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Combined Measurements of Cardiac Troponin T and N-Terminal Pro-Brain Natriuretic Peptide in Patients With Heart Failure

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Background To examine the prognostic contribution of combined cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with heart failure (CHF) in the absence of acute coronary syndrome.

Methods and Results Between July 2001 and March 2002, 71 consecutive patients (mean age=68.4±1.4 years, 37 men), hospitalised for heart failure, were studied during hospitalisation and follow up until December 2002. Serum cTnT and NT-proBNP were measured on admission. Actuarial rates of adverse cardiac events, including sudden or CHF death, or rehospitalisation for CHF during follow up were compared with patients grouped according to initial serum cTnT and/or NT-proBNP concentrations. The adverse cardiac event-free rate among the 20 patients with cTnT≥0.01 ng/ml was significantly lower than the 51 patients with cTnT<0.01 ng/ml ($P<0.05$). Similarly, the adverse cardiac event-free rate among the 36 patients with NT-proBNP≥1,357 pg/ml (median) was significantly lower than the 35 patients with NT-proBNP<1,357 pg/ml ($P<0.01$). The 16 patients with high concentrations of both cTnT and NT-proBNP had a lower adverse cardiac event-free rate than the 31 patients with low cTnT and low NT-proBNP upon commencement of the study ($P<0.005$).

Conclusion Measurements of serum cTnT and NT-proBNP were reliable prognostic markers of adverse cardiac event in patients with CHF. (*Circ J* 2004; **68:** 1160–1164)

Key Words: Heart failure; Pro-brain natriuretic peptide; Prognosis; Troponin

Chronic heart failure (CHF) is associated with a dismal long-term prognosis and remains a major health concern world wide[1,2] While various management strategies have become available, clinical tools to stage CHF remain few. The New York Heart Association (NYHA) functional classification, along with several tests, including chest roentgenogram, echocardiogram, myocardial scintigraphy, cardiopulmonary exercise, and hemodynamic measurements are useful to estimate the degree of CHF, although they are subject to inter-observer variations in interpretation[3,4] Serial measurements of reliable and objective biochemical markers would be advantageous to monitor the long-term prognosis of patients with CHF.

The troponin complex consists of 3 proteins attached to the actin thin filament, known as subunits I, T, and C, which regulate the force and velocity of muscle contraction. Cardiac troponin T (cTnT) is a highly sensitive and specific marker of myocardial injury in acute coronary syndromes, and a revised definition of acute myocardial infarction has been developed, based on rises in cardiac troponins in the blood[5,6] We found that patients with idiopathic dilated cardiomyopathy, who had a particularly poor prognosis, had increased serum concentrations of cTnT in the absence of significant coronary stenoses[7–10] Most patients with poor outcomes had persistently high cTnT. This often occurred during periods when CHF was stabilised by conventional treatment, and there was no evidence of dyspnea, roentgenographic and auscultatory signs of pulmonary congestion[8,9] Therefore, an increase in serum cTnT concentrations seems to be a reliable indicator of ongoing subclinical myocyte injury rather than an indicator

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Table 1 Demographic and Baseline Clinical Characteristics of Study Population (n=71)

Age, mean±SE (years)	*68.4±1.4*
M/F	*37/34*
NYHA functional class I/II/III/IV	*10/22/22/17*
Underlying heart disease	
Dilated cardiomyopathy	*20 (28)*
Hypertrophic cardiomyopathy	*8 (11)*
Ischemic	*8 (11)*
Congenital or valvular	*22 (31)*
Hypertensive	*9 (13)*
Other	*4 (6)*
Oral drug regimen	
β-adrenergic blockade	*24 (34)*
ACEI or ARB	*33 (46)*
Spironolactone	*33 (46)*
Furosemide	*49 (69)*

Unless indicated otherwise, values are number (%) of patients. Other heart diseases include incessant tachyarrythmias (n=2), cardiac amyloidosis (n=1) and restrictive cardiomyopathy (n=1).
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association.

Table 2 Mean NT-ProBNP, CK, Age, and LVEF Among Patients With High and Low cTnT Values at Time of Hospital Admission

	NT-proBNP (pg/ml)	CK (IU/L)	Age (years)	LVEF (%)
cTnT high (n=20)	13,260±5,035*	90.2±9.2	68.5±3.5	49.6±3.1
cTnT low (n=51)	1,847±311	91.8±6.1	68.3±1.5	53.9±2.7

*P<0.001, other between-group differences are not statistically significant.
CK, creatine kinase; cTnT, cardiac troponin T; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3 Comparison Between Patients With and Without Cardiac Decompensation

	Decompensation (+) (n=45)	Decompensation (−) (n=26)
Age, mean±SE (years)	70.4±1.7	64.8±2.4
M/F	21/24	16/10
LVEF (%)	49.5±2.5	58.1±3.6
NYHA functional class I/II/III/IV	0/12/16/17	10/10/6/0
TnT positive (%)	16/45 (35)	4/26 (15)
Mean TnT of positive patients (ng/ml)	0.037±0.004	0.038±0.002
NT-proBNP (pg/ml)	7,233±2,369	1,303±291*
Creatinine (mg/dl)	1.1±0.1	1.0±0.1
Underlying heart disease		
Dilated cardiomyopathy	14 (31)	6 (23)
Ischemic	5 (11)	3 (11)
Congenital or valvular	14 (31)	8 (31)
Hypertensive	8 (17)	1 (4)
Oral drug regimen		
β-adrenergic blockade	12 (27)	12 (46)
ACEI or ARB	22 (48)	11 (42)
Spironolactone	26 (58)	7 (27)*
Furosemide	37 (82)	12 (46)**
Cardiac event (%)	10 (22)	0 (0)*

*P<0.05, **P<0.01
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TnT, Troponin T.

of circulatory congestion.

However, N-terminal pro-brain natriuretic peptide (NT-proBNP) represents the N-terminal fragment of pro-BNP, the high molecular weight precursor of biologically active BNP. N-terminal pro-brain natriuretic peptide has a relatively long half-life and is stable in whole blood. Concentrations of NT pro-BNP are increased in patients with CHF and correlate with prognosis[11–13] Since CHF is a complex clinical syndrome, a single biomarker may not reflect all of its characteristics. Theoretically, cTnT is a marker of myocyte injury while NT-proBNP reflects cardiac load.

This study examines the contribution of combined measurements of cTnT and NT-proBNP in patients with CHF in absence of acute coronary syndrome.

Methods

Subjects

The study population consisted of 71 consecutive patients admitted to our hospital between July 2001 and March 2002 for the management or evaluation of decompensated CHF. No patient had suffered a myocardial infarction or unstable angina pectoris within 3 months prior to hospitalisation, and no electrocardiographic changes or increase in creatine kinase (CK) were present upon admission. The criteria for a diagnosis of left heart decompensation on initial presentation used in this study were: (1) dyspnea or orthopnea requiring emergency hospitalisation, intravenous furosemide, and infusion of nitrates or inotropic agents, and (2) roentgenographically apparent pulmonary oedema and presence of moist rales on auscultation. Patients with cancer and undergoing hemodialysis were excluded. The demographic and baseline clinical characteristics of the study population are presented in Table 1.

Serum cTnT and NT-proBNP were measured with commercially available immunoassay kits (Roche Diagnostics, Tokyo, Japan). All study procedures were in accordance with the ethical institutional guidelines of Kyoto University.

Long-Term Clinical Events

The subsequent incidence of adverse cardiac events was recorded until December 2002. Significant adverse cardiac events were defined as sudden death without apparent ischemia, death from CHF, or rehospitalisation of the patient for management of cardiac decompensation with pulmonary oedema. Information pertinent to a patient's death occurring outside the hospital between follow-up visits was obtained from the family.

Statistical Analysis

Data are expressed as mean±standard error. The study variables were compared by factorial analysis of variance for continuous variables. A receiver–operator characteristic (ROC) curve was used to determine the cut-off value of NT-proBNP which predicts cardiac decompensation and cardiac events. Adverse cardiac event-free rate, were constructed by Kaplan–Meier's method, log-rank test. A P value<0.05 was considered statistically significant.

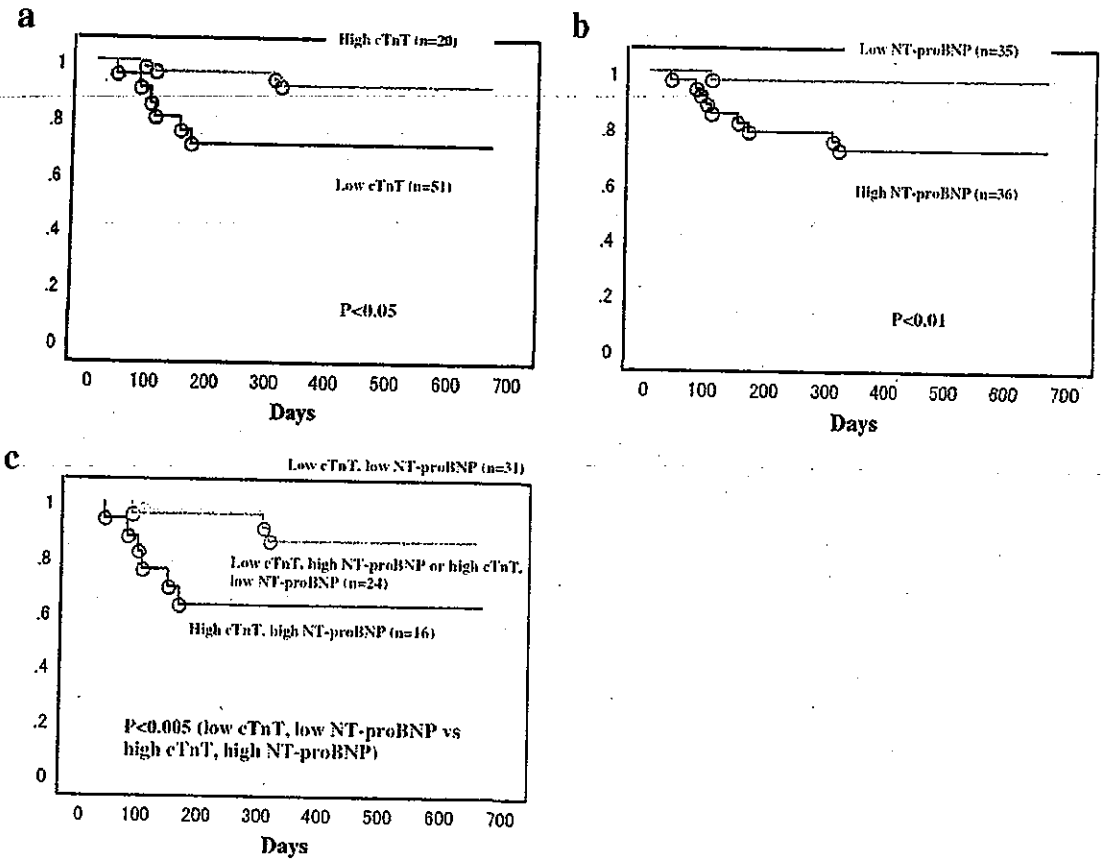

Fig 1. (a) Adverse cardiac event-free rate of patients with cTnT concentrations ≥0.01 ng/ml vs patients with cTnT concentrations <0.01 ng/ml. (b) Adverse cardiac event-free rate of patients with NT-proBNP concentrations ≥1,357 pg/ml vs patients with NT-proBNP concentrations <1,357 pg/ml. (c) Adverse cardiac event-free rate of patients with combined measurements of cTnT and NT-proBNP concentrations.

Results

Measurements of NT-ProBNP and TnT

The mean serum NT-proBNP concentration upon hospital admission of the 71 patients was 5,062±1,537 pg/ml (median=1,357 pg/ml). The mean NT-proBNP concentrations in patients of the NYHA functional class I, II, III, and IV were 954±361 (n=10), 1,673±473 (n=22), 2,902±771 (n=22), and 14,659±5,839 pg/ml (n=17), respectively. The cut-off value determined by ROC analysis for cardiac decompensation and cardiac events was 1,050 pg/ml (sensitivity 80%, specificity 67%) and 2,000 pg/ml (sensitivity 59%, specificity 67%), respectively. Age, CK concentration, and left ventricular ejection fraction and enddiastolic dimension measured echocardiographically did not correlate with NT-proBNP in this small population (data not shown).

The serum concentration of cTnT upon admission into the hospital was ≥0.01 ng/ml in 20 of the 71 patients (0.037±0.003 ng/ml). Cardiac troponin T was ≥0.01 ng/ml in 0/10 (0%), 6/22 (27%; 0.037±0.004 ng/ml), 7/22 (31%; 0.031±0.005 ng/ml) and 7/17 (41%; 0.046±0.008 ng/ml) patients in the NYHA functional classes I, II, III, and IV, respectively.

The mean serum concentration of NT-proBNP in the group of patients with high cTnT was significantly higher than in patients with low cTnT values (P<0.001). In contrast, age, CK and left ventricular ejection fraction were similar in both cTnT groups (Table 2). Comparisons between patients with and without cardiac decompensation are shown in Table 3. Concentrations of NT-proBNP in patients with cardiac decompensation were significantly higher than those in patients without (P<0.05).

Measurements of cTnT and NT-ProBNP, and Adverse Cardiac Events

Adverse cardiac events were observed in 10 patients (2 deaths from CHF and 8 cases of rehospitalisation for the management of cardiac decompensation with pulmonary oedema). The patients were divided into groups according to values of cTnT and NT-proBNP. The adverse cardiac event-free rate among the 20 patients with cTnT concentrations ≥0.01 ng/ml was significantly lower than the 51 patients with cTnT concentrations <0.01 ng/ml (P<0.05, Fig 1a). Similarly, the adverse cardiac event-free rate among the 36 patients with NT-proBNP concentrations ≥1,357 pg/ml was significantly lower than the 35 patients with NT-proBNP <1,357 pg/ml (P<0.01, Fig 1b). When groups were allocated according to both cTnT and NT-proBNP measurements, the 16 patients with high concentrations of both cTnT and NT-proBNP had a significantly lower adverse cardiac event-free rate than the 31 patients who had low cTnT and low NT-proBNP concentrations upon commencement of the study (P<0.005, Fig 1c).

Table 4 Hypothesis of Relationship Between Measurements of NT-ProBNP and TnT

	Low TnT	*High TnT*
Low NT-proBNP	*Without ongoing myocyte injury or myocardial load.*	*No myocardial load however, subclinical myocyte injury is ongoing. Patient is at risk of heart failure in the near future.*
High NT-proBNP	*Patient has heart failure without ongoing myocyte injury. Patient will stabilize with optimal treatment for heart failure.*	*Patient has heart failure with ongoing myocyte injury. If TnT concentrations do not decrease, heart failure may progress*

NT-proBNP, N-terminal pro-brain natriuretic peptide; TnT, Troponin T.

Discussion

In the present study, cTnT and NT-proBNP were reliable prognostic markers, both singly and in combination. Serum concentrations of cTnT≥0.01 ng/ml were considered significant.[14] Assay of NT-proBNP is a new technology and normal values were reported approximately as 20 pg/ml.[15,16] In our study, while mean NT-proBNP rose in the NYHA functional class, a similar correlation was not observed with mean cTnT concentrations. Moreover, 65% of patients with cardiac decompensation did not have a high serum cTnT concentration, and 15% had elevated concentrations despite being in a compensated state (Table 3). Troponin T seems to be a less sensitive marker of congestion.

We recently hypothesised that when managing heart failure, the therapeutic goals should be: (1) the relief of circulatory congestion and rapid lowering of markers of myocardial load, and (2) the mitigation of myocyte injury and lowering of markers of myocyte injury during long-term follow up.[17] In this hypothesis, cTnT and NT-proBNP are important biochemical markers. The relationship between TnT and BNP and heart failure, based on our hypothesis, is shown in Table 4. These markers are easy to determine within a few hours and can be repeated for patient follow up, without inter-observer variability. In the future, the combination of these tests may be used in bedside clinical settings.[18,19] Unfortunately, a multivariate analysis was not used to evaluate the prognostic value of these parameters because of our small sample numbers. Recently, Ishii et al reported that elevated cTnT and BNP on admission independently correlated with an increase in cardiac event rates in patients who were admitted to the coronary care unit for worsening chronic heart failure.[14]

Although the mechanism of myocyte injury and the release of cTnT in CHF is not completely understood, cTnT seems to reflect ongoing myocyte injury even during compensated periods of CHF.[7–10] Whether this indicates irreversible or reversible myocyte injury requires further investigation. The cytosolic pool for cTnT has been estimated at 6–8%. The release of protein may be because of a transient leak from the cytosol due to loss of sarcolemmal integrity during reversible ischemia, or from its continuous release when ischemic injury is irreversible.[20,21]

No guidelines have been issued regarding the use of biochemical markers as part of the management of CHF. Recently, Maeda et al reported that BNP after optimized treatment for heart failure, rather than BNP before treatment, is an independent risk factor for morbidity and mortality in patients with congestive heart failure.[22] We were unable to obtain follow up NT-proBNP data. While further studies are necessary, we anticipate that these assays will become the new monitoring standards in this patient population.

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