Serum Cardiac Troponin I is Related to Increased Left Ventricular Wall Thickness, Left Ventricular Dysfunction, and Male Gender in Hypertrophic Cardiomyopathy

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ABSTRACT

Background: Serum cardiac troponin I (cTnI) is a sensitive and specific marker of myocardial injury. However, a systematic evaluation of cTnI in hypertrophic cardiomyopathy (HCM) patients has not been performed.
Hypothesis: The purpose of this study is to evaluate cTnI and determine its relationship to clinical features in HCM.
Methods: We studied serum cTnI in 162 consecutive HCM patients.
Results: Serum cTnI ranged from 0.01 to 0.83 ng/mL (mean, 0.068 ± 0.100 ng/mL) and was higher in male patients ($P < .001$), those with atrial fibrillation ($P = .033$), and left ventricular (LV) systolic dysfunction ($P = .046$). Serum cTnI values were also correlated with maximum LV wall thickness ($r = 0.30$, $P < .001$), LV end-systolic diameter ($r = 0.20$, $P = .012$), and E/Ea (peak early transmitral filling velocity/early diastolic mitral annulus velocity; $r = 0.24$, $P = .004$). Serum cTnI levels were not significantly different among New York Heart Association (NYHA) functional class and there was no difference between patients with or without LV outflow tract obstruction; although B-type natriuretic peptide (BNP) levels showed significant difference in those variables. Serum cTnI had very weak correlation with BNP values ($r = 0.18$, $P = .023$). Multivariate analysis revealed an independent relationship between cTnI and maximum LV wall thickness, E/Ea, and male gender.
Conclusions: In patients with HCM, serum cTnI was associated with important clinical indices such as maximum LV wall thickness, LV dysfunction, and male gender. Serum cTnI seemed to have clinical significance different from that of BNP and may not be reflecting cardiac load but the LV remodeling process in HCM.

Introduction

Serum cardiac troponin T and I (cTnI; a sensitive and specific marker of myocardial injury) are well established diagnostic and prognostic markers in acute coronary syndrome. These troponins have been reported to predict adverse outcome in patients with heart failure even in the absence of coronary artery stenosis.[1,2]

Hypertrophic cardiomyopathy (HCM) is a heterogeneous myocardial disorder with a broad spectrum of phenotypic expression and clinical course.[3,4] Myocardial injury may be associated with these clinical features including distribution and extent of hypertherapy, cardiac function, clinical presentation, and left ventricular (LV) remodeling. However, systematic evaluation of cTnI has not been performed in patients with HCM. The aim of this study is to evaluate serum cTnI and determine its relationship to clinical features in HCM.

None of the authors have a conflict of interest to disclose in connection with our manuscript.

Methods

Subjects

We studied 172 consecutive patients with HCM evaluated between October 2004 and November 2007 at Kochi Medical School Hospital. In this study, we excluded patients with evidence of coronary artery disease (8 patients with history of percutaneous coronary intervention) and patients with renal failure (2 patients with serum creatinine ≥3 mg/dL). The final study population consisted of 162 patients.

The diagnosis of HCM was based on echocardiographic demonstration of an unexplained LVH, that is, maximum LV wall thickness ≥15 mm. Informed consent was obtained

Received: March 12, 2008
Accepted: April 22, 2009

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20622

from all patients or their parents in accordance with the guidelines of the ethics committee on medical research of the Kochi Medical School.

Clinical Evaluation

Evaluation of patients included medical history, clinical examination, 12-lead electrocardiography, M-mode, 2-dimensional (2D), and Doppler echocardiography. Maximum LV wall thickness was defined as the greatest thickness in any single segment. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were measured from M-mode and 2D images obtained from parasternal long-axis views. Global ejection fraction (EF) was determined from apical 2-chamber and 4-chamber views. Mitral inflow velocities were determined using pulsed-wave Doppler with the sample volume positioned at the tips of the mitral leaflets in the 4-chamber view. Peak early (E) transmitral filling velocity was measured. Tissue Doppler imaging was performed in the pulse-Doppler mode to allow for a spectral display and recording of mitral annulus velocities at septal and lateral corners. Peak early diastolic (Ea) velocity was measured, and the E/Ea ratio was calculated. Left ventricular outflow tract gradient was calculated from continuous-wave Doppler using the simplified Bernoulli equation.

Using morphologic and hemodynamic findings assessed by echocardiography, we classified the patients into 4 groups: (1) The dilated phase of HCM (D-HCM) was defined as LV systolic dysfunction of global EF $<50\%$. Concomitant coronary artery disease was excluded by coronary angiography and/or myocardial scintigraphy. Hypertrophic cardiomyopathy without LV systolic dysfunction includes: (2) HCM with obstruction: presence of basal LV outflow tract obstruction (gradient ≥ 30 mm Hg at rest), (3) HCM without obstruction, and (4) apical HCM: HCM without obstruction with hypertrophy (≥ 15 mm) confined to the LV apex below the papillary muscle level.

Measurement of cTnI

Peripheral blood samples were collected for the measurement of serum cTnI at the time of clinical evaluation. Serum cTnI was measured by a Beckman Coulter Unicel DxI 800 Access Immunoassay System in accordance with the manual of the manufacturer. Normal range is ≤ 0.03 ng/mL (97.5 percentile). B-type natriuretic peptide (BNP) was also measured.

Statistical Analysis

All data are expressed as mean $\pm$ SD (range) or frequency (percentage). Serum cTnI and BNP values were subjected to logarithmic transformation for statistical analysis. Differences in means of continuous variables were assessed using a student t test with the Bonferroni correction. Pearson's χ^2 test was used for categorical noncontinuous variables. Multiple regression analysis of cTnI on study variables was performed in order to detect clinical characteristics related to cTnI after adjustment for interrelationships among study variables. Statistical analysis was performed using SPSS (version 14.0J) statistical software (SPSS Inc., Japan, Tokyo).

Table 1. Clinical Characteristics in 162 Patients With HCM

Characteristic	Value
Age, years	62.0 ± 15.2 (9–88)
Gender: men, n (%)	103 (64%)
Atrial fibrillation, n (%)	41 (25%)
Serum cTnI, ng/mL	0.068 ± 0.100 (0.01–0.83)
BNP, pg/mL	279.5 ± 286.5 (4–1920)
NYHA class (at presentation), n (%)	
I, n (%)	97 (60%)
II, n (%)	56 (34%)
III and IV, n (%)	9 (6%)
Subtypes in HCM	
D-HCM, n (%)	10 (6%)
HCM with obstruction, n (%)	18 (11%)
HCM without obstruction, n (%)	108 (67%)
Apical HCM, n (%)	26 (16%)
LV end-diastolic diameter, mm	45.9 ± 6.0 (31–62)
Fractional shortening, %	42.0 ± 9.0 (13–62)
Left atrial diameter, mm	44.5 ± 7.4 (29–72)
IVS, mm	15.4 ± 4.4 (7–30)
PW, mm	11.0 ± 2.0 (6–22)
Maximum LV wall thickness, mm	20.1 ± 3.9 (12–33)
E/Ea (septal)	11.0 ± 4.9 (2.9–30.6)
E/Ea (lateral)	8.1 ± 4.2 (2.2–30.2)

Abbreviations: BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; D-HCM, dilated phase of hypertrophic cardiomyopathy; E/Ea, peak early transmitral filling velocity/peak early diastolic mitral annulus velocity on tissue Doppler imaging; HCM, hypertrophic cardiomyopathy; IVS, interventricular wall thickness; LV, left ventricular; NYHA, New York Heart Association functional class; PW, posterior wall thickness.
Data are shown as mean ± SD (range) or number (percent).

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20622

Results

Patient Characteristics

Clinical characteristics of the patients in the present study are summarized in Table 1. Serum cTnI ranged from 0.01 to 0.83 ng/mL (mean, 0.068 ± 0.100 ng/mL; median, 0.04 ng/mL). B-type natriuretic peptide ranged from 4 to 1920 pg/mL (mean, 279.5 ± 286.5 pg/mL; median, 200.0 pg/mL).

Relationship Between cTnI and Clinical Variables

Associations of cTnI with age, BNP, maximum LV wall thickness, left atrial diameter, E/Ea (lateral), and LVESD in patients with HCM are depicted in Figure 1. These clinical variables, except for age, were associated with cTnI. Serum cTnI had significant but weaker correlation with E/Ea (septal) and LVEDD than that of E/Ea (lateral) and LVESD, respectively (data not shown).

Serum cTnI levels were higher in male patients than female patients (cTnI: 0.081 ± 0.118 vs 0.045 ± 0.049 ng/mL; $P < .001$; Table 2), whereas BNP levels were significantly lower in males compared to females (BNP: 216.2 ± 224.7 vs 388.7 ± 345.2 pg/mL; $P < .001$). Serum cTnI were also higher in patients with atrial fibrillation than in those with sinus rhythm (cTnI: 0.094 ± 0.142 vs 0.059 ± 0.079 ng/mL; $P = .033$). Higher cTnI levels were also observed in patients with D-HCM than those without LV systolic dysfunction (cTnI: 0.143 ± 0.246 vs 0.063 ± 0.081 ng/mL; $P = .046$).

Because the progression into D-HCM is usually accompanied by wall thinning, HCM patients without LV systolic dysfunction were classified into 3 subgroups with respect to the degree of maximum LV wall thickness. Serum cTnI values were significantly higher in the greatest maximum LV wall thickness group (Figure 2). On the other hand, BNP was not significantly different between greatest and lowest maximum LV wall thickness groups.

cTnI and BNP in HCM without LV Systolic Dysfunction

Among the 152 HCM patients without LV systolic dysfunction, serum cTnI values were significantly different only between HCM without obstruction and apical HCM (cTnI: 0.070 ± 0.089 vs 0.033 ± 0.022 ng/mL; $P = .002$; Table 2). There was no difference in serum cTnI values between patients with LV outflow tract obstruction (cTnI: 0.063 ± 0.080 ng/mL) and patients without obstruction. On the other hand, BNP was significantly higher in patients with outflow obstruction than in those without obstruction.

Relationship of cTnI and BNP to New York Heart Association Functional Class

Serum cTnI values were not significantly different among New York Heart Association (NYHA) functional class (Table 2). Serum cTnI values were 0.061 ± 0.087 ng/mL in NYHA class I, 0.064 ± 0.071 ng/mL in NYHA class II, and 0.167 ± 0.253 ng/mL in NYHA class III. On the other hand, BNP was significantly higher with respect to progressive severity of heart failure symptoms, as judged by NYHA functional class.

Multivariable Analysis

Serum cTnI was related to maximum LV wall thickness and E/Ea (lateral) even after adjustment of other clinical variables including presence of atrial fibrillation and D-HCM, BNP levels, left atrial diameter, and LVESD by the multivariable analysis. Male gender was also independently related to serum cTnI.

Discussion

Hypertrophic cardiomyopathy is a heterogeneous myocardial disorder and myocardial injury may be associated with morphologic features, cardiac function, and clinical presentation.[3,4] In the present study, we assessed the significance of cTnI in relation to the clinical features of HCM, since serum cTnI is considered to be a good marker for ongoing myocyte injury and there are few reliable biochemical markers as part of the management of HCM patients. Serum cTnI values were related to maximum LV wall thickness, E/Ea ratio as an index of LV diastolic dysfunction, and male gender. This biomarker seemed to have clinical significance different from that of BNP in patients with HCM.

Relationship between cTnI and Clinical Variables

Assessment of the relationship of cTnI to clinical variables showed that higher serum cTnI was associated with findings supporting clinical deterioration in HCM, that is, presence of atrial fibrillation and greater maximum LV wall thickness, left atrial diameter, LV size, and E/Ea ratio. Multivariate analysis revealed that serum cTnI was related to maximum LV wall thickness, E/Ea (lateral) ratio, and male gender.

Relationship between cTnI and Maximum LV Wall Thickness

Maximum LV wall thickness is one of the most important clinical markers associated with sudden death and progression to LV systolic dysfunction in HCM.[5,6] Although the mechanisms of myocyte injury and release of cTnI in HCM remain unresolved, it may be caused by relative myocardial ischemia resulting from an imbalance between inappropriate hypertrophy of the myocardium and insufficient coronary arterial supply. Our result that serum cTnI values were significantly higher in the greatest maximum LV wall thickness group can be explained by this hypothesis (relative myocardial ischemia model). Recently, Petersen et al reported that patients with HCM showed a reduced myocardial perfusion reserve, assessed by magnetic resonance imaging (MRI), that was in proportion to the magnitude of hypertrophy.[7] Their results showing an association of vasodilator response impairment and wall thickness indicated that ischemia was more prevalent and more severe in hypertrophied segments. Furthermore,

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DOI:10.1002/clc.20622

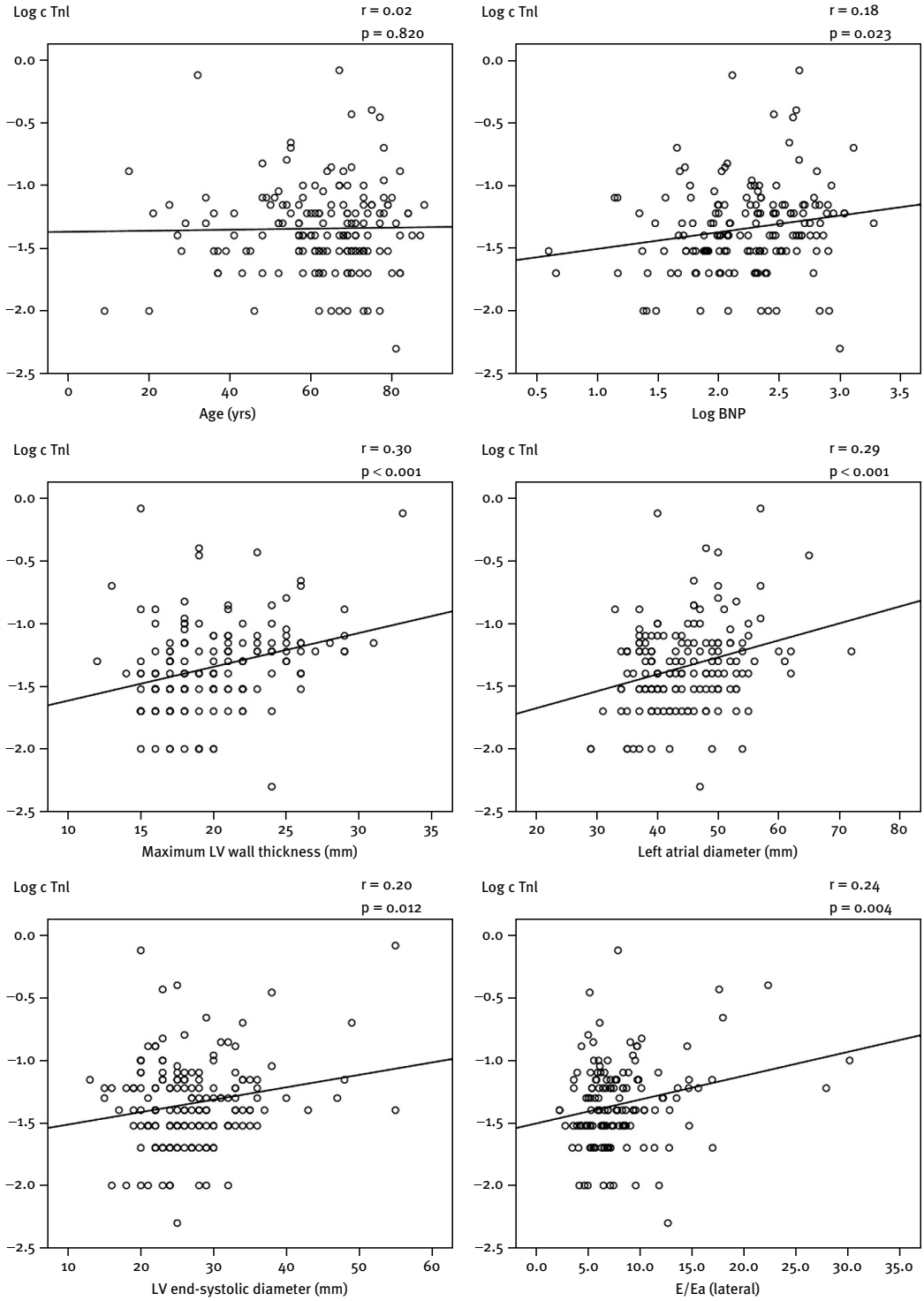

Figure 1. Associations of cTnI levels with age, BNP, maximum LV wall thickness, left atrial size, LV end-systolic diameter, and E/Ea ratio in patients with HCM. Abbreviations: BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; E/Ea, peak early transmitral filling velocity/peak early diastolic mitral annulus velocity on tissue Doppler imaging; LV, left ventricular.

Table 2. Serum cTnI and BNP Values in 162 HCM Patients With Respect to Clinical Characteristics

	Serum cTnI (ng/mL)	P	BNP (pg/mL)	P
Gender, (n = 162)				
Male, (103)	0.081 ± 0.118 (0.01–0.83)	<0.001	216.2 ± 224.7 (5–1310)	<0.001
Female, (59)	0.045 ± 0.049 (0.01–0.37)		388.7 ± 345.2 (4–1920)	
Atrial fibrillation, (n = 162)				
Present, (41)	0.094 ± 0.142 (0.01–0.83)	0.033	460.0 ± 372.4 (62–1920)	<0.001
Absent, (121)	0.059 ± 0.079 (0.01–0.76)		216.3 ± 218.5 (4–1010)	
LV systolic function, (n = 162)				
D-HCM (EF <50%), (10)	0.143 ± 0.246 (0.04–0.83)	0.046	454.6 ± 336.4 (113–1310)	0.002
Normal systolic function, (152)	0.063 ± 0.081 (0.01–0.76)		267.7 ± 280.2 (4–1920)	
Subtypes in HCM without LV systolic dysfunction, (n = 152)				
HCM with obstruction, (18)	0.063 ± 0.080 (0.01–0.37)	1.000	444.7 ± 241.3 (82–893)	0.010
HCM without obstruction, (108)	0.070 ± 0.089 (0.01–0.76)	0.002	280.0 ± 295.0 (14–1920)	<0.001
		0.191		<0.001
Apical HCM, (26)	0.033 ± 0.022 (0.01–0.10)		90.4 ± 76.0 (4–288)	
NYHA functional class, (n = 162)				
I, (97)	0.061 ± 0.087 (0.01–0.76)	1.000	182.0 ± 176.7 (4–811)	<0.001
II, (56)	0.064 ± 0.071 (0.01–0.40)		369.7 ± 269.5 (22–1098)	
III and IV, (9)	0.167 ± 0.253 (0.04–0.83)	0.894	747.3 ± 586.2 (113–1920)	0.002
		0.677		0.183

Abbreviations: BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; D-HCM, dilated phase of hypertrophic cardiomyopathy; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LV, left ventricular; NYHA, New York Heart Association functional class.
Data are shown as mean ± SD (range).

they found that the decreased prevalence of myocardial fibrosis assessed by the delayed contrast enhancement of an MRI was accompanied by increasing hyperemic myocardial blood flow. This observation suggests a pathophysiological link between repetitive hypoperfusion during stress and development of myocardial fibrosis. In HCM, the vasodilator response was reduced in proportion to the magnitude of hypertrophy. Microvascular dysfunction and subsequent ischemia may be important components of the risk attributable to HCM. Although we did not evaluate the presence and extent of fibrosis using late gadolinium-enhanced MRI, the fact that serum cTnI was independently correlated with maximum LV wall thickness may reflect microvessel ischemia and subsequent fibrosis in HCM. Further studies on the correlations between serum cTnI levels and extent of delayed contrast enhancement of MRI are needed.

Relationship between cTnI and LV Diastolic Function

Although E/Ea ratio was independently associated with serum cTnI values, correlation between BNP and E/Ea (lateral) was stronger than that of cTnI (data not shown; $r = 0.43$, $P < .001$). Furthermore, cTnI levels were not different between patients with or without obstruction. In contrast, BNP was significantly higher in the LV obstruction group as previously reported.[8] In addition, serum cTnI values were not significantly different among the NYHA functional classes, whereas BNP rose with the increase in NYHA functional class.[9] From those results, BNP is likely to reflect cardiac load, but cTnI seems to be a less sensitive marker of LV filling pressure. We speculate that release of cTnI was not due to cardiac load, but occurred at the time of myocyte injury, resulting in replacement fibrosis that leads to LV diastolic dysfunction. In fact, serum cTnI values in patients with NYHA class III/IV who were considered to be in a clinically more advanced stage were not low (0.167 ± 0.253 ng/mL) and some patients with NYHA

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20622

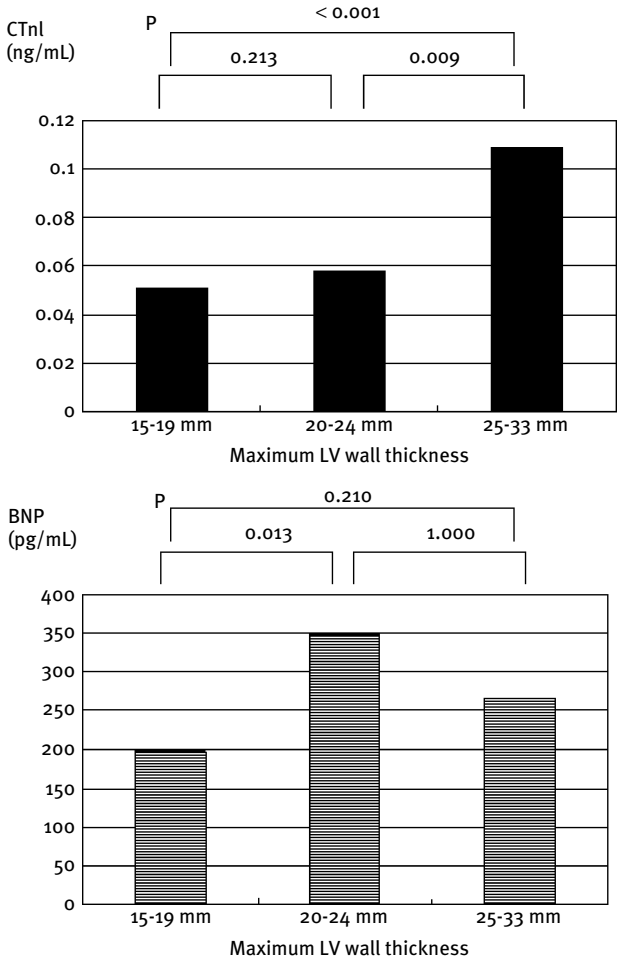

Figure 2. Relationships of serum cTnI and BNP to subgroups with respect to degree of maximum LV wall thickness in 152 HCM patients without LV systolic dysfunction. Abbreviations: BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; LV, left ventricular. *P* values of mean difference were shown.

class I or II had very high cTnI levels despite having mild symptoms or no symptoms at all.

Relationship between cTnI and Gender

Varnava et al reported a quantitative assessment of the relationship among disarray, fibrosis, and small vessel disease in HCM and they showed that fibrosis was influenced by gender (percentage of fibrosis in the heart: 7% in male and 4% in female).[10] Our results showing association between elevated serum cTnI levels and male gender suggest that fibrosis may be more prevalent in males.

Relationship between cTnI and LV Systolic Function

In patients with D-HCM, characterized by LV systolic dysfunction and cavity dilatation, a poor clinical course with refractory heart failure is thought to be related to pathological findings.[11] Several studies have shown that microscopic fibrosis is greater in hearts with D-HCM than in hearts with HCM without LV systolic dysfunction.[10] In the present study, serum cTnI as well as BNP values were significantly higher in patients with D-HCM than in HCM patients without LV systolic dysfunction. Horwich et al reported cTnI levels in patients with advanced heart failure due to LV systolic dysfunction referred for cardiac transplantation evaluation.[2] The patients with high cTnI levels (cTnI $\geq$0.04 ng/mL) had significantly higher BNP levels and more impaired hemodynamic profiles. Furthermore, a significant correlation was found between high cTnI levels and progressive decline in LV ejection fraction over time. In the present study, elevation of cTnI was associated with LV systolic dysfunction in patients with HCM. There were also some HCM patients without LV systolic dysfunction who showed high cTnI levels. This may suggest that ongoing myocyte injury is present even in patients with normal LV systolic function. Taking into account that greater wall thickness is one of the important risk factors for progression to D-HCM and serum cTnI values were related to maximum LV wall thickness, it is possible that progression to D-HCM may be more likely to occur in patients with higher cTnI levels.[6]

Clinical Implications

In patients with HCM, it is not easy to predict cardiovascular events such as sudden death, arrhythmias, and heart failure because of the diverse clinical spectrum of HCM. Although plasma BNP has been established to be a useful tool to manage heart failure patients, particularly patients with systolic dysfunction, the usefulness of this marker is still controversial for assessing and predicting the precise characterization of the clinical status of HCM.[12–15] From our results, higher serum cTnI was associated with findings supporting clinical deterioration in HCM, measurement of both serum cTnI and plasma BNP may supplement each other and may become more reliable prognostic markers of adverse cardiovascular events in patients with HCM.

Limitations

This is a cross-sectional study. We need to evaluate serial cTnI levels because some studies showed that persistently increased serum concentrations of cardiac troponin T in patients with systolic dysfunction were predictive of adverse outcomes.[2,16] To further clarify the significance of cTnI levels in terms of clinical events or longitudinal evolution to LV systolic dysfunction, analysis of follow-up data obtained in individual patients is needed.

Conclusions

The present study shows that serum cTnI is associated with maximum LV wall thickness, LV dysfunction, and male

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DOI:10.1002/clc.20622

gender in HCM. Serum cTnI seemed to have clinical significance different from that of BNP and may not be reflecting cardiac load but the LV remodeling process in HCM.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20622