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Prognostic values of highly sensitive cardiac troponin T and B-type natriuretic peptide for clinical features in hypertrophic obstructive cardiomyopathy: a cross-sectional study

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CONFLICTS OF INTEREST

All other authors have no conflicts to declare.

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ABSTRACT

Objectives: Although B-type natriuretic peptide (BNP) and highly sensitive cardiac troponin T (cTnT) are useful for the evaluation of clinical features in various cardiovascular diseases, there are comparatively few data regarding the utility of these parameters in patients with hypertrophic obstructive cardiomyopathy (HOCM). The goal of this study was to assess the association between BNP, cTnT and clinical parameters in patients with HOCM.

Design: Cross sectional survey

Settings: The relationship between BNP, cTnT, and clinical endpoints and echocardiographic data was investigated.

Participants: This study included 102 consecutive outpatients with HOCM who were clinically stable.

Results: BNP was significantly associated with both max left ventricular (LV) wall thickness ($r = 0.28$; $P = 0.003$), and septal peak early transmitral filling velocity/peak early diastolic mitral annulus velocity ($r = 0.51$; $P = 0.0001$). No statistically significant associations were seen between cTnT and any echocardiographic parameters, but the presence of atrial fibrillation (AF) was associated with a high level of cTnT ($P = 0.01$).

Conclusion: BNP is useful for monitoring clinical parameters and as a reflection of both LV systolic/diastolic function and increased LV pressure in patients with HOCM. A high level of serum cTnT is associated with the presence of AF.

Strengths and limitations of this study

1. This is a first study to explore the relationship between BNP and cTnT and clinical features in patients with HOCM and to demonstrate that increased cTnT levels are associated with the presence of AF in patients with HOCM
2. The patient sample size is small due to the relative rarity of this disease.

KEY WORDS: hypertrophic obstructive cardiomyopathy, hypertrophic cardiomyopathy, cardiac troponin T, B-type natriuretic peptide

Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) is a type of hypertrophic cardiomyopathy characterized by dynamic left ventricular (LV) outflow-tract obstruction caused by asymmetrical septal hypertrophy. Depending in part upon the site and extent of cardiac hypertrophy, patients with HOCM can develop several abnormalities, such as LV outflow obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation. Therefore, the structural and functional abnormalities associated with HOCM can produce a variety of symptoms, including fatigue, dyspnea, chest pain, palpitations, presyncope or syncope.

B-type natriuretic peptide (BNP) levels are elevated in proportion to the severity of LV diastolic and systolic dysfunction.[1-3] Previous studies have demonstrated that BNP is useful for the prediction of outcomes in patients with hypertrophic cardiomyopathy, hypertensive heart disease, and aortic stenosis,[4-10] indicating the significance of BNP elevation in heart disease characterized by LV hypertrophy. Highly sensitive cardiac troponin T (cTnT) is another cardiac marker that can detect myocardial damage. Although cTnT is a strong predictor of adverse outcomes in patients with acute coronary syndrome,[11 12] stable coronary artery disease,[13 14] congestive heart failure,[15-17] and hypertrophic cardiomyopathy, including hypertrophic non-obstructive cardiomyopathy,[18 19] there are comparatively few data regarding the utility of cTnT in only HOCM. Further, it is not clear whether BNP and/or cTnT are useful for monitoring the clinical status of patients with only HOCM. Therefore, the goal of this study was to assess the relationship between BNP, cTnT and clinical parameters in patients with HOCM.

METHODS

Study design and subject recruitment

We analyzed consecutive outpatients with HOCM who were clinically stable and who visited the "HOCM clinic" at Nippon Medical School Hospital for periodical follow-up between January 2011 and June 2012. The diagnosis of HOCM was based on typical clinical, electrocardiographic, and hemodynamic features with echocardiographic demonstration of a non-dilated, asymmetrically hypertrophied LV in the absence of other cardiac or systemic diseases that can produce LV hypertrophy. Patients with significant organic coronary stenosis, valvular heart disease, systemic hypertension, concomitant neoplasm, infection, connective tissue disease, or diabetes mellitus were excluded from study. A complete history and clinical examination was performed along with New York Heart Association (NYHA) functional class assessment, presence of atrial fibrillation (AF), blood examination, and echocardiography. The Nippon Medical School Research Ethics Committee approved this study, and written consent was obtained from all patients.

Echocardiography study

Two-dimensional, M-mode, and Doppler echocardiographic studies were performed with PHILIPS IE 33 or GE Vivid E 9 ultrasound systems on the same day that serum cTnT and BNP were measured. Wall thickness (IVST, interventricular septal thickness; PWT, posterior wall thickness; MWT, max LV wall thickness), cavity size (LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter), LV diastolic dysfunction (E/Ea, peak early transmitral filling velocity/peak early diastolic mitral annulus velocity on tissue Doppler imaging), max pressure gradient (Max PG, max peak gradient in the LV), tricuspid regurgitation peak gradient, and wall motion were measured from M-mode and 2D images. MWT was defined as the greatest thickness in any single segment.

LV diastolic function was assessed by septal, and lateral E/Ea. The ventricular volume and ejection fraction were computed using the biapical Simpson's rule.

Measurement of cardiac troponin-t and b-type natriuretic peptide

Peripheral blood samples were collected for measurement of serum BNP and cTnT at the same time as other examinations. Serum BNP and cTnT were measured with a AIA-2000ST analyzer (TOSOH, Tokyo, Japan) in accordance with the manufacturer's instructions. The assay detection limit was ≥ 0.003 ng/ml. Patients were divided into low or high BNP groups and into low and high cTnT groups according to previously reported cutoff points (200 pg/ml for BNP and 0.014 ng/ml for cTnT).[10 19] **Statistical methods**

Continuous variables were tested for normal distribution by the Shapiro-Wilk test. The normal distributed continuous variables are shown as means ± Standard Deviation (SD), and nonparametrically distributed variables are shown as medians (interquartile range). Categorical variables are presented as frequencies (percentages). Correlation between two continuous variables was examined by Pearson's test (if relevant by Spearman's test). Logistic regression analyses were performed with the presence/absence of elevated cTnT or BNP levels as dependent variable (cTnT cutoff point ≥ 0.014 ng/ml, BNP cutoff point ≥ 200 pg/ml) and different clinical factors as covariables. Multiple regression analyses of the relationship between cTnT or BNP and study variables were performed in order to detect clinical characteristics related to these markers after adjustment for interrelationship among study variables. A two-sided probability value of $P < 0.05$ was considered to be statistically significant. JMP (version 9.0.3, North Carolina, USA) was used for analysis.

RESULTS

There were 104 patients who visited the "HOCM clinic" during the examination period, of which two patients were excluded due to absence of echocardiographic data. Therefore, the study population consisted of 102 consecutive patients who underwent complete clinical, echocardiographic, and serum-marker assessment. Baseline characteristics of the 102 patients are shown in Table 1. There were 84 patients (82.3%) with LV outflow obstruction, 13 patients (12.7%) with mid-cavity obstruction, and five patients (4.9%) with apical obstruction. Serum BNP ranged from 33.6 to 2593 pg/ml (mean, 286.5±334 pg/ml; median, 174.4 pg/ml). Twenty-four patients (23.5%) had an BNP level above the cutoff point (400 pg/ml), including three patients (2.9%) with a level ≥ 1000 pg/ml. Serum cTnT ranged from 0.003 to 0.09 ng/ml (mean, 0.015±0.015 ng/ml; median, 0.011 ng/ml). Eighty-six patients (84.3%) had a cTnT level above the detection limit of assay (0.003 ng/ml), including 37 patients (36.2%) with a level ≥ 0.014 ng/ml and five patients (4.9%) with a level ≥ 0.05 ng/ml. There was no significant association between BNP and cTnT levels (r = 0.06, P = 0.10, by Spearman's rank-correlation test).

Relationship between biomarkers, clinical features, and echocardiographic characteristics

BNP was significantly associated with IVST (r = 0.31; P = 0.001), MWT (r = 0.28; P = 0.003), septal E/Ea (r = 0.51; P = 0.0001), and lateral E/Ea (r = 0.41; P = 0.0001) (Table 2). BNP negatively associated with LVEDD (r = -0.39; P = 0.001) and LVESD (r = -0.20; P = 0.04; Table 2). Patients were divided into two groups according to BNP level: the low BNP group (BNP <200 pg/ml) and the high BNP group (BNP ≥200 pg/ml) (Table 3). More patients had NYHA functional class II in the high BNP group than in the low BNP group, and LVEDD and lateral E/Ea were greater in the high BNP group than in the low BNP group (Table 3).

There were no statistically significant associations between cTnT and any echocardiographic parameters (Table 2). Patients were also divided into two groups according to cTnT level: the low cTnT group (cTnT<0.014 ng/ml) and the high cTnT group (cTnT ≥0.014 ng/ml) (Table 3). There were no significant differences in age, female, or any echocardiographic parameters between the low cTnT group and the high level cTnT group and the presence of AF was significantly higher in the high cTnT group than in the low cTnT group (40.5% vs. 16.9%; P = 0.01) (Table 3).

Relationship between atrial fibrillation and cTnT

Univariate logistic regression analysis was performed using the patient characteristics to investigate factors associated with presence of AF. As shown in Table 4A, large left atrium diameter (large LAD ≥50 mm), high BNP (BNP ≥200 pg/ml), and high cTnT (cTnT ≥0.014 ng/ml) were significantly associated with presence of AF. Multivariate logistic regression analysis using the significant factors obtained within univariate analysis revealed that high LAD and high cTnT were each independent factors for the presence of AF (Table 4B). Moreover, cTnT levels in patients with persistent AF appeared to be significantly higher than that in patients with paroxysmal AF or in those without AF (median, 0.028 vs. 0.013 vs. 0.01 ng/ml; P < 0.001) (Figure).

DISCUSSION

This study demonstrated that BNP was a more useful and reliable biomarker than cTnT for the clinical status of patients with HOCM. The levels were positively associated with various clinical and echocardiographic parameters, including dyspnea (NYHA functional class), LV filling pressure, diastolic dysfunction (septal and lateral E/Ea), and LV wall thickness (IVST, MWT), whereas high cTnT levels were significantly associated only with the presence of AF. Further, this study demonstrated that BNP levels were significantly and negatively associated with LV volume

(LV end-diastolic / systolic diameters). Finally, cTnT level was independently associated with the presence of AF, and levels of cTnT in patients with persistent AF were significantly higher than those with paroxysmal AF or without AF.

Previous studies have demonstrated that BNP is a useful biomarker of clinical parameters and can predict adverse outcomes in patients with heart failure, cardiomyopathy and ischemic heart disease.[6-9] Previous studies have also reported that serum BNP levels in patient with hypertrophic cardiomyopathy (HCM) and hypertension, which typically occurs in the absence of LV cavity volume expansion and the presence of systolic dysfunction, are independently associated with the presence and magnitude of heart failure symptom.[18-21] Although the present study enrolled only patients with HOCM, the data we obtained were primarily consistent with data from previous studies involving patients with non-obstructive HCM. The present study also demonstrated a positive association between BNP levels and various parameters, including NYHA functional class, septal and lateral E/e', IVST, and MWT, Therefore, these findings serve to extend the principle, that serum BNP levels are associated with the presence and magnitude of heart failure symptoms, for non-obstructive hypertrophic cardiomyopathy into patients with HOCM. Of note, BNP levels were also negatively associated with LVEDD and LVESD, indicating that BNP levels increase in the context of reduced cavity volume and increased end-diastolic pressure. In other words, the present study suggests that LV volume reduction leads to impaired diastolic function and reflects increasing pressure in LV. Prior to the present study, there have been very few investigations of the significance of BNP levels in patients with HOCM.[22]

In contrast to BNP, serum cTnT levels were not associated with most of the clinical parameters investigated in this

study, including diastolic function, LV wall thickness, or the magnitude of dyspnea in HOCM. A previous study reported that the prevalence of elevated cTnT levels (lower limit of detection is 0.01 ng/ml) in the general population was 0.7%.[23] Further, serum cTnT levels are higher in patients with HCM than in the general population.[19] These observations are consistent with data from the present study, in which the mean cTnT level was 0.015 ng/ml and the prevalence of elevated cTnT levels (equal or above 0.01 ng/dl) was 57.8%. Although prior studies reported that cTnT levels were related to the clinical parameters, such as LV wall thickness, E/e', or LV outflow tract gradient in patients with HCM (including those with HOCM) and that cTnT was an independent predictor of outcomes,[18 19 24] the present study failed to show these relationships. Specifically, the present study found that cTnT elevation was related only to the presence of AF among all clinical parameters investigated. Elevations of cTnT are related to cardiac remodeling that leads to the development of AF,[19 25 26] and Anegawa et al. reported that the high cTnT level was associated with AF in a general population.[27] However, the relationship between cTnT and AF has not been reported in patients with HCM, including those with HOCM. There are several possible mechanistic explanations for the association between cTnT and presence of AF. First, modest elevations in cTnT may be caused by leakage from the atrium because of cardiac remodeling, including atrial myocyte death and fibrosis. Second, HOCM is characterized by LV outflow obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation. Thus, the presence of AF in HOCM may potentiate these abnormalities, particularly in regards to myocardial ischemia. In other words, AF with rapid ventricular response may reduce diastolic filling time, leading to impaired LV filling in patients with HOCM, especially in those with pre-existing diastolic dysfunction. Further, the atrial kick is very important in achieving adequate ventricular filling, and the loss of atrial

kick in the context of AF results in decreased LV filling. AF is also often poorly tolerated in HCM patients and may be associated with significant clinical deterioration.[28-30] Therefore, the present findings may indicate that AF might contribute to cardiac ischemia and progression of cardiac remodeling, including myocyte necrosis. In combination with observations from the present study, this suggests that cTnT may have utility for the detection of ischemia and cardiac remodeling. By contrast, BNP might be more useful as a reflection of hemodynamic parameters, magnitude of symptoms, and systolic/diastolic function. These may explain why cTnT significantly correlated only with AF. To our knowledge, this is a first study to explore the relationship between BNP and cTnT and clinical features in patients with HOCM and to demonstrate that increased cTnT levels are associated with the presence of AF in patients with HOCM. BNP is useful for monitoring clinical parameters and as a reflection of both LV systolic/diastolic function and increased LV pressure in patients with HOCM. Furthermore, a high level of serum cTnT appears to be associated with the presence of AF and may thus be a good marker of cardiac remodeling or ischemia in patients with HOCM.

The principal limitation of the present study was its cross-sectional design. Additional limitations include the small patient sample size due to the relative rarity of this disease. Although the number of enrolled patients in the present study might not be sufficient for our results to be generalized, the patient number was equivalent to that in previous studies of patients with HOCM [22] and in patients with HCM (including those with HOCM).[18 19]

Contributors: SN participated in study concept and design, drafting of the manuscript, administrative, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.

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Data sharing statement: No additional data available.

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Table 1. Baseline Characteristics for the Study Samples

Age (years)	67.1±11.7
Female, n (%)	71 (69.6%)
NYHA functional class	
Ⅰ, n (%)	62 (60.8%)
Ⅱ, n (%)	39 (38.3%)
Ⅲ-Ⅳ, n (%)	1 (0.9%)
Atrial fibrillation, n (%)	76 (74.5%)
Echocardiographic data	
LVEF (%)	73.5±8.0
IVS (mm)	14.7±4.9
PWT (mm)	10.2±1.8
MWT (mm)	16.2±4.0
LV end-diastolic dimension (mm)	43.7±5.6
Left atrial dimension (mm)	43.5±8.2
Septal E/Ea	16.5±8.9
Lateral E/Ea	12.0±5.6
LV pressure gradient (mmHg)	42.6±40.4
TR pressure gradient (mmHg)	27.6±8.5
Medications	
Beta-blocker, n (%)	86 (86.0%)
Calcium channel blocker, n (%)	38 (38.3%)
Cibenzoline, n (%)	65 (65.6%)

Abbreviations: NYHA functional class denotes New York Heart Association functional class; LVEF, left ventricular ejection fraction; IVS, interventricular septal thickness; PWT, posterior wall thickness; MWT, max LV wall thickness; E/Ea, peak early transmitral filling velocity/peak early diastolic mitral annulus velocity on tissue Doppler imaging; TR pressure gradient, tricuspid valve regurgitation. Data are expressed as mean ± standard deviation or number of the patients (percentage).

Table 2. Associations between BNP or cTnT and clinical parameters

	BNP		cTnT	
	r value	P value	r value	P value
Age	-0.02	0.81	0.08	0.38
IVST	0.31	0.0013	0.03	0.70
PWT	0.014	0.88	0.08	0.40
MWT	0.28	0.0039	0.15	0.11
LAD	0.14	0.13	0.18	0.06
LVEDD	-0.39	0.001	0.11	0.24
LVESD	-0.20	0.04	0.16	0.09
LVEF	-0.10	0.28	-0.12	0.20
Septal E/Ea	0.51	0.0001	0.06	0.51
Lateral E/Ea	0.41	0.0001	0.10	0.33
Max PG	0.06	0.52	-0.10	0.30
TRPG	0.08	0.43	-0.005	0.96

Abbreviations: BNP denotes B-type natriuretic peptide; cTnT, highly sensitive cardiac troponin T; LAD, left atrial diameter; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; Max PG, max peak gradient in the left ventricle; TRPG, tricuspid regurgitation peak gradient. Other abbreviations are described in Table 1.

Table 3. BNP, cTnT and characteristics of the patients

	BNP (pg/ml)			cTnT (ng/ml)		
	BNP <200	BNP ≧200	P Value	cTnT <0.014	cTnT ≧0.014	P Value
Age, years	66.9±10.7	67.4±12.7	0.8	66.5±11.9	68.4 ±11.3	0.4
Female, %	33 (63.4%)	38 76.0%)	0.19	45(69.2)	26(70.2)	1.00
NYHA class	14(26.9%)	24(48.0%)	0.04	24(36.9%)	14(37.8%)	1.0
AF	9(17.3%)	17(34.0%)	0.06	11(16.9%)	15(40.5%)	0.01
MWT	15.6±3.5	16.9±4.4	0.09	16.2±4.5	16.2±3.1	0.9
LVEDD	45.2±5.6	42.0±5.1	0.003	43.5±5.7	44.0±5.5	0.6
LVEF	74.4±7.6	72.5±8.4	0.2	74.4±6.5	71.8±10.1	0.12
LAD	42.2±6.5	44.8±9.5	0.11	42.3±6.3	45.5±10.6	0.06
Lateral E/Ea	9.5±3.7	14.9±6.2	0.002	12.3±5.7	11.3±5.6	0.4
Max PG	39.0±37.6	46.4±43.2	0.3	45.6±41.3	37.1±38.6	0.3

Abbreviations: NYHA class denotes New York Heart Association functional class; AF, atrial fibrillation. Other abbreviations are described in table 1 or 2. Data are expressed as mean ± standard deviation or number of the patients (percentage).

Table 4A. Univariate logistic regression analysis of the prevalence of AF versus clinical features

	odds ratio	P Value
Age	1.00 (0.96-1.04)	0.68
Female	2.00 (0.80-5.20)	0.14
NYHA class ≥ II	0.68 (0.26-1.76)	0.48
MWT	3.04 (0.07-307.2)	0.58
LAD ≥50 mm	8.87 (2.77-31.9)	0.0002
LVEF	5.97 (0.47-78.1)	0.16
E/e' lat ≥15	1.73 (0.61-4.89)	0.42
Max PG	8.47 (1.31-75.5)	0.23
High BNP	2.46 (0.97-6.21)	0.06
High cTnT	3.34 (1.33-8.42)	0.01

Abbreviations: High BNP denotes high type-B Natriuretic Peptide level (serum BNP level ≥200 pg/ml); High cTnT, high cardiac troponin T level (serum cTnT level ≥0.014 ng/ml). Other abbreviations are described tables 1, 2, or 3.

Table 4B. Multivariate logistic regression analysis of the prevalence of AF versus clinical features

	odds ratio	P Value
Female	2.37	0.13
High BNP	2.53	0.09
High cTnT	3.96	0.008
LAD ≥50 mm	6.91	0.002

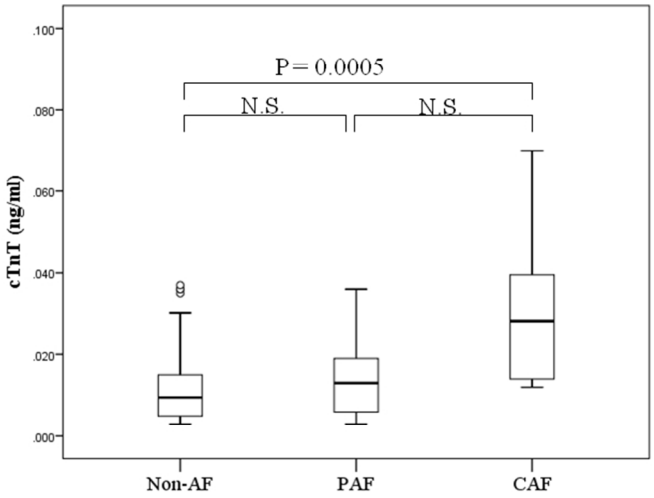
Abbreviations are described tables 2,3, or 4A.

Figure legends

Figure 1. cTnT levels in patients with HOCM according to the presence, absence, or type of AF.

cTnT, highly sensitive cardiac troponin T; HOCM, hypertrophic obstructive cardiomyopathy; AF, atrial fibrillation; N.S., not significant.

Figure 1. cTnT levels in patients with HOCM according to the presence, absence, or type of AF.



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Prognostic values of highly sensitive cardiac troponin T and B-type natriuretic peptide for clinical features in hypertrophic obstructive cardiomyopathy: a cross-sectional study

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ABSTRACT

Objectives: Although B-type natriuretic peptide (BNP) and highly sensitive cardiac troponin T (cTnT) are useful for the evaluation of clinical features in various cardiovascular diseases, there are comparatively few data regarding the utility of these parameters in patients with hypertrophic obstructive cardiomyopathy (HOCM). The goal of this study was to assess the association between BNP, cTnT and clinical parameters in patients with HOCM.

Design: Cross sectional survey

Settings: The relationship between BNP, cTnT, and clinical endpoints and echocardiographic data was investigated.

Participants: This study included 102 consecutive outpatients with HOCM who were clinically stable.

Results: BNP was significantly associated with both max left ventricular (LV) wall thickness ($r = 0.28$; $P = 0.003$), and septal peak early transmitral filling velocity/peak early diastolic mitral annulus velocity ($r = 0.51$; $P = 0.0001$). No statistically significant associations were seen between cTnT and any echocardiographic parameters, but the presence of atrial fibrillation (AF) was associated with a high level of cTnT ($P = 0.01$).

Conclusion: BNP is useful for monitoring clinical parameters and as a reflection of both LV systolic/diastolic function and increased LV pressure in patients with HOCM. A high level of serum cTnT is associated with the presence of AF.

Strengths and limitations of this study

1. This is a first study to explore the relationship between BNP and cTnT and clinical features in patients with HOCM and to demonstrate that increased cTnT levels are associated with the presence of AF in patients with HOCM
2. The patient sample size is small due to the relative rarity of this disease.

KEY WORDS: hypertrophic obstructive cardiomyopathy, hypertrophic cardiomyopathy, cardiac troponin T, B-type natriuretic peptide

Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) is a type of hypertrophic cardiomyopathy characterized by dynamic left ventricular (LV) outflow-tract obstruction caused by asymmetrical septal hypertrophy. Depending in part upon the site and extent of cardiac hypertrophy, patients with HOCM can develop several abnormalities, such as LV outflow obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation. Therefore, the structural and functional abnormalities associated with HOCM can produce a variety of symptoms, including fatigue, dyspnea, chest pain, palpitations, presyncope or syncope.

B-type natriuretic peptide (BNP) levels are elevated in proportion to the severity of LV diastolic and systolic dysfunction.[1-3] Previous studies have demonstrated that BNP is useful for the prediction of outcomes in patients with hypertrophic cardiomyopathy, hypertensive heart disease, and aortic stenosis,[4-10] indicating the significance of BNP elevation in heart disease characterized by LV hypertrophy. Highly sensitive cardiac troponin T (cTnT) is another cardiac marker that can detect myocardial damage. Although cTnT is a strong predictor of adverse outcomes in patients with acute coronary syndrome,[11 12] stable coronary artery disease,[13 14] congestive heart failure,[15-17] and hypertrophic cardiomyopathy, including hypertrophic non-obstructive cardiomyopathy,[18 19] there are comparatively few data regarding the utility of cTnT in only HOCM. Further, it is not clear whether BNP and/or cTnT are useful for monitoring the clinical status of patients with only HOCM. Therefore, the goal of this study was to assess the relationship between BNP, cTnT and clinical parameters in patients with HOCM.

METHODS

Study design and subject recruitment

We analyzed consecutive outpatients with HOCM who were clinically stable and who visited the "HOCM clinic" at Nippon Medical School Hospital for periodical follow-up between January 2011 and June 2012. The diagnosis of HOCM was based on typical clinical, electrocardiographic, and hemodynamic features with echocardiographic demonstration of a non-dilated, asymmetrically hypertrophied LV in the absence of other cardiac or systemic diseases that can produce LV hypertrophy. Patients with significant organic coronary stenosis, valvular heart disease, systemic hypertension, concomitant neoplasm, infection, connective tissue disease, or diabetes mellitus were excluded from study. A complete history and clinical examination was performed along with New York Heart Association (NYHA) functional class assessment, presence of atrial fibrillation (AF), blood examination, and echocardiography. The Nippon Medical School Research Ethics Committee approved this study, and written consent was obtained from all patients.

Echocardiography study

Two-dimensional, M-mode, and Doppler echocardiographic studies were performed with PHILIPS IE 33 or GE Vivid E 9 ultrasound systems on the same day that serum cTnT and BNP were measured. Wall thickness (IVST, interventricular septal thickness; PWT, posterior wall thickness; MWT, max LV wall thickness), cavity size (LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter), LV diastolic dysfunction (E/Ea, peak early transmitral filling velocity/peak early diastolic mitral annulus velocity on tissue Doppler imaging), max pressure gradient (Max PG, max peak gradient in the LV), tricuspid regurgitation peak gradient, and wall motion were measured from M-mode and 2D images. MWT was defined as the greatest thickness in any single segment.

LV diastolic function was assessed by septal, and lateral E/Ea. The ventricular volume and ejection fraction were computed using the biapical Simpson's rule.

Measurement of cardiac troponin-T and B-type natriuretic peptide

Peripheral blood samples were collected for measurement of serum BNP and cTnT at the same time as other examinations. Serum BNP and cTnT were measured with an AIA-2000ST analyzer (TOSOH, Tokyo, Japan) in accordance with the manufacturer's instructions. The assay detection limit was ≥ 0.003 ng/ml. Patients were divided into low or high BNP groups and into low and high cTnT groups according to previously reported cutoff points (200 pg/ml for BNP and 0.014 ng/ml for cTnT).[10 19]

Statistical methods

Continuous variables were tested for normal distribution by the Shapiro-Wilk test. The normal distributed continuous variables are shown as means ± Standard Deviation (SD), and nonparametrically distributed variables are shown as medians (interquartile range). Categorical variables are presented as frequencies (percentages). Correlation between two continuous variables was examined by Pearson's test (if relevant by Spearman's test). Logistic regression analyses were performed with the presence/absence of elevated cTnT or BNP levels as dependent variable (cTnT cutoff point ≥ 0.014 ng/ml, BNP cutoff point ≥ 200 pg/ml) and different clinical factors as covariables. Multiple regression analyses of the relationship between cTnT or BNP and study variables were performed in order to detect clinical characteristics related to these markers after adjustment for interrelationship among study variables. A two-sided probability value of $P < 0.05$ was considered to be statistically significant. JMP (version 9.0.3, North Carolina, USA) was used for analysis.

RESULTS

There were 104 patients who visited the "HOCM clinic" during the examination period, of which two patients were excluded due to absence of echocardiographic data. Therefore, the study population consisted of 102 consecutive patients who underwent complete clinical, echocardiographic, and serum-marker assessment. Baseline characteristics of the 102 patients are shown in Table 1. There were 84 patients (82.3%) with LV outflow obstruction, 13 patients (12.7%) with mid-cavity obstruction, and five patients (4.9%) with apical obstruction. Serum BNP ranged from 33.6 to 2593 pg/ml (mean, 286.5±334 pg/ml; median, 174.4 pg/ml). Twenty-four patients (23.5%) had an BNP level above the cutoff point (400 pg/ml), including three patients (2.9%) with a level ≥ 1000 pg/ml. Serum cTnT ranged from 0.003 to 0.09 ng/ml (mean, 0.015±0.015 ng/ml; median, 0.011 ng/ml). Eighty-six patients (84.3%) had a cTnT level above the detection limit of assay (0.003 ng/ml), including 37 patients (36.2%) with a level ≥ 0.014 ng/ml and five patients (4.9%) with a level ≥ 0.05 ng/ml. There was no significant association between BNP and cTnT levels (r = 0.06, P = 0.10, by Spearman's rank-correlation test).

Relationship between biomarkers, clinical features, and echocardiographic characteristics

BNP was significantly associated with IVST (r = 0.31; P = 0.001), MWT (r = 0.28; P = 0.003), septal E/Ea (r = 0.51; P = 0.0001), and lateral E/Ea (r = 0.41; P = 0.0001) (Table 2). BNP negatively associated with LVEDD (r = -0.39; P = 0.001) and LVESD (r = -0.20; P = 0.04; Table 2). Patients were divided into two groups according to BNP level: the low BNP group (BNP <200 pg/ml) and the high BNP group (BNP ≥200 pg/ml) (Table 3). More patients had NYHA functional class II in the high BNP group than in the low BNP group, and LVEDD and lateral E/Ea were greater in the high BNP group than in the low BNP group (Table 3).

There were no statistically significant associations between cTnT and any echocardiographic parameters (Table 2). Patients were also divided into two groups according to cTnT level: the low cTnT group (cTnT<0.014 ng/ml) and the high cTnT group (cTnT ≥0.014 ng/ml) (Table 3). There were no significant differences in age, female, or any echocardiographic parameters between the low cTnT group and the high level cTnT group and the presence of AF was significantly higher in the high cTnT group than in the low cTnT group (40.5% vs. 16.9%; P = 0.01) (Table 3).

Relationship between atrial fibrillation and cTnT

Univariate logistic regression analysis was performed using the patient characteristics to investigate factors associated with presence of AF. As shown in Table 4A, large left atrium diameter (large LAD ≥50 mm), high BNP (BNP ≥200 pg/ml), and high cTnT (cTnT ≥0.014 ng/ml) were significantly associated with presence of AF. Multivariate logistic regression analysis using the significant factors obtained within univariate analysis revealed that high LAD and high cTnT were each independent factors for the presence of AF (Table 4B). Moreover, cTnT levels in patients with persistent AF appeared to be significantly higher than that in patients with paroxysmal AF or in those without AF (median, 0.028 vs. 0.013 vs. 0.01 ng/ml; P < 0.001) (Figure).

DISCUSSION

This study demonstrated that BNP was a more useful and reliable biomarker than cTnT for the clinical status of patients with HOCM. The levels were positively associated with various clinical and echocardiographic parameters, including dyspnea (NYHA functional class), LV filling pressure, diastolic dysfunction (septal and lateral E/Ea), and LV wall thickness (IVST, MWT), whereas high cTnT levels were significantly associated only with the presence of AF. Further, this study demonstrated that BNP levels were significantly and negatively associated with LV volume

(LV end-diastolic / systolic diameters). Finally, cTnT level was independently associated with the presence of AF, and levels of cTnT in patients with persistent AF were significantly higher than those with paroxysmal AF or without AF.

Previous studies have demonstrated that BNP is a useful biomarker of clinical parameters and can predict adverse outcomes in patients with heart failure, cardiomyopathy and ischemic heart disease.[6-9] Previous studies have also reported that serum BNP levels in patient with hypertrophic cardiomyopathy (HCM) and hypertension, which typically occurs in the absence of LV cavity volume expansion and the presence of systolic dysfunction, are independently associated with the presence and magnitude of heart failure symptom.[18-21] Although the present study enrolled only patients with HOCM, the data we obtained were primarily consistent with data from previous studies involving patients with non-obstructive HCM. The present study also demonstrated a positive association between BNP levels and various parameters, including NYHA functional class, septal and lateral E/e', IVST, and MWT, Therefore, these findings serve to extend the principle, that serum BNP levels are associated with the presence and magnitude of heart failure symptoms, for non-obstructive hypertrophic cardiomyopathy into patients with HOCM. Of note, BNP levels were also negatively associated with LVEDD and LVESD, indicating that BNP levels increase in the context of reduced cavity volume and increased end-diastolic pressure. In other words, the present study suggests that LV volume reduction leads to impaired diastolic function and reflects increasing pressure in LV. Prior to the present study, there have been very few investigations of the significance of BNP levels in patients with HOCM.[22]

In contrast to BNP, serum cTnT levels were not associated with most of the clinical parameters investigated in this

study, including diastolic function, LV wall thickness, or the magnitude of dyspnea in HOCM. A previous study reported that the prevalence of elevated cTnT levels (lower limit of detection is 0.01 ng/ml) in the general population was 0.7%.[23] Further, serum cTnT levels are higher in patients with HCM than in the general population.[19] These observations are consistent with data from the present study, in which the mean cTnT level was 0.015 ng/ml and the prevalence of elevated cTnT levels (equal or above 0.01 ng/dl) was 57.8%. Although prior studies reported that cTnT levels were related to the clinical parameters, such as LV wall thickness, E/e', or LV outflow tract gradient in patients with HCM (including those with HOCM) and that cTnT was an independent predictor of outcomes,[18 19 24] the present study failed to show these relationships. Specifically, the present study found that cTnT elevation was related only to the presence of AF among all clinical parameters investigated.

Elevations of cTnT are related to cardiac remodeling that leads to the development of AF,[19 25 26] and Anegawa et al. reported that the high cTnT level was associated with AF in a general population.[27] However, the relationship between cTnT and AF has not been reported in patients with HCM, including those with HOCM. There are several possible mechanistic explanations for the association between cTnT and presence of AF. First, modest elevations in cTnT may be caused by leakage from the atrium because of cardiac remodeling, including atrial myocyte death and fibrosis. Second, HOCM is characterized by LV outflow obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation. Thus, the presence of AF in HOCM may potentiate these abnormalities, particularly in regards to myocardial ischemia. In other words, AF with rapid ventricular response may reduce diastolic filling time, leading to impaired LV filling in patients with HOCM, especially in those with pre-existing diastolic dysfunction. Further, the atrial kick is very important in achieving adequate ventricular filling, and the loss of atrial

kick in the context of AF results in decreased LV filling. AF is also often poorly tolerated in HCM patients and may be associated with significant clinical deterioration.[28-30] Therefore, the present findings may indicate that AF might contribute to cardiac ischemia and progression of cardiac remodeling, including myocyte necrosis. In combination with observations from the present study, this suggests that cTnT may have utility for the detection of ischemia and cardiac remodeling. By contrast, BNP might be more useful as a reflection of hemodynamic parameters, magnitude of symptoms, and systolic/diastolic function. These may explain why cTnT significantly correlated only with AF. However, several reports have been reported that cTnT is related to echocardiographic parameters such as maximum LV wall thickness, and left atrial dimension. Our results showed that cTnT tended to be associated with maximum LV wall thickness and left atrium dimension which did not reach to the statistical significance. This discrepancy could be explained by the small study sample size.

The principal limitation of the present study was its cross-sectional design. Additional limitations include the small patient sample size due to the relative rarity of this disease. Although the number of enrolled patients in the present study might not be sufficient for our results to be generalized, the patient number was equivalent to that in previous studies of patients with HOCM [22] and in patients with HCM (including those with HOCM).[18 19]

To our knowledge, this is a first study to explore the relationship between BNP and cTnT and clinical features in patients with HOCM and to demonstrate that increased cTnT levels are associated with the presence of AF in patients with HOCM. BNP is useful for monitoring clinical parameters and as a reflection of both LV systolic/diastolic function and increased LV pressure in patients with HOCM. Furthermore, a high level of serum

cTnT appears to be associated with the presence of AF and may thus be a good marker of cardiac remodeling or ischemia in patients with HOCM.

Contributors: SN, HT, JM, DC, MK, KM, KA, MY, and MT participated in study concept and design, drafting of the manuscript, administrative, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. WS participated in study concept and design, drafting of the manuscript, administrative, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and final approval of the article.

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Table 1. Baseline Characteristics for the Study Samples

Age (years)	67.1 ± 11.7
Female, n (%)	71 (69.6%)
Types of obstruction	
LVOT obstruction	84 (82.3%)
Mid-ventricular obstruction	13 (12.7%)
Apical obstruction	5 (5.0 %)
NYHA functional class	
Ⅰ, n (%)	62 (60.8%)
Ⅱ, n (%)	39 (38.3%)
Ⅲ-Ⅳ, n (%)	1 (0.9%)
Atrial fibrillation, n (%)	76 (74.5%)
eGFR (ml/min/1.73^2)	75.1 ± 26.2
Echocardiographic data	
LVEF (%)	73.5 ± 8.0
IVS (mm)	14.7 ± 4.9
PWT (mm)	10.2 ± 1.8
MWT (mm)	16.2 ± 4.0
LV end-diastolic dimension (mm)	43.7 ± 5.6
Left atrial dimension (mm)	43.5 ± 8.2
Septal E/Ea	16.5 ± 8.9
Lateral E/Ea	12.0 ± 5.6
LV pressure gradient (mmHg)	42.6 ± 40.4
TR pressure gradient (mmHg)	27.6 ± 8.5
Medications	
Beta-blocker, n (%)	86 (86.0 %)
Calcium channel blocker, n (%)	38 (38.3 %)
Cibenzoline, n (%)	65 (65.6 %)

Abbreviations: NYHA functional class denotes New York Heart Association functional class; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; IVS, interventricular septal thickness; PWT, posterior wall thickness; MWT, max LV wall thickness; E/Ea, peak early transmitral filling velocity/peak early diastolic mitral annulus velocity on tissue Doppler imaging; TR pressure gradient, tricuspid valve regurgitation.

Data are expressed as mean ± standard deviation or number of the patients (percentage).

Table 2. Associations between BNP or cTnT and clinical parameters

	BNP		cTnT	
	r value	P value	r value	P value
Age	-0.02	0.81	0.08	0.38
IVST	0.31	0.0013	0.03	0.70
PWT	0.014	0.88	0.08	0.40
MWT	0.28	0.0039	0.15	0.11
LAD	0.14	0.13	0.18	0.06
LVEDD	-0.39	0.001	0.11	0.24
LVESD	-0.20	0.04	0.16	0.09
LVEF	-0.10	0.28	-0.12	0.20
Septal E/Ea	0.51	0.0001	0.06	0.51
Lateral E/Ea	0.41	0.0001	0.10	0.33
Max PG	0.06	0.52	-0.10	0.30
TRPG	0.08	0.43	-0.005	0.96

Abbreviations: BNP denotes B-type natriuretic peptide; cTnT, highly sensitive cardiac troponin T; LAD, left atrial diameter; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; Max PG, max peak gradient in the left ventricle; TRPG, tricuspid regurgitation peak gradient. Other abbreviations are described in Table 1.

Table 3. BNP, cTnT and characteristics of the patients

	BNP (pg/ml)			cTnT (ng/ml)		
	BNP < 200	BNP ≥ 200	P Value	cTnT < 0.014	cTnT ≥ 0.014	P Value
Age, years	66.9 ± 10.7	67.4 ± 12.7	0.8	66.5 ± 11.9	68.4 ±11.3	0.4
Female, %	33 (63.4 %)	38 (76.0 %)	0.19	45 (69.2 %)	26 (70.2 %)	1.00
NYHA class	14 (26.9 %)	24 (48.0 %)	0.04	24 (36.9 %)	14 (37.8 %)	1.0
AF	9 (17.3 %)	17 (34.0 %)	0.06	11 (16.9 %)	15 (40.5 %)	0.01
eGFR	75.1 ± 26.5	74.9 ± 25.7	1.0	70.8 ± 26.9	77.5 ± 25.7	0.21
MWT	15.6 ± 3.5	16.9 ± 4.4	0.09	16.2 ± 4.5	16.2 ± 3.1	0.9
LVEDD	45.2 ± 5.6	42.0 ± 5.1	0.003	43.5 ± 5.7	44.0 ± 5.5	0.6
LVEF	74.4 ± 7.6	72.5 ± 8.4	0.2	74.4 ± 6.5	71.8 ± 10.1	0.12
LAD	42.2 ± 6.5	44.8 ± 9.5	0.11	42.3 ± 6.3	45.5 ± 10.6	0.06
Lateral E/Ea	9.5 ± 3.7	14.9 ± 6.2	0.002	12.3 ± 5.7	11.3 ± 5.6	0.4
Max PG	39.0 ± 37.6	46.4 ± 43.2	0.3	45.6 ± 41.3	37.1 ± 38.6	0.3

Abbreviations: NYHA class denotes New York Heart Association functional class; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate. The other abbreviations are described in table 1 or 2. Data are expressed as mean ± standard deviation or number of the patients (percentage).

Table 4A. Univariate logistic regression analysis of the prevalence of AF versus clinical features

	odds ratio	P Value
Age	1.00 (0.96-1.04)	0.68
Female	2.00 (0.80-5.20)	0.14
NYHA class ≥ II	0.68 (0.26-1.76)	0.48
MWT	3.04 (0.07-307.2)	0.58
LAD ≥50 mm	8.87 (2.77-31.9)	0.0002
LVEF	5.97 (0.47-78.1)	0.16
E/e' lat ≥15	1.73 (0.61-4.89)	0.42
Max PG	8.47 (1.31-75.5)	0.23
High BNP	2.46 (0.97-6.21)	0.06
High cTnT	3.34 (1.33-8.42)	0.01

Abbreviations: High BNP denotes high type-B Natriuretic Peptide level (serum BNP level ≥200 pg/ml); High cTnT, high cardiac troponin T level (serum cTnT level ≥0.014 ng/ml). Other abbreviations are described tables 1, 2, or 3.

Table 4B. Multivariate logistic regression analysis of the prevalence of AF versus clinical features

	odds ratio	P Value
Female	2.37	0.13
High BNP	2.53	0.09
High cTnT	3.96	0.008
LAD ≥50 mm	6.91	0.002

Abbreviations are described tables 2, 3 or 4A.

Figure legends

Figure 1. cTnT levels in patients with HOCM according to the presence, absence, or types of AF.

cTnT, highly sensitive cardiac troponin T; HOCM, hypertrophic obstructive cardiomyopathy; AF, atrial fibrillation; N.S., not significant. Paroxysmal AF: episodes that come and go, but resolve themselves within 7 days; Persistent AF: episodes that last beyond seven days; Chronic AF: continuous AF that lasts longer than one year.

Prognostic values of highly sensitive cardiac troponin T and B-type natriuretic peptide for clinical features in hypertrophic obstructive cardiomyopathy: a cross-sectional study

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CONFLICTS OF INTEREST

All other authors have no conflicts to declare.

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ABSTRACT

Objectives: Although B-type natriuretic peptide (BNP) and highly sensitive cardiac troponin T (cTnT) are useful for the evaluation of clinical features in various cardiovascular diseases, there are comparatively few data regarding the utility of these parameters in patients with hypertrophic obstructive cardiomyopathy (HOCM). The goal of this study was to assess the association between BNP, cTnT and clinical parameters in patients with HOCM.

Design: Cross sectional survey

Settings: The relationship between BNP, cTnT, and clinical endpoints and echocardiographic data was investigated.

Participants: This study included 102 consecutive outpatients with HOCM who were clinically stable.

Results: BNP was significantly associated with both max left ventricular (LV) wall thickness ($r = 0.28$; $P = 0.003$), and septal peak early transmitral filling velocity/peak early diastolic mitral annulus velocity ($r = 0.51$; $P = 0.0001$). No statistically significant associations were seen between cTnT and any echocardiographic parameters, but the presence of atrial fibrillation (AF) was associated with a high level of cTnT ($P = 0.01$).

Conclusion: BNP is useful for monitoring clinical parameters and as a reflection of both LV systolic/diastolic function and increased LV pressure in patients with HOCM. A high level of serum cTnT is associated with the presence of AF.

Strengths and limitations of this study

1. This is a first study to explore the relationship between BNP and cTnT and clinical features in patients with HOCM and to demonstrate that increased cTnT levels are associated with the presence of AF in patients with HOCM
2. The patient sample size is small due to the relative rarity of this disease.

KEY WORDS: hypertrophic obstructive cardiomyopathy, hypertrophic cardiomyopathy, cardiac troponin T, B-type natriuretic peptide

Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) is a type of hypertrophic cardiomyopathy characterized by dynamic left ventricular (LV) outflow-tract obstruction caused by asymmetrical septal hypertrophy. Depending in part upon the site and extent of cardiac hypertrophy, patients with HOCM can develop several abnormalities, such as LV outflow obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation. Therefore, the structural and functional abnormalities associated with HOCM can produce a variety of symptoms, including fatigue, dyspnea, chest pain, palpitations, presyncope or syncope.

B-type natriuretic peptide (BNP) levels are elevated in proportion to the severity of LV diastolic and systolic dysfunction.[1-3] Previous studies have demonstrated that BNP is useful for the prediction of outcomes in patients with hypertrophic cardiomyopathy, hypertensive heart disease, and aortic stenosis,[4-10] indicating the significance of BNP elevation in heart disease characterized by LV hypertrophy. Highly sensitive cardiac troponin T (cTnT) is another cardiac marker that can detect myocardial damage. Although cTnT is a strong predictor of adverse outcomes in patients with acute coronary syndrome,[11 12] stable coronary artery disease,[13 14] congestive heart failure,[15-17] and hypertrophic cardiomyopathy, including hypertrophic non-obstructive cardiomyopathy,[18 19] there are comparatively few data regarding the utility of cTnT in only HOCM. Further, it is not clear whether BNP and/or cTnT are useful for monitoring the clinical status of patients with only HOCM. Therefore, the goal of this study was to assess the relationship between BNP, cTnT and clinical parameters in patients with HOCM.

METHODS

Study design and subject recruitment

We analyzed consecutive outpatients with HOCM who were clinically stable and who visited the "HOCM clinic" at Nippon Medical School Hospital for periodical follow-up between January 2011 and June 2012. The diagnosis of HOCM was based on typical clinical, electrocardiographic, and hemodynamic features with echocardiographic demonstration of a non-dilated, asymmetrically hypertrophied LV in the absence of other cardiac or systemic diseases that can produce LV hypertrophy. Patients with significant organic coronary stenosis, valvular heart disease, systemic hypertension, concomitant neoplasm, infection, connective tissue disease, or diabetes mellitus were excluded from study. A complete history and clinical examination was performed along with New York Heart Association (NYHA) functional class assessment, presence of atrial fibrillation (AF), blood examination, and echocardiography. The Nippon Medical School Research Ethics Committee approved this study, and written consent was obtained from all patients.

Echocardiography study

Two-dimensional, M-mode, and Doppler echocardiographic studies were performed with PHILIPS IE 33 or GE Vivid E 9 ultrasound systems on the same day that serum cTnT and BNP were measured. Wall thickness (IVST, interventricular septal thickness; PWT, posterior wall thickness; MWT, max LV wall thickness), cavity size (LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter), LV diastolic dysfunction (E/Ea, peak early transmitral filling velocity/peak early diastolic mitral annulus velocity on tissue Doppler imaging), max pressure gradient (Max PG, max peak gradient in the LV), tricuspid regurgitation peak gradient, and wall motion were measured from M-mode and 2D images. MWT was defined as the greatest thickness in any single segment.

LV diastolic function was assessed by septal, and lateral E/Ea. The ventricular volume and ejection fraction were computed using the biapical Simpson's rule.

Measurement of cardiac troponin-T and B-type natriuretic peptide

Peripheral blood samples were collected for measurement of serum BNP and cTnT at the same time as other examinations. Serum BNP and cTnT were measured with an AIA-2000ST analyzer (TOSOH, Tokyo, Japan) in accordance with the manufacturer's instructions. The assay detection limit was ≥ 0.003 ng/ml. Patients were divided into low or high BNP groups and into low and high cTnT groups according to previously reported cutoff points (200 pg/ml for BNP and 0.014 ng/ml for cTnT).[10 19]

Statistical methods

Continuous variables were tested for normal distribution by the Shapiro-Wilk test. The normal distributed continuous variables are shown as means ± Standard Deviation (SD), and nonparametrically distributed variables are shown as medians (interquartile range). Categorical variables are presented as frequencies (percentages). Correlation between two continuous variables was examined by Pearson's test (if relevant by Spearman's test). Logistic regression analyses were performed with the presence/absence of elevated cTnT or BNP levels as dependent variable (cTnT cutoff point ≥ 0.014 ng/ml, BNP cutoff point ≥ 200 pg/ml) and different clinical factors as covariables. Multiple regression analyses of the relationship between cTnT or BNP and study variables were performed in order to detect clinical characteristics related to these markers after adjustment for interrelationship among study variables. A two-sided probability value of $P < 0.05$ was considered to be statistically significant. JMP (version 9.0.3, North Carolina, USA) was used for analysis.

RESULTS

There were 104 patients who visited the "HOCM clinic" during the examination period, of which two patients were excluded due to absence of echocardiographic data. Therefore, the study population consisted of 102 consecutive patients who underwent complete clinical, echocardiographic, and serum-marker assessment. Baseline characteristics of the 102 patients are shown in Table 1. There were 84 patients (82.3%) with LV outflow obstruction, 13 patients (12.7%) with mid-cavity obstruction, and five patients (4.9%) with apical obstruction. Serum BNP ranged from 33.6 to 2593 pg/ml (mean, 286.5±334 pg/ml; median, 174.4 pg/ml). Twenty-four patients (23.5%) had an BNP level above the cutoff point (400 pg/ml), including three patients (2.9%) with a level ≥ 1000 pg/ml. Serum cTnT ranged from 0.003 to 0.09 ng/ml (mean, 0.015±0.015 ng/ml; median, 0.011 ng/ml). Eighty-six patients (84.3%) had a cTnT level above the detection limit of assay (0.003 ng/ml), including 37 patients (36.2%) with a level ≥ 0.014 ng/ml and five patients (4.9%) with a level ≥ 0.05 ng/ml. There was no significant association between BNP and cTnT levels (r = 0.06, P = 0.10, by Spearman's rank-correlation test).

Relationship between biomarkers, clinical features, and echocardiographic characteristics

BNP was significantly associated with IVST (r = 0.31; P = 0.001), MWT (r = 0.28; P = 0.003), septal E/Ea (r = 0.51; P = 0.0001), and lateral E/Ea (r = 0.41; P = 0.0001) (Table 2). BNP negatively associated with LVEDD (r = -0.39; P = 0.001) and LVESD (r = -0.20; P = 0.04; Table 2). Patients were divided into two groups according to BNP level: the low BNP group (BNP <200 pg/ml) and the high BNP group (BNP ≥200 pg/ml) (Table 3). More patients had NYHA functional class II in the high BNP group than in the low BNP group, and LVEDD and lateral E/Ea were greater in the high BNP group than in the low BNP group (Table 3).

There were no statistically significant associations between cTnT and any echocardiographic parameters (Table 2). Patients were also divided into two groups according to cTnT level: the low cTnT group (cTnT<0.014 ng/ml) and the high cTnT group (cTnT ≥0.014 ng/ml) (Table 3). There were no significant differences in age, female, or any echocardiographic parameters between the low cTnT group and the high level cTnT group and the presence of AF was significantly higher in the high cTnT group than in the low cTnT group (40.5% vs. 16.9%; P = 0.01) (Table 3).

Relationship between atrial fibrillation and cTnT

Univariate logistic regression analysis was performed using the patient characteristics to investigate factors associated with presence of AF. As shown in Table 4A, large left atrium diameter (large LAD ≥50 mm), high BNP (BNP ≥200 pg/ml), and high cTnT (cTnT ≥0.014 ng/ml) were significantly associated with presence of AF. Multivariate logistic regression analysis using the significant factors obtained within univariate analysis revealed that high LAD and high cTnT were each independent factors for the presence of AF (Table 4B). Moreover, cTnT levels in patients with persistent AF appeared to be significantly higher than that in patients with paroxysmal AF or in those without AF (median, 0.028 vs. 0.013 vs. 0.01 ng/ml; P < 0.001) (Figure).

DISCUSSION

This study demonstrated that BNP was a more useful and reliable biomarker than cTnT for the clinical status of patients with HOCM. The levels were positively associated with various clinical and echocardiographic parameters, including dyspnea (NYHA functional class), LV filling pressure, diastolic dysfunction (septal and lateral E/Ea), and LV wall thickness (IVST, MWT), whereas high cTnT levels were significantly associated only with the presence of AF. Further, this study demonstrated that BNP levels were significantly and negatively associated with LV volume

(LV end-diastolic / systolic diameters). Finally, cTnT level was independently associated with the presence of AF, and levels of cTnT in patients with persistent AF were significantly higher than those with paroxysmal AF or without AF.

Previous studies have demonstrated that BNP is a useful biomarker of clinical parameters and can predict adverse outcomes in patients with heart failure, cardiomyopathy and ischemic heart disease.[6-9] Previous studies have also reported that serum BNP levels in patient with hypertrophic cardiomyopathy (HCM) and hypertension, which typically occurs in the absence of LV cavity volume expansion and the presence of systolic dysfunction, are independently associated with the presence and magnitude of heart failure symptom.[18-21] Although the present study enrolled only patients with HOCM, the data we obtained were primarily consistent with data from previous studies involving patients with non-obstructive HCM. The present study also demonstrated a positive association between BNP levels and various parameters, including NYHA functional class, septal and lateral E/e', IVST, and MWT, Therefore, these findings serve to extend the principle, that serum BNP levels are associated with the presence and magnitude of heart failure symptoms, for non-obstructive hypertrophic cardiomyopathy into patients with HOCM. Of note, BNP levels were also negatively associated with LVEDD and LVESD, indicating that BNP levels increase in the context of reduced cavity volume and increased end-diastolic pressure. In other words, the present study suggests that LV volume reduction leads to impaired diastolic function and reflects increasing pressure in LV. Prior to the present study, there have been very few investigations of the significance of BNP levels in patients with HOCM.[22]

In contrast to BNP, serum cTnT levels were not associated with most of the clinical parameters investigated in this

study, including diastolic function, LV wall thickness, or the magnitude of dyspnea in HOCM. A previous study reported that the prevalence of elevated cTnT levels (lower limit of detection is 0.01 ng/ml) in the general population was 0.7%.[23] Further, serum cTnT levels are higher in patients with HCM than in the general population.[19] These observations are consistent with data from the present study, in which the mean cTnT level was 0.015 ng/ml and the prevalence of elevated cTnT levels (equal or above 0.01 ng/dl) was 57.8%. Although prior studies reported that cTnT levels were related to the clinical parameters, such as LV wall thickness, E/e', or LV outflow tract gradient in patients with HCM (including those with HOCM) and that cTnT was an independent predictor of outcomes,[18 19 24] the present study failed to show these relationships. Specifically, the present study found that cTnT elevation was related only to the presence of AF among all clinical parameters investigated.

Elevations of cTnT are related to cardiac remodeling that leads to the development of AF,[19 25 26] and Anegawa et al. reported that the high cTnT level was associated with AF in a general population.[27] However, the relationship between cTnT and AF has not been reported in patients with HCM, including those with HOCM. There are several possible mechanistic explanations for the association between cTnT and presence of AF. First, modest elevations in cTnT may be caused by leakage from the atrium because of cardiac remodeling, including atrial myocyte death and fibrosis. Second, HOCM is characterized by LV outflow obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation. Thus, the presence of AF in HOCM may potentiate these abnormalities, particularly in regards to myocardial ischemia. In other words, AF with rapid ventricular response may reduce diastolic filling time, leading to impaired LV filling in patients with HOCM, especially in those with pre-existing diastolic dysfunction. Further, the atrial kick is very important in achieving adequate ventricular filling, and the loss of atrial

kick in the context of AF results in decreased LV filling. AF is also often poorly tolerated in HCM patients and may be associated with significant clinical deterioration.[28-30] Therefore, the present findings may indicate that AF might contribute to cardiac ischemia and progression of cardiac remodeling, including myocyte necrosis. In combination with observations from the present study, this suggests that cTnT may have utility for the detection of ischemia and cardiac remodeling. By contrast, BNP might be more useful as a reflection of hemodynamic parameters, magnitude of symptoms, and systolic/diastolic function. These may explain why cTnT significantly correlated only with AF. However, several reports have been reported that cTnT is related to echocardiographic parameters such as maximum LV wall thickness, and left atrial dimension. Our results showed that cTnT tended to be associated with maximum LV wall thickness and left atrium dimension which did not reach to the statistical significance. This discrepancy could be explained by the small study sample size.

The principal limitation of the present study was its cross-sectional design. Additional limitations include the small patient sample size due to the relative rarity of this disease. Although the number of enrolled patients in the present study might not be sufficient for our results to be generalized, the patient number was equivalent to that in previous studies of patients with HOCM [22] and in patients with HCM (including those with HOCM).[18 19]

To our knowledge, this is a first study to explore the relationship between BNP and cTnT and clinical features in patients with HOCM and to demonstrate that increased cTnT levels are associated with the presence of AF in patients with HOCM. BNP is useful for monitoring clinical parameters and as a reflection of both LV systolic/diastolic function and increased LV pressure in patients with HOCM. Furthermore, a high level of serum

cTnT appears to be associated with the presence of AF and may thus be a good marker of cardiac remodeling or ischemia in patients with HOCM.

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Table 1. Baseline Characteristics for the Study Samples

Age (years)	67.1 ± 11.7
Female, n (%)	71 (69.6%)
Types of obstruction	
LVOT obstruction	84 (82.3%)
Mid-ventricular obstruction	13 (12.7%)
Apical obstruction	5 (5.0 %)
NYHA functional class	
Ⅰ, n (%)	62 (60.8%)
Ⅱ, n (%)	39 (38.3%)
Ⅲ-Ⅳ, n (%)	1 (0.9%)
Atrial fibrillation, n (%)	76 (74.5%)
eGFR (ml/min/1.73^2)	75.1 ± 26.2
Echocardiographic data	
LVEF (%)	73.5 ± 8.0
IVS (mm)	14.7 ± 4.9
PWT (mm)	10.2 ± 1.8
MWT (mm)	16.2 ± 4.0
LV end-diastolic dimension (mm)	43.7 ± 5.6
Left atrial dimension (mm)	43.5 ± 8.2
Septal E/Ea	16.5 ± 8.9
Lateral E/Ea	12.0 ± 5.6
LV pressure gradient (mmHg)	42.6 ± 40.4
TR pressure gradient (mmHg)	27.6 ± 8.5
Medications	
Beta-blocker, n (%)	86 (86.0 %)
Calcium channel blocker, n (%)	38 (38.3 %)
Cibenzoline, n (%)	65 (65.6 %)

Abbreviations: NYHA functional class denotes New York Heart Association functional class; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; IVS, interventricular septal thickness; PWT, posterior wall thickness; MWT, max LV wall thickness; E/Ea, peak early transmitral filling velocity/peak early diastolic mitral annulus velocity on tissue Doppler imaging; TR pressure gradient, tricuspid valve regurgitation.

Data are expressed as mean ± standard deviation or number of the patients (percentage).

Table 2. Associations between BNP or cTnT and clinical parameters

	BNP		cTnT	
	r value	P value	r value	P value
Age	-0.02	0.81	0.08	0.38
IVST	0.31	0.0013	0.03	0.70
PWT	0.014	0.88	0.08	0.40
MWT	0.28	0.0039	0.15	0.11
LAD	0.14	0.13	0.18	0.06
LVEDD	-0.39	0.001	0.11	0.24
LVESD	-0.20	0.04	0.16	0.09
LVEF	-0.10	0.28	-0.12	0.20
Septal E/Ea	0.51	0.0001	0.06	0.51
Lateral E/Ea	0.41	0.0001	0.10	0.33
Max PG	0.06	0.52	-0.10	0.30
TRPG	0.08	0.43	-0.005	0.96

Abbreviations: BNP denotes B-type natriuretic peptide; cTnT, highly sensitive cardiac troponin T; LAD, left atrial diameter; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; Max PG, max peak gradient in the left ventricle; TRPG, tricuspid regurgitation peak gradient. Other abbreviations are described in Table 1.

Table 3. BNP, cTnT and characteristics of the patients

	BNP (pg/ml)			cTnT (ng/ml)		
	BNP < 200	BNP ≥ 200	P Value	cTnT < 0.014	cTnT ≥ 0.014	P Value
Age, years	66.9 ± 10.7	67.4 ± 12.7	0.8	66.5 ± 11.9	68.4 ±11.3	0.4
Female, %	33 (63.4 %)	38 (76.0 %)	0.19	45 (69.2 %)	26 (70.2 %)	1.00
NYHA class	14 (26.9 %)	24 (48.0 %)	0.04	24 (36.9 %)	14 (37.8 %)	1.0
AF	9 (17.3 %)	17 (34.0 %)	0.06	11 (16.9 %)	15 (40.5 %)	0.01
eGFR	75.1 ± 26.5	74.9 ± 25.7	1.0	70.8 ± 26.9	77.5 ± 25.7	0.21
MWT	15.6 ± 3.5	16.9 ± 4.4	0.09	16.2 ± 4.5	16.2 ± 3.1	0.9
LVEDD	45.2 ± 5.6	42.0 ± 5.1	0.003	43.5 ± 5.7	44.0 ± 5.5	0.6
LVEF	74.4 ± 7.6	72.5 ± 8.4	0.2	74.4 ± 6.5	71.8 ± 10.1	0.12
LAD	42.2 ± 6.5	44.8 ± 9.5	0.11	42.3 ± 6.3	45.5 ± 10.6	0.06
Lateral E/Ea	9.5 ± 3.7	14.9 ± 6.2	0.002	12.3 ± 5.7	11.3 ± 5.6	0.4
Max PG	39.0 ± 37.6	46.4 ± 43.2	0.3	45.6 ± 41.3	37.1 ± 38.6	0.3

Abbreviations: NYHA class denotes New York Heart Association functional class; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate. The other abbreviations are described in table 1 or 2. Data are expressed as mean ± standard deviation or number of the patients (percentage).

Table 4A. Univariate logistic regression analysis of the prevalence of AF versus clinical features

	odds ratio	P Value
Age	1.00 (0.96-1.04)	0.68
Female	2.00 (0.80-5.20)	0.14
NYHA class ≥ II	0.68 (0.26-1.76)	0.48
MWT	3.04 (0.07-307.2)	0.58
LAD ≥50 mm	8.87 (2.77-31.9)	0.0002
LVEF	5.97 (0.47-78.1)	0.16
E/e' lat ≥15	1.73 (0.61-4.89)	0.42
Max PG	8.47 (1.31-75.5)	0.23
High BNP	2.46 (0.97-6.21)	0.06
High cTnT	3.34 (1.33-8.42)	0.01

Abbreviations: High BNP denotes high type-B Natriuretic Peptide level (serum BNP level ≥200 pg/ml); High cTnT, high cardiac troponin T level (serum cTnT level ≥0.014 ng/ml). Other abbreviations are described tables 1, 2, or 3.

Table 4B. Multivariate logistic regression analysis of the prevalence of AF versus clinical features

	odds ratio	P Value
Female	2.37	0.13
High BNP	2.53	0.09
High cTnT	3.96	0.008
LAD ≥50 mm	6.91	0.002

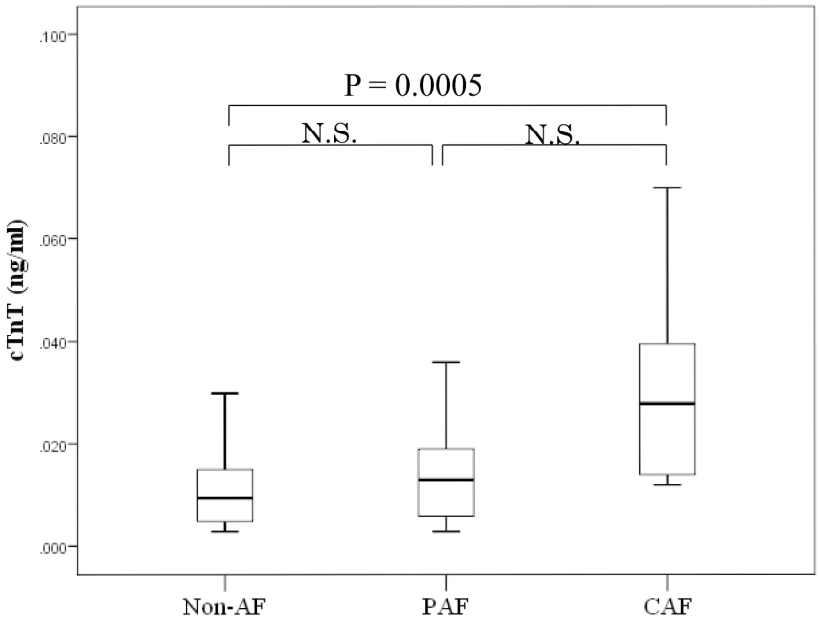
Abbreviations are described tables 2, 3 or 4A.

Figure legends

Figure 1. cTnT levels in patients with HOCM according to the presence, absence, or types of AF.

cTnT, highly sensitive cardiac troponin T; HOCM, hypertrophic obstructive cardiomyopathy; AF, atrial fibrillation; N.S., not significant. Paroxysmal AF: episodes that come and go, but resolve themselves within 7 days; Persistent AF: episodes that last beyond seven days; Chronic AF: continuous AF that lasts longer than one year.

Figure 1. cTnT levels in patients with HOCM according to the presence, absence, or type of AF.



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