VIA MEDICA
ORIGINAL ARTICLE
Cardiology Journal
2010, Vol. 17, No. 1, pp. 42–48

ISSN 1897–5593

Prognostic value of cardiac troponin T elevation is independent of renal function and clinical findings in heart failure patients

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Abstract

Background: *The aim of this study is to determine the prevalence and prognostic value of elevated cardiac troponin (cTnT) and its association with clinical characteristics according to renal function status in patients with stable heart failure.*

Methods: *In a prospective observational study, 152 consecutive patients from the Heart Failure Clinic of the INCMNSZ were followed for a period of 42 months. All underwent clinical evaluation, echocardiography, and determination of body composition by electric bioimpedance to identify hypervolemia. Concentrations of cTnT were quantified by immunoassay with electrochemoluminescence and ≥ 0.02 ng/mL levels were considered elevated. Also glomerular filtration rate (eGFR) was estimated using the Cockcroft-Gault equation.*

Results: *Elevated cTnT was significantly associated with increased all-cause mortality in the observational period even after adjusting for eGFR < 60 mL/min/1.73 m^2 and clinical findings such as hypertension, functional class, loop diuretics, angiotensin converting enzyme inhibitors, pulmonary pressure and hypervolemia in Cox regression analysis with a hazard ratio of 4.58 (95% confidence interval: 1.84–11.45).*

Conclusions: *Heart failure patients with elevated cardiac-specific troponin T are at increased risk of death independently of the presence of chronic kidney disease.* (Cardiol J 2010; 17, 1: 42–48)

Key words: troponin elevation, clinical findings, kidney and heart failure

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Received: 2.06.2009 Accepted: 7.09.2009

Introduction

Heart failure (HF), a clinical syndrome with diverse causes, is one of the commonest, most costly and most incapacitating medical conditions. It accounts for at least 20% of all hospital admissions [1, 2].

The structural and functional alterations caused by HF are progressive and are often accompanied by evidence of lesion and the death of myocardial cells as part of the ventricular remodeling process and/or apoptosis, regardless of the etiology [3, 4].

Damage to cardiac myocytes associated with the progression of HF in the absence of ischemic events explains elevated concentrations of troponin as a marker of acute or chronic subclinical myocardial damage. This is the result of liberation of cytosolic troponin after the rupture of the cardiac myocytic membrane which is associated with increased severity of the disease, diminished ejection fraction and higher incidence of death [5–13].

In patients with kidney failure, who have a high risk of developing heart failure [14], troponin concentrations are often elevated without evidence of acute myocardial ischemia [15]. Thus, many of the studies that evaluate elevated troponin concentrations in HF exclude patients with elevated serum creatinine. However, elevated troponin concentrations have been associated with volume overload, a common finding in patients with renal dysfunction as well as heart failure [14].

This study was designed to determine the prevalence and prognostic value of elevated cardiac troponin (cTnT) and its association with clinical characteristics regardless of renal function status in patients with chronic stable heart failure.

Methods

Study population

In a longitudinal, prospective and comparative study, we consecutively studied a group of patients with HF in the Heart Failure Clinic of the INCMNSZ over a period of 42 months.

The population included men and women over 18 years of age with left and/or right ventricular dysfunction with optimal standard treatment (diuretics, angiotensin converting enzyme inhibitors or angiotensin II antagonists, digitalis, beta-blockers and aldosterone receptor antagonists). Patients were ambulatory and had no admissions to the hospital nor changes in their HF medication during the preceding three months.

Patients were excluded if they had: myopericarditis; cardiac trauma; neoplastic and infiltrative processes; chemotherapy; pulmonary embolism; end-stage kidney failure or terminal liver failure; recent (within three months) coronary syndromes such as acute myocardial infarction, unstable angina and/or coronary bypass surgery; uncontrolled arrhythmias; use of vasodilators and/or intravenous inotropic drugs.

The protocol was approved by the Committee of Biomedical Investigation in Humans of the INCMNSZ. Written informed consent was obtained from each patient before inclusion in the study.

Laboratory diagnostics

Blood samples were collected for determination of serum levels of cTnT by a third-generation electrochemoluminescence immunoanalysis (Elecsys autoanalyzer 2010, Roche Diagnostics, Mannheim, Germany). The minimum level of detection was 0.010 ng/mL, and levels ≥ 0.02 ng/mL were considered to be elevated [12]. Also serum electrolytes, lipid profile (total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol), microalbuminuria in 24 hour urine samples and levels of myoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH) and creatine kinase (CK) were determined. Glomerular filtration rate (eGFR) was calculated by Cockcroft-Gault equation. An abnormal glomerular filtration rate was defined as < 60 mL/min/1.73 m^2.

Echocardiographic measurements

Echocardiographic measurements were performed using Hewlett Packard Sonos 5500 equipment with M-mode, two dimensional and Doppler images in parasternal long and short axis and two and four chamber apical views. The cardiologist who performed the echocardiograms did not have access to the cTnT values.

Bioelectrical impedance analysis

Whole-body impedance was measured using a BodyStat QuadScan 4000 tetrapolar and multiple frequencies equipment (BodyStat Ltd, Isle of Man, British Isles). Using 50 kHz frequency resistance (R50), reactance (Xc50) and phase angle were obtained by the BodyStat® Phase Angle Software Program (version 1.0). The resistance and reactance values were normalized by the height (H) of the subjects, thus expressing both R/H and Xc/H in Ohm/m and were plotted in the RXc graph (abscissa R/H, ordinate Xc/H). The points that fell outside the lower half of the reference curve of 75% of the RXc graph were interpreted as hypervolemic. The points that fell outside the right lower side of the

reference curve of 75% on the RXc graph were classified as cachetic [16]. Also, the whole-body impedance ratio at 200 kHz to that at 5 kHz (Z200/Z5) was obtained; this served as an indicator of water distribution [17].

Statistical analysis

Continuous data is expressed as the mean value ± standard deviation and categorical variables in percentages. Comparisons of all continuous variables between groups defined according to the troponin T level (cTnT ≥ 0.02 ng/mL or cTnT < 0.02 ng/mL) and eGFR (< 60 mL/min/1.73 m^2 or ≥ 60 mL/min/1.73 m^2 were calculated using analysis of variance (ANOVA) statistics. The χ^2 test was used for categorical variables to compare the four groups.

The primary end point was all-cause mortality stratified by cTnT levels and eGFR that were compared by log-rank test and presented as Kaplan-Meier curve. A multivariable analysis was performed with Cox proportional hazards model to evaluate the prognostic value of cTnT (≥ 0.02 ng/mL versus cTnT < 0.02 ng/mL). The model included all the variables statistically significant in the univariate analysis and cTnT status.

Two-sided p values < 0.05 were considered to be statistically significant. Statistical calculations were performed using the statistical package SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

One hundred and fifty-two patients, with a mean age of 63.64 ± 16.91 years, were included. Men predominated (53.9%). In 39 (25.7%) cases, cTnT ≥ 0.02 ng/mL was found and 21 (53.8%) of them presented also eGFR< 60 mL/min/1.73 m^2.

Systolic ventricular dysfunction predominated in the high cTnT levels group (61.1%) and isolated right ventricular dysfunction was also found in 5.6% (Fig. 1).

Base-line demographic and clinical characteristics according to cTnT status and glomerular filtration rate are presented in Table 1. Patients with both abnormal cTnT and eGFR had lower body mass index, more dyspnea, significant water retention measured by electric bioimpedance, lower phase angle, a significantly greater proportion of excess liquid in the extravascular space, worse functional class, lower levels of hemoglobin, hematocrit, sodium and myoglobin, and greater kidney damage. A higher percentage of patients with elevated cTnT

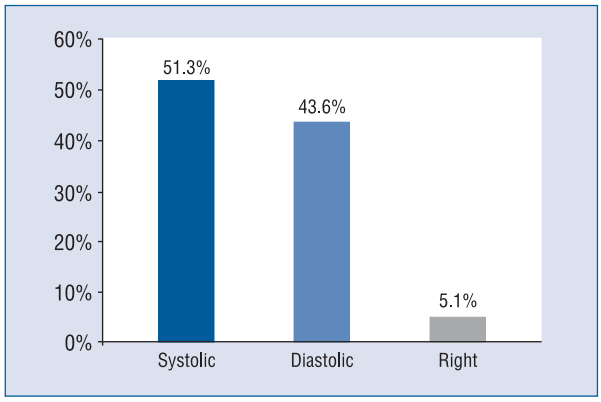

Figure 1. Prevalence of types of ventricular dysfunction in patients with cardiac troponin T (cTnT) concentrations ≥ 0.02 ng/mL.

were on loop diuretics at the beginning of the study than patients with normal cTnT, while more patients with normal cTnT were using thiazide diuretics. There were no other statistical differences among other medications between the four groups.

Table 2 shows that the aortic diameter was lower in patients with cTnT ≥ 0.02 ng/mL and that patients in the group with both abnormal cTnT and eGFR had higher pulmonary systolic pressure.

Kaplan-Meier curve for all-cause mortality by troponin T level (cTnT ≥ 0.02 ng/mL or cTnT < 0.02 ng/mL) and eGFR (< 60 mL/min/1.73 m^2 or ≥ 60 mL/min/1.73 m^2) is shown in Figure 2. The crude mortality rate after a follow-up of 42 months was 14.6% in the group with normal cTnT and eGFR, 30% in the group with eGFR < 60 mL/min/1.73 m^2, 73.7% in the group with both abnormal cTnT and eGFR, and 77.8% in the group with cTnT ≥ 0.02 ng/mL.

The association between concentrations of cTnT and overall mortality was tested by Cox multivariable analysis considering as categorical variable (≥ 0.02 ng/mL versus cTnT < 0.02 ng/mL). In a model including cTnT and demographic, clinical and echocardiographic variables having a significant univariate relationship with outcome, this marker had the strongest association with all-cause mortality followed by hypervolemia on RXc graph (Table 3).

Discussion

A high prevalence of elevated cTnT has been described in acute or decompensate chronic HF [18, 19]. For this study, we excluded heart failure patients with unstable ischemic disease, as other

Table 1. Demographic and clinical characteristics according to groups defined by troponin T status (cTnT) and estimated glomerular filtration rate (eGFR).

Variable	cTnT < 0.02 ng/mL and eGFR ≥ 60 mL/min/1.73 m^2 (n = 82)	cTnT ≥ 0.02 ng/mL (n = 18)	eGFR < 60 mL/min/1.73 m^2 (n = 31)	cTnT ≥ 0.02 ng/mL and eGFR < 60 mL/min/1.73 m^2 (n = 21)	p
Men (%)	50 (61)	13 (72)	9 (29)	10 (47.6)	0.007
Age (years)	59.83 ± 16.20	69.03 ± 18.00	70.87 ± 13.35	63.19 ± 19.65	0.007
Body mass index [kg/m^2]	31.66 ± 9.28	25.80 ± 4.61	27.13 ± 5.10	24.08 ± 5.18	< 0.0001
History of hypertension (%)	63 (76.8)	12 (66.7)	21 (67.7)	15 (71.4)	0.7
History of diabetes (%)	49 (58.8)	9 (50.0)	17 (54.8)	10 (47.6)	0.7
Dyspnea (%)	12 (14.6)	5 (27.8)	5 (16.1)	11 (52.4)	0.002
Fatigue (%)	28 (34.1)	10 (56.6)	4 (12.9)	11 (52.4)	0.005
Edema (%)	9 (11)	3 (33.3)	2 (6.5)	4 (19)	0.04
Hypervolemia on RXc graph (%)	34 (47.9)	12 (70.6)	10 (35.7)	15 (75)	0.002
Phase angle (°)	5.77 ± 1.74	4.48 ± 1.20	5.23 ± 1.00	4.32 ± 1.16	< 0.0001
Impedance ratio (Z200/Z5 Khz)	0.81 ± 0.03	0.83 (0.04)	0.82 ± 0.03	0.85 ± 0.03	< 0.0001
Cachexia (%)	55 (77.5)	16 (94.1)	20 (71.4)	18 (91.0)	0.017
NYHA functional class					0.001
I (%)	54 (65.9)	8 (47.1)	25 (80.6)	4 (20.1)	
II (%)	21 (25.6)	7 (41.2)	5 (16.1)	9 (45.0)	
III (%)	7 (8.5)	1 (11.8)	1 (3.2)	7 (35)	
ACEI/A-II RA (%)	75 (91.5)	16 (88.9)	24 (77.4)	20 (95.2)	0.2
Beta-blockers (%)	76 (92.7)	17 (94.4)	28 (90.3)	19 (90.5)	0.9
Digitalis (%)	38 (46.3)	12 (66.7)	17 (54.8)	10 (46.7)	0.43
Loop diuretic (%)	18 (22.0)	5 (27.8)	5 (16.13)	7 (33.3)	0.4
Thiazide diuretics (%)	63 (76.8)	10 (55.6)	15 (50.00)	5 (23.8)	< 0.0001
Spirinolactone (%)	69 (73.2)	15 (83.3)	23 (74.2)	11 (52.4)	0.15
Hemoglobin [g/dL]	15.99 ± 2.7	14.32 ± 1.97	13.71 ± 1.82	13.41 ± 3.17	0.005
Hematocrit (%)	44.26 ± 5.64	42.58 ± 5.86	40.49 ± 5.34	40.19 ± 10.04	0.02
Glucose [mg/dL]	109.90 ± 39.19	118.22 ± 48.27	134.32 ± 70.81	127.67 ± 70.14	0.14
Sodium [mmol/L]	137.44 ± 1.79	135.97 ± 3.54	137.80 ± 3.27	135.63 ± 3.66	0.04
Potassium [mmol/L]	4.51 ± 0.48	4.33 ± 0.59	4.62 ± 0.54	4.92 ± 0.79	0.01
Microalbuminuria (%)	20 (35.7)	5 (50.0)	9 (37.5)	10 (90.9)	0.008
Creatinine [mg/dL]	0.96 ± 0.26	1.10 ± 0.24	1.17 ± 0.32	1.29 ± 0.32	< 0.0001
Myoglobin [ng/mL]	48.55 ± 20.53	65.47 ± 39.7	48.82 ± 14.20	106.67 ± 58.73	< 0.0001

Data is presented as the mean value ± standard deviation or number (%) of patients; NYHA — New York Heart Association; ACEI — angiotensin converting enzyme inhibitors; A-II RA — angiotensin II receptor antagonists

Table 2. Echocardiographic characteristics according to groups defined by troponin T status (cTnT) and estimated glomerular filtration rate (eGFR).

Parameter	cTnT < 0.02 ng/mL and eGFR ≥ 60 mL/min/1.73 m² (n = 82)	cTnT ≥ 0.02 ng/mL (n = 18)	eGFR < 60 mL/min/1.73 m² (n = 31)	cTnT ≥ 0.02 ng/mL and eGFR < 60 mL/min/1.73 m² (n = 21)	p
LVDD [mm]	52.21 ± 9.12	56.12 ± 7.7	49.58 ± 9.45	50.14 ± 12.08	0.12
LVSD [mm]	38.41 ± 11.12	43.27 ± 10.25	35.58 ± 11.81	38.52 ± 13.61	0.18
Interventricular septum [mm]	11.79 ± 2.82	12.0 ± 2.78	12.10 ± 2.81	12.37 ± 3.40	0.90
Posterior wall [mm]	10.12 ± 2.23	11.34 ± 2.19	10.87 ± 1.71	10.61 ± 1.75	0.09
Aortic diameter [mm]	33.33 ± 4.11	26.40 ± 8.82	31.44 ± 6.38	28.36 ± 6.62	0.02
Left atrial diameter [mm]	47.16 ± 9.02	44.87 ± 7.63	44.40 ± 8.13	47.63 ± 9.20	0.39
LA/Ao	1.37 ± 0.19	1.32 ± 0.22	1.45 ± 0.28	1.53 ± 0.23	0.15
Fractional shortening (%)	24.96 ± 9.6	24.73 ± 11.53	24.95 ± 10.85	22.06 ± 11.53	0.78
LVEF (%)	44.00 ± 14.09	43.59 ± 16.63	44.83 ± 15.95	41.24 ± 20.03	0.87
RVDD [mm]	42.07 ± 7.65	41.00 ± 13.71	43.36 ± 8.31	39.57 ± 10.44	0.73
LVIRT [ms]	108.81 ± 20.95	101.14 ± 33.00	116.25 ± 42.91	90.20 ± 24.18	0.14
PAP [mm Hg]	48.87 ± 14.11	52.43 ± 10.35	58.47 ± 19.47	69.43 ± 14.12	< 0.0001

Data is presented as the mean value ± standard deviation; LVDD — left ventricular diastolic diameter; LVSD — left ventricular systolic diameter; LA/Ao — left atrium/aortic diameter ratio; LVEF — left ventricular ejection fraction; RVDD — right ventricular diastolic diameter; LVIRT — left ventricular isovolumetric relaxation time; PAP — pulmonary arterial pressure

authors have recommended [20, 21]. Although we found no statistically significant difference in cause or type of heart failure, 25.7% of the patients had elevated cTnT.

While elevations in cTnT have been reported to be more frequent in cases of systolic heart failure, they have also been documented in cases of diastolic heart failure, hypertrophic cardiomyopathy and cardiac sudden death as evidence of chronic subclinical damage in the absence of acute coronary syndrome [12]. In our patients with chronic, stable HF under optimal treatment we found no difference in type of heart failure, including those with isolated right heart failure secondary to chronic obstructive pulmonary disease reported to be associated with a poor prognosis [9, 19].

Also in association with water retention, patients with elevated cTnT had a higher frequency of hypervolemia. A similar situation has been observed in patients in peritoneal dialysis, in which hypervolemia markers with bioelectric impedance vector analysis (BIVA) such as a smaller phase angle and hypoalbuminemia were associated with higher levels of B-type natriuretic peptide and cTnT. In these cases, higher levels of cTnT associated with increased volume overload and heart rate could be attributed to excessive activation of the rennin–angiotensin–aldosterone system and of the central nervous system [18, 22].

Throughout the 42 month follow-up of the study population, disregarding co-existent conditions, mortality was higher in cTnT elevated cases compared to those with normal cTnT, and higher even than in patients with reduced eGFR ($p < < 0.0001$). This is consistent with the findings of other authors, even in patients in hemodialysis [23–26]. The increased frequency of microalbuminuria in patients with higher cTnT levels might be explained in part by kidney damage, but it is also a marker for endothelial dysfunction, a condition often found in cases of HF and associated with other indicators of a poor prognosis [27]. In addition, this group with elevated troponin levels tended to have higher pulmonary artery systolic pressure and left ventricular diameters which are associated with a poor prognosis [28].

Patients with elevated troponin had lower body mass indices, as well as lower myoglobin levels, compared to groups with low troponin. This suggests cachexia (confirmed by BIVA) and the loss of muscle mass that occurs in advanced cases of HF [29–31]. This constellation of factors point to the marked activation of neurohumoral systems with liberation of cytokines such as tumor necrosis fac-

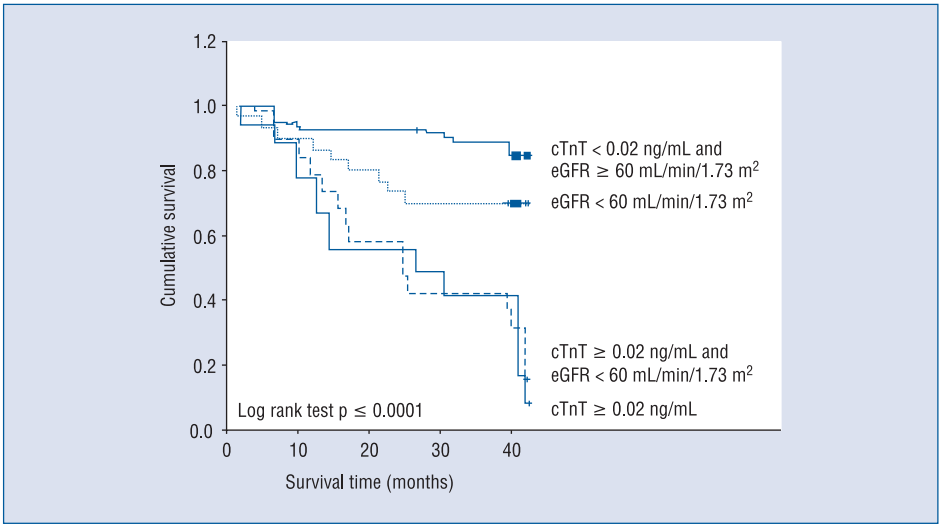

Figure 2. Kaplan-Meier cumulative curves for survival according to cardiac troponin T (cTnT) status and glomerular filtration rate (eGFR).

Table 3. Univariate and multivariate predictors of overall mortality by Cox proportional hazard model.

Variables	Univariate (p)	Hazard ratio (95% CI)	Multivariate (p)
Age (years)	0.77	1.0 (0.97–1.02)	0.77
Hypertension (yes/no)	0.01	0.63 (0.26–1.51)	0.31
NYHA functional class (I–III)	< 0.0001	1.45 (0.80–2.64)	0.22
ACEI (yes/no)	0.04	1.51 (0.60–3.77)	0.40
Loop diuretics (yes/no)	0.006	0.42 (0.15–1.16)	0.10
PAP [mm Hg]	0.02	1.02 (0.99–1.05)	0.21
cTnT ≥ 0.02 (yes/no)	< 0.0001	4.58 (1.84–11.45)	0.001
eGFR < 60 mL/min/1.73 m^2	0.003	1.27 (0.5–3.38)	0.63
Hypervolemia on RXc graph (yes/no)	0.0003	2.45 (1.04–5.79)	0.04

CI — confidence interval; NYHA — New York Heart Association; ACEI — angiotensin converting enzyme inhibitors; PAP — pulmonary arterial pressure; RXc graph — resistance/reactance graph

tor-alpha, interleukin-1 and interleukin-6 reported in the literature [17, 32] and found in our patients. These cytokines are associated with exacerbation of symptoms and deterioration of functional class in relation to a decrease in free fat mass and increase in total and extracellular body water assessed by BIVA.

Limitations of the study

Unfortunately, it was not possible to obtain end point determinations of cTnT and myoglobin levels, and the small sample size made it difficult to establish greater differences in ventricular remodeling in the distinct types of HF and their echocardiographic characteristics and to determine whether it is equally sensitive to define cardiovascular mortality in patients with elevated cTnT.

Conclusions

Mortality was significantly higher in the groups with elevated cTnT, independent of chronic kidney disease. Elevated troponin T levels were associated with worse clinical conditions, including greater water retention and New York Heart Association functional class. The prevalence of elevated cTnT was independent of the type of heart failure. Volume overload is a determining factor in the elevated prevalence of cTnT, especially in cases of kidney dysfunction.

Acknowledgements

The authors do not report any conflict of interest regarding this work.

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