5.6 ± 2.3%). The first and second left intraventricular pressure gradients in the hypertrophic nonobstructive cardiomyopathy group were within the physiologic range in all patients. Interventricular septal thickness and the interventricular septal/left ventricular posterior wall thickness ratio were not significantly different between the hypertrophic obstructive and nonobstructive cardiomyopathy groups (Table 1). There was no significant difference in left ventricular end-diastolic volume index among the five patient groups (Table 1).

Plasma concentrations of natriuretic peptides. Plasma levels of brain natriuretic peptide were 397.1 ± 167.8 pg/ml for hypertrophic obstructive cardiomyopathy, 60.0 ± 48.1 pg/ml for hypertrophic nonobstructive cardiomyopathy, 53.9 ± 31.4 pg/ml for hypertensive heart disease, 75.4 ± 54.3 pg/ml for aortic stenosis and 9.8 ± 6.4 pg/ml for normal subjects (Fig. 1). Plasma concentrations of brain natriuretic peptide in all patient groups were significantly higher than those in normal subjects. Moreover, brain natriuretic peptide levels in patients with hypertrophic obstructive cardiomyopathy were markedly higher than those in the other patient groups and in normal subjects (~6-fold relative to the other patient groups, 40-fold relative to normal subjects). In contrast, plasma concentrations of atrial natriuretic peptide (hypertrophic obstructive cardiomyopathy: 99.6 ± 41.6 pg/ml; hypertrophic nonobstructive cardiomyopathy: 48.6 ± 24.2 pg/ml; hypertensive heart disease: 47.2 ± 22.4 pg/ml; aortic stenosis: 60.5 ± 26.6 pg/ml) were also higher in all patient groups than in normal subjects (17.3 ± 8.0 pg/ml); those in patients with hypertrophic obstructive cardiomyopathy were six times higher than those in normal subjects. The plasma concentration ratio of brain to atrial natriuretic peptide in patients with hypertrophic obstructive cardiomyopathy (4.5 ± 2.3) was significantly higher than that in the other patient groups (hypertrophic nonobstructive cardiomyopathy: 1.4 ± 1.1; hypertensive heart disease: 1.1 ± 0.3; aortic stenosis: 1.4 ± 1.2) and in normal subjects (0.7 ± 0.5). The sensitivity and specificity of hypertrophic obstructive cardiomyopathy for plasma brain natriuretic peptide levels >200 pg/ml were 86.7% and 93.3%, respectively, and 80.0% and 73.3%, respectively, for the plasma brain/atrial natriuretic peptide ratio >2.5. The reproducibilities of both plasma brain and atrial natriuretic peptide levels at intervals of 2 weeks were <6.8% and 4.7%, respectively.

Correlation between plasma natriuretic peptides and echocardiographic and hemodynamic variables. Plasma atrial natriuretic peptide levels were not correlated with any echocardiographic or hemodynamic variables shown in Table 1 in all

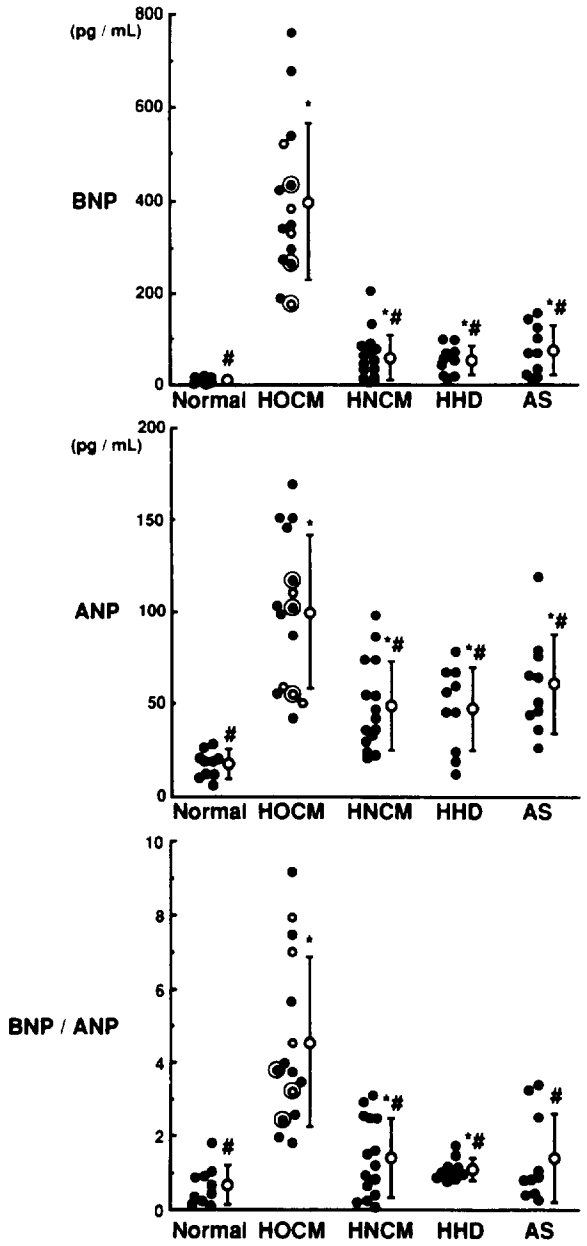

Figure 1. Comparisons of plasma concentrations of brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) and plasma brain/atrial natriuretic peptide ratios in patients groups and normal control subjects. AS = aortic stenosis; HHD = hypertensive heart disease; HNCM = hypertrophic nonobstructive cardiomyopathy; HOCM = hypertrophic obstructive cardiomyopathy. In the hypertrophic obstructive cardiomyopathy group, **solid circles** = rest left ventricular outflow tract obstruction; **open circles** = provoked left ventricular outflow tract obstruction; **circles with solid centers** = rest midventricular obstruction cases; **circles with open centers** = provoked midventricular obstruction. *p < 0.05 versus normal subjects. #p < 0.05 versus hypertrophic obstructive cardiomyopathy. Results are mean value ± SD.

patient groups. Plasma brain natriuretic peptide levels were significantly correlated with left ventricular end-diastolic pressure in aortic stenosis but not in hypertrophic obstructive cardiomyopathy, hypertrophic nonobstructive cardiomyopathy and hypertensive heart disease. Plasma brain natriuretic peptide levels were significantly correlated with pressure gradient through the aortic valve in aortic stenosis ($r = 0.631$, $p < 0.05$) but not with the intraventricular pressure gradient at the obstructed site in hypertrophic obstructive cardiomyopathy (Fig. 2). Plasma brain natriuretic peptide levels were significantly correlated with interventricular septal thickness and interventricular septal thickness/left ventricular posterior wall thickness ratios in hypertrophic obstructive cardiomyopathy, hypertrophic nonobstructive cardiomyopathy and hypertensive heart disease but not aortic stenosis (Fig. 3). There were no significant correlations between plasma brain natriuretic peptide levels and other hemodynamic or echocardiographic variables shown in Table 1 for each of the five groups.

Discussion

Definition of hypertrophic obstructive cardiomyopathy and reproducibility of pressure gradients and plasma natriuretic peptide levels. On Doppler echocardiography, significant systolic pressure gradient indicating obstruction is >16 mm Hg (flow velocity >2 m/s; Pressure gradients = 4 × (Flow velocity)^2 mm Hg [simplified Bernoulli equation]) with intraventricular acceleration flow images at a site from the stenotic region to the ventricular outflow tract during systole in color images (14,15). At cardiac catheterization, significant systolic left intraventricular pressure gradient was >20 mm Hg, although the cut point of significant pressure gradient depends on the investigators. In addition, the diagnoses of both midventricular and subaortic obstructions were made on the basis of typical left ventriculographic and echocardiographic features: The former is characterized by an hourglass appearance of the left ventricle with midventricular obstruction and an apical chamber, whereas the latter is characterized by the obstruction at the site of the left ventricular outflow tract (16).

In the present study, systolic intraventricular pressure gradient in hypertrophic nonobstructive cardiomyopathy was zero in all 15 patients by cardiac catheterization. On Doppler echocardiography, the flow velocity was 0.6 to 1.4 m/s (when flow velocity was <2 m/s, calculation of mm Hg by simplified Bernoulli equation was not used generally). There was no evidence of intraventricular acceleration flow images or morphologic findings of obstruction in any patient.

In contrast, all 15 patients with hypertrophic obstructive cardiomyopathy had a systolic intraventricular pressure gradient of 18 to 70 mm Hg by Doppler echocardiography and 21 to 73 mm Hg by cardiac catheterization. In all 15 patients, intraventricular acceleration flow images were seen at the site of the stenotic region extending to the left ventricular outflow tract during systole in color images on Doppler echocardiography. In addition, typical morphologic features of obstruction were observed by echocardiography and left ventriculography. Therefore, our definition of hypertrophic obstructive and nonobstructive cardiomyopathy is similar to that used generally.

It has been established that there are precise positive

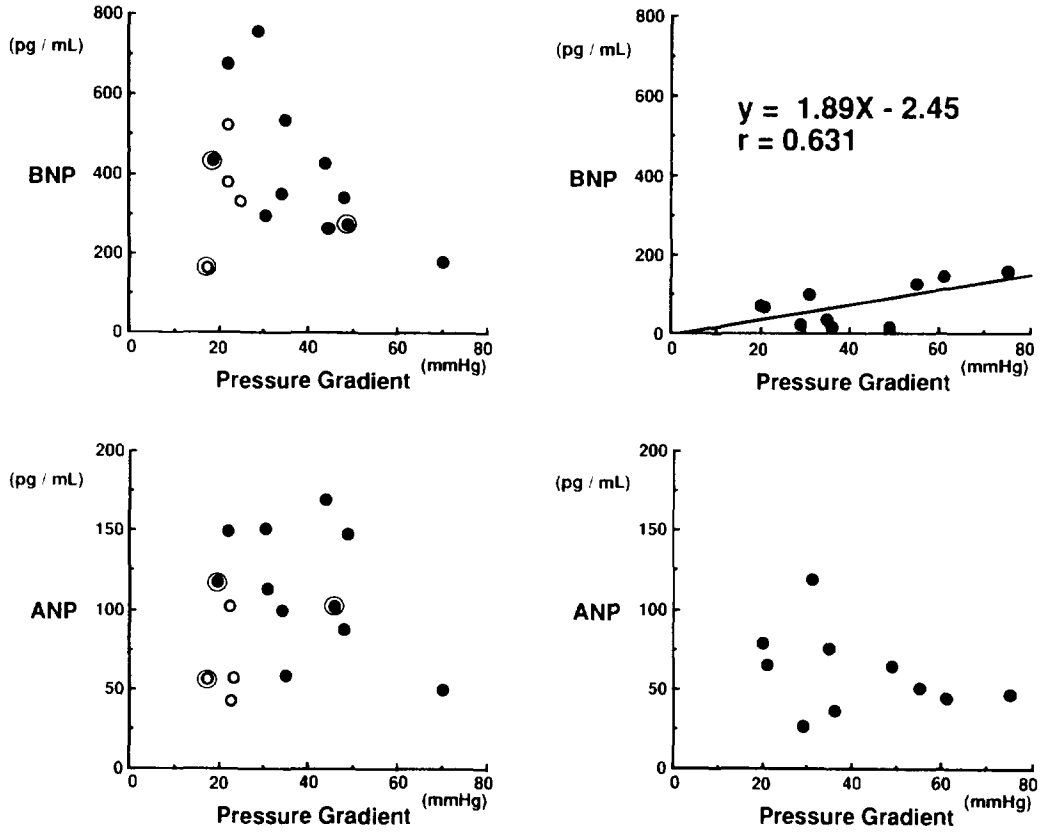

Figure 2. Correlation of left intraventricular pressure gradient in patients with hypertrophic obstructive cardiomyopathy **(left)** or pressure gradient through the aortic valve in patients with aortic stenosis **(right)** and plasma concentrations of brain (BNP) and atrial natriuretic peptide (ANP). Symbols as in Figure 1.

correlations between the Doppler-determined pressure gradient and the simultaneously measured catheter pressure gradient both in patients with aortic stenosis and in those with hypertrophic obstructive cardiomyopathy (15,20). This correlation was confirmed by the present data on pressure gradients between Doppler echocardiography and cardiac catheterization ($r = 0.93$, $p < 0.05$ in hypertrophic obstructive cardiomyopathy; $r = 0.96$, $p < 0.05$ in aortic stenosis). The present study used Doppler echocardiography to show that the variability of pressure gradients at mean intervals of 3 weeks was very small in the hypertrophic obstructive and nonobstructive cardiomyopathy groups. Brain and atrial natriuretic peptide plasma levels at intervals of 2 weeks were similar in the hypertrophic obstructive cardiomyopathy and hypertrophic nonobstructive cardiomyopathy groups. These findings indicate that pressure gradients and plasma natriuretic peptide levels were stable in hypertrophic cardiomyopathy.

Brain natriuretic peptide plasma levels and plasma brain/atrial natriuretic peptide ratios in hypertrophic obstructive cardiomyopathy versus other cardiac diseases. The present study revealed marked increases in plasma brain natriuretic peptide levels and the plasma brain/atrial natriuretic peptide ratio in hypertrophic obstructive cardiomyopathy. Our findings regarding hypertrophic nonobstructive cardiomyopathy, hypertensive heart disease and aortic stenosis confirmed those of previous reports (11,21,22). Hypertrophic nonobstructive and obstructive cardiomyopathy showed a similar interventricular septal thickness, left ventricular posterior wall thickness, interventricular septal thickness/left ventricular posterior wall thickness ratio, left ventricular end-diastolic pressure and left ventricular end-diastolic volume index. The hypertensive heart disease group had left ventricular concentric hypertrophy resulting from a severe, continuous pressure overload, and the aortic stenosis group had pressure gradient similar to the hypertrophic obstructive cardiomyopathy group. However, plasma brain natriuretic peptide levels and the plasma brain/atrial natriuretic peptide ratio in hypertrophic obstructive cardiomyopathy were clearly higher than in the other diseases, indicating that an increase in brain natriuretic peptide levels in hypertrophic obstructive cardiomyopathy cannot be explained by cardiac hypertrophy, asymmetric septal hypertrophy or pressure overload.

Most patients with hypertrophic obstructive cardiomyopathy were in functional class I. In patients with congestive heart failure, plasma brain natriuretic peptide increases in relation to functional class or left ventricular end-diastolic pressure and becomes marked in severe congestive heart failure (functional class IV). However, the plasma brain/atrial natriuretic peptide ratio was ~1.7, even for function class IV. This ratio was clearly low compared with that for hypertrophic obstructive

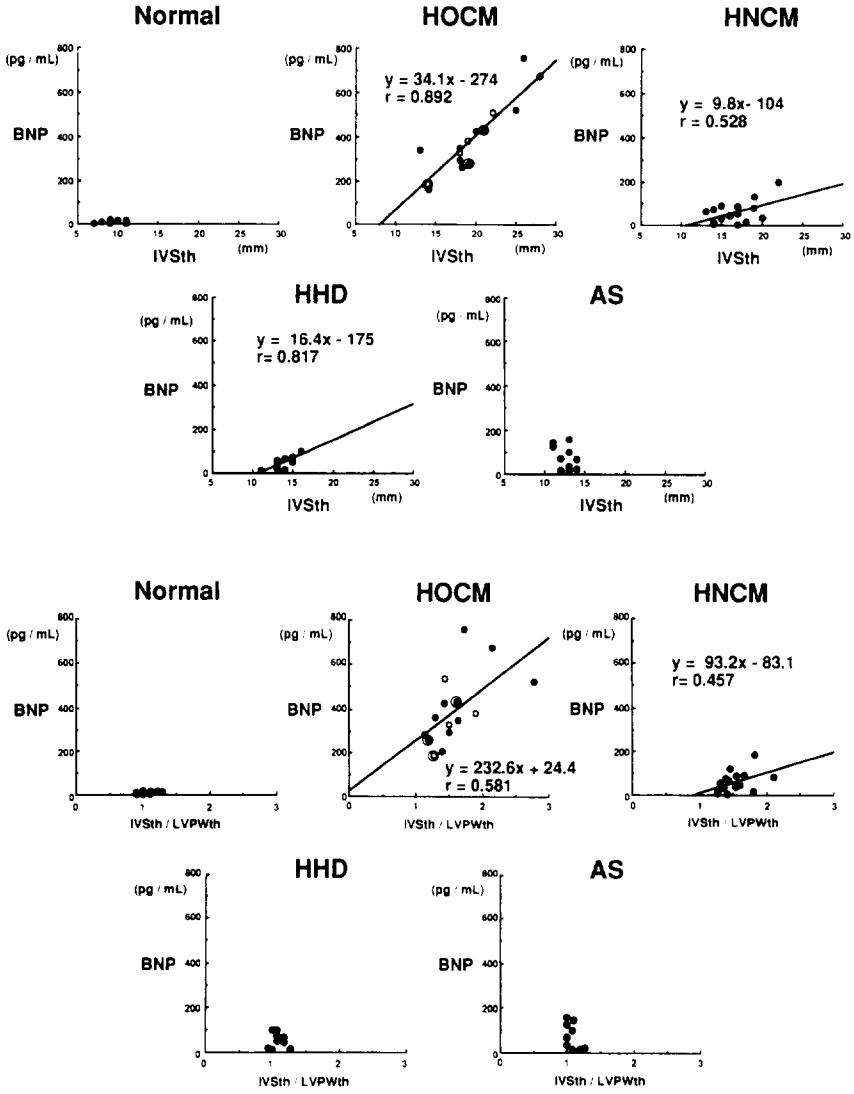

Figure 3. Correlation of plasma concentrations of brain natriuretic peptide (BNP) and interventricular septal thickness (IVSth) (**upper panels**) and between plasma brain natriuretic peptide and the interventricular septal thickness/left ventricular wall thickness ratio (IVSth/LVPWth) (**lower panels**) in four patient groups and normal subjects. Other abbreviations and symbols as in Figure 1.

cardiomyopathy (4.5 ± 2.3) in the present study. In contrast, it has been reported (23) that plasma brain natriuretic peptide levels and the plasma brain/atrial natriuretic peptide ratio are elevated markedly in the acute stage of myocardial infarction. Our findings in the hypertrophic obstructive cardiomyopathy group are similar to those in the acute stage of myocardial infarction, although hypertrophic obstructive cardiomyopathy is not an acute necrotic disease.

Correlation between elevation of plasma brain natriuretic peptide levels and hemodynamic or echocardiographic data in hypertrophic obstructive cardiomyopathy. The present study showed that plasma brain natriuretic peptide levels in hypertrophic obstructive cardiomyopathy were not correlated with any hemodynamic variables, such as pressure gradient or left ventricular end-diastolic pressure. However, the degree of pressure gradient may change in hypertrophic obstructive cardiomyopathy, and changes in the pressure gradient may be related to plasma brain natriuretic peptide levels. We cannot exclude this possibility. However, the difference in pressure gradient over a period of ~3 weeks was very small.

Elevation of plasma brain natriuretic peptide levels correlated positively with interventricular septal thickness and the interventricular septal thickness/left ventricular posterior wall thickness ratio in both hypertrophic obstructive and nonobstructive cardiomyopathy. This finding indicates the importance of ventricular septal mass in the expression of plasma brain natriuretic peptide in hypertrophic obstructive cardiomyopathy. At echocardiographic analysis, the hypertrophic obstructive cardiomyopathy group had an interventricular septal thickness and interventricular septal thickness/left ventricular posterior wall thickness ratio similar to that in the hypertrophic nonobstructive cardiomyopathy group. Because plasma brain natriuretic peptide levels were higher in the hypertrophic obstructive cardiomyopathy than the hypertrophic nonobstructive cardiomyopathy group (approximately sixfold), differences in the contents of tissues that express brain natriuretic peptide in the ventricular septum between hypertrophic obstructive and nonobstructive cardiomyopathy should be considered. However, there is no evidence of significant differences between hypertrophic obstructive and nonobstructive cardiomy-

opathy in the size of myocytes, extent of fibrosis or extent of disarray, according to findings from endomyocardial biopsy and autopsy studies (24,25).

The sensitivity and specificity of hypertrophic obstructive cardiomyopathy for plasma brain natriuretic peptide levels >200 pg/ml and of hypertrophic obstructive cardiomyopathy for a plasma brain/atrial natriuretic peptide ratio >2.5 were high. These findings indicate that 1) plasma brain natriuretic peptide elevation in hypertrophic obstructive cardiomyopathy may be a special feature that can be used to distinguish hypertrophic obstructive from hypertrophic nonobstructive cardiomyopathy; and 2) it is difficult to explain the abnormal elevation of plasma brain natriuretic peptide levels from hemodynamic and echocardiographic data.

Possible mechanism of abnormal elevations of plasma brain natriuretic peptide levels in hypertrophic obstructive cardiomyopathy. The first question is whether elevation of plasma brain natriuretic peptide levels is due to a decrease in its excretion or an increase in its production. We previously reported (11) that the expression of brain natriuretic peptide in ventricular myocytes was not seen in hypertrophic nonobstructive cardiomyopathy but was seen in hypertrophic obstructive cardiomyopathy. This finding indicates an increase in the production of brain natriuretic peptide in the ventricular myocytes in hypertrophic obstructive cardiomyopathy. The second question is, what is the stimulus for release of brain natriuretic peptide? Generally, myocyte stretching has been recognized as an important stimulus for release of both atrial and brain natriuretic peptide (26). Atrial or ventricular stretching is a strong inducer of increases in brain rather than atrial natriuretic peptide gene expression, suggesting differential regulation of atrial and brain natriuretic peptide. However, myocyte stretching is not considered to be important for the abnormal increase of plasma brain natriuretic peptide in hypertrophic obstructive cardiomyopathy versus hypertrophic nonobstructive cardiomyopathy, hypertensive heart disease and aortic stenosis because it is difficult to explain the marked elevation of plasma brain natriuretic peptide levels from hemodynamic and echocardiographic data, as discussed earlier in this report. Recently, the gradual disappearance of natriuretic peptide receptor-C transcripts was reported (27) in rat cardiac hypertrophy accompanied by increased atrial and brain natriuretic peptide mRNA levels, indicating the presence of a downregulation of natriuretic peptide receptor after increases in plasma atrial and brain natriuretic peptide levels. However, whether this downregulation occurs in humans with hypertrophic obstructive cardiomyopathy is unknown. These findings suggest differences in brain natriuretic peptide levels at the level of gene expression between patients with hypertrophic obstructive and those with nonobstructive cardiomyopathy or other cardiac hypertrophy, although hypertrophic obstructive and nonobstructive cardiomyopathy have been grouped together because of their similar pathogenic mechanisms. Further investigations are warranted.

Conclusions. The abnormal elevation of brain natriuretic peptide levels and brain/atrial natriuretic peptide ratio, which cannot be explained by hemodynamic or echocardiographic findings, is a special feature in hypertrophic obstructive cardiomyopathy at rest. This elevation of brain natriuretic peptide levels may play an important role in the pathophysiology of hypertrophic obstructive cardiomyopathy.

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