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Original Research

Is Cardiac Troponin I Valuable to Detect Low-Level Myocardial Damage in Congestive Heart Failure?

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Abstract

Objectives: Congestive heart failure (CHF) is a heart disease with a growing incidence and prevalence. Creatine kinase-myocardial base (CK-MB) is generally used to determine myocardial damage; however, it is insufficiently sensitive to measure the relatively low level of myocardial damage that typically occurs in heart failure (HF). The use of cardiac troponins, which are far more sensitive and specific, has become common to identify myocardial damage and permits the detection of even minute amounts of damage. The aim of this study was to ascertain whether cardiac troponin I (cTnI) can be used to detect low-level myocardial damage occurring in CHF in real-life conditions.

Methods: Fifty patients with CHF symptoms (Group I) and 20 patients who were evaluated as normal (Group II) were included in this prospective study. The Framingham criteria were used to diagnose HF. Group I was divided into 3 subgroups according to the New York Heart Association classification of functional capacity: Class II, Group A; Class III, Group B, and Class IV, Group C. On the first day of admission, CK-MB and cTnI levels were measured and assessed quantitatively. The cTnI level was compared between these 3 subgroups and between Groups I and II. Linear regression analysis was performed to investigate the relationship between ejection fraction (EF) and cTnI.

Results: The mean cTnI value was 0.084±0.07 ng/mL in Group I and 0.018±0.012 ng/mL in Group II (p=0.0001). The mean cTnI value was 0.047±0.016 ng/mL, 0.080±0.048 ng/mL, and 0.175± 0.102 ng/mL in Groups A, B, and C, respectively. The difference between the subgroups of Group I was statistically significant. In addition, it was observed that there was a significant difference in the EF (%) value between Groups I and II and between Groups A, B, and C. Linear regression analysis revealed an inverse relationship between EF and cTnI (r: -0.66) (p=0.0001).

Conclusion: As the severity of HF increased, the cTnI serum level also increased. This increase was inversely related to the EF value. These results are consistent with other studies in the literature, suggesting that the cTnI level may be a useful marker in the diagnosis and evaluation of severity of HF.

Keywords: Cardiac troponin I; heart failure; troponins.

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Congestive heart failure (CHF) is a complex clinical syndrome that is a result of a structural defect, which creates a reduction in ventricular filling or ejection fraction (EF). This clinical syndrome can be classified into systolic and diastolic groups, and heart failure (HF) with preserved left ventricle (LV) EF or low LV EF.

The diagnosis of HF is not based on a single diagnostic test. It is a clinical diagnosis based on a careful history and phys-

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ical examination. The causes of CHF may be related to the pericardium, myocardium, endocardium, heart valves, major vessel anomalies, or some metabolic diseases. However, the symptoms of most of HF patients are due to impaired LV myocardial dysfunction and reduced EF.[1]

Regardless of the cause, myocyte loss, ventricular remodeling, extracellular matrix hyperplasia, and decreased myocyte function may lead to deterioration of cardiac pump function.[2] It has been established that myocardial myoglobin decreased in animal models of dilated cardiomyopathy and that there is a significant decrease in cardiac troponin (cTn) T and I concentrations in pig myocardia exposed to post-infarction remodeling.[3, 4]

Accordingly, serum markers of myocardial necrosis (cTnI and CK-MB) should be detectable in patients with advanced HF. However, CK-MB, which is commonly used as a marker for myocardial injury, is insufficient to detect low-level cardiac damage in HF.

With the introduction of the ability to measure cardiac troponins, which are more sensitive and specific, there is the possibility to detect low-level cardiac damage. Troponins and tropomyosin are structural proteins involved in the regulation of skeletal and cardiac muscle contraction. They are coded by different genes and have different amino acid sequences.

Due to unique amino acid sequences, immunoassay detection of proteins released from a damaged myocardium with a high intracellular concentration using the antibodies against them can provide a sensitive and specific serum marker of myocardial damage.[5–8]

The measurement of troponins has a greater clinical sensitivity due to the high level seen in heart tissue compared with other markers and the low circulating blood level in healthy individuals.[9, 10] The very high specificity is a result of the presence and detection of cardiac-specific cTnT and cTnI isoforms.[9, 11]

Some patients with HF have been reported to have myocardial damage associated with a low EF that could be detected by the presence of cardiac troponins.[12, 13]

The objective of this study was to investigate whether myocardial injury occurring in HF could be determined using the measurement of cTnI.

Methods

The study participants were selected from among patients of the emergency department and outpatient clinics of internal medicine. In all, 50 patients who presented with signs and symptoms of CHF were included in the study group (Group I) and 20 who were evaluated as normal constituted the control group (Group II).

Table 1. Framingham criteria for the diagnosis of congestive heart failure

Major Criteria
1. Paroxysmal nocturnal dyspnea or orthopnea
2. Neck vein distention
3. Rales
4. Cardiomegaly
5. Acute pulmonary edema
6. S3 gallop rhythm
7. Increased jugular venous pressure >16 mmHg
8. Circulation time >25 sec
9. Hepatojugular reflux
Minor Criteria
1. Ankle edema
2. Nocturnal cough
3. Dyspnea on exertion
4. Hepatomegaly
5. Pleural effusion
6. Decrease in vital capacity (1/3 decrease from maximum)
7. Tachycardia (heart rate >120 bpm)
Major or Minor Criterion
Weight loss 4.5 kg in 5 days in response to treatment
Diagnosis of congestive heart failure: 2 major criteria or 1 major + 2 minor criteria

The Framingham criteria were used for the diagnosis of CHF (Table 1). The functional capacity of the patients in Group I was assessed according to New York Heart Association (NYHA) criteria and Class II patients were included in Group A (n=19), Class III patients were categorized in Group B (n=22), and Class IV patients made up Group C (n=9).

On the first day of hospitalization, blood samples were drawn into dry tubes without heparin, and CK-MB and cTnI levels were measured.

A Roche chemical inhibition assay was used to measure CK-MB (cut-off value: 0-24 U/L) in a Hitachi 747 autoanalyzer (Hitachi Ltd., Tokyo, Japan). Chemoluminescence was used to measure cTnI using Beckman kits in an Access immunoassay analyzer (Beckman Coulter, Inc., Brea, CA, USA) (cut-off value: 0-0.04 ng/mL; values >0.50 ng/mL were considered significant for acute myocardial infarction).

The appropriate medical treatment protocol was applied to all of the patients. After stabilization, echocardiographic examinations were performed with the patient in the left lateral decubitus position using a Sonos 4500 echocardiography device (HP/ Philips Medical Systems International B.V., Best, Netherlands) on the same day. A 2.5-MHz probe was used to perform the measurements. M-mode

measurement was performed at the anterior mitral valve leaflet tip. The mean of 5 successive cycles was used for the systolic and diastolic LV diameter. EF was calculated using 2-dimensional echocardiography according to a modified Simpson method.

Patients with an EF <45% were included in the study (none of the patients in the study group of 50 patients constructed based on Framingham criteria, and symptoms and signs of heart failure had an EF >45%).

An ischemic and non-ischemic differentiation according to etiology was made based on the anamnesis, electrocardiogram findings, and echocardiography results.

The patients were asked about conditions that might cause an elevation of troponin, and these were used as exclusion criteria.

The study was approved by the ethics committee of Şişli Etfal Training and Researh Hospital and informed consent was obtained from each of the participants prior to the study.

Inclusion Criterias

1. The presence of NYHA Class II, III, or IV heart failure
2. Echocardiographic finding of EF <45%
3. Creatinine level <1.5 mg/dL

Exclusion Criterias

1. Acute coronary syndrome
2. Myocarditis and/or pericarditis
3. Major heart valve disease
4. Diabetes mellitus
5. Kidney or liver disease
6. Acute or chronic pulmonary disease (chronic obstructive pulmonary disorder, pneumonia, pulmonary embolism)
7. Musculoskeletal diseases
8. Malignancy
9. Sepsis
10. Acute ischemic stroke
11. The presence of trauma
12. Thyrotoxicosis or hyperthyroidism
13. Hyperdynamic circulation (anemia, etc.)

Statistical Analysis

Continuous variables were expressed as mean±SD and categorical variables as percentages. Comparison of 2 independent continuous variables with normal distribution was performed using the Mann-Whitney U test. Categorical variables were compared with a chi-square test. Linear regression analysis was performed. P<0.05 was considered statistically significant.

Results

Fifty patients aged between 43 and 75 years and a control group of 20 individuals, made up of 12 males and 8 females, were enrolled in the study. HF patients were classified as Group I and the control group as Group II. The mean age was 63.77 years in Group I, and 66.81 years in Group II without any statistically significant difference between the groups (p=0.26).

Group I consisted of 32 male and 18 female patients. Group II comprised 12 male and 8 female patients, without any statistically significant difference between the groups (p=0.52).

The mean CK-MB value in Group I and II was 14.84±4.7 U/L and 14.25±4.8 U/L, respectively, without any statistically significant difference between the groups (p=0.64).

The mean cTnI value in Groups I and II was 0.084±0.07 ng/mL and 0.018±0.012 ng/mL, and there was a statistically significant intergroup difference (p=0.0001).

The mean EF in Group I and II was 32.4±6.9% and 60.9±4.3%, respectively, with a statistically significant intergroup difference (p=0.0001). The characteristics of the 2 groups are summarized in Table 2.

Group I was divided into 3 subgroups according to NYHA functional capacity: Class II (Group A, n=19), Class III (Group B, n=22), and Class IV (Group C, n=9).

The mean age was 59.7±7.7 years in Group A, 65.7±7.5 in Group B and 66.3±5.2 in Group C. A statistically significant difference was found between Groups A and C (p=0.02), but not between Group A and Group B and not between Group B and C (p=0.18, p=0.78).

The mean CK-MB value was 14±4.5 U/L in Group A, 16.1±4.2 U/L in Group B, and 16.6±2.3 U/L in Group C, without any statistically significant difference between the 3 groups (p=0.13, p=0.66, and p=0.11).

The mean cTnI value was 0.047±0.016 ng/mL in Group A, 0.080±0.048 ng/mL in Group B, and 0.175±0.1 ng/mL in Group C. There was a statistically significant difference between Group A and Group B, Group B and Group C, and

Table 2. Characteristics of the patient and the control groups

	Group I	Group II	p
Age (years)	63.5±7.7	66.8±11.9	0.26
Gender	18F/32M	8F/12M	0.52
cTnI (ng/mL)	0.084±0.07	0.018±0.012	0.0001
CK-MB (U/L)	14.84±4.7	14.25±4.8	0.64
EF (%)	32.4±6.9	60.9±4.3	0.0001

CK-MB: Creatinine kinase myocardial band; cTnI: Cardiac troponin I; EF: Ejection fraction.

between Group A and Group C (p=0.005, p=0.001, and p=0.0001, respectively). This difference was most pronounced between Groups A and C.

The mean EF value was 34.7±3.5% in Group A, 30.9±4.56% in Group B, and 22.8±3.3% in Group C. The difference between Groups A and B, Groups B and C, and between Groups A and C was statistically significant (p=0.004, p=0.0001, and p=0.0001, respectively).

Linear regression analysis performed to investigate the relationship between EF and cTnI revealed an inverse relationship (r: -0.66) (p=0.0001). A lower EF value was associated with a higher cTnI level. The characteristics of the groups are summarized in Table 3.

Discussion

CHF is an example of cardiovascular disease with a growing incidence and prevalence, and it is a health problem with a rather poor prognosis.[14–16] The frequency of heart failure increases with age, as indicated by the results of the Framingham study.[17] In our study, we found a statistically significant difference in the age of the patients between Groups A and C, which was likely a manifestation of the natural course of the disease and increase in incidence with age.

Since the detection of myofibrillar cardiac proteins in the sera of some patients with end-stage HF, the relationship between serum markers of myocardial necrosis (cTnI, cTnT, and CK-MB) and the measurement of cardiac myocytes in these patients has been investigated with increasing interest. CK-MB, which is widely used to detect myocardial injury, has not yet been shown to detect low-level cardiac damage in HF.[18]

Cardiac troponins appear to be a more sensitive and specific means of detection of myocardial damage in patients with HF with no underlying coronary artery disease or apparent myocardial ischemia.[5–8]

In 1995, Missov et al.[19] first suggested that chronic myocardial cell destruction might be visible in the examination of cardiac troponins in the blood. Missov et al. compared 35 patients with advanced HF to those with no known heart disease and healthy subjects and blood bank donors and found a mean cTnI level of 72.1±15.8 pg/mL in patients with Class III and IV functional capacity, 20.4±3.2 pg/mL in blood donors and 36.5±5.5 pg/mL in healthy subjects. In a total of 115 cases, the cTnI level was significantly higher in patients with HF, whereas the level of CK-MB and myoglobin was within normal limits in all groups.

La Vecchia et al.[13] reported that they detected cTnI-positivity in 6 of 26 patients with CHF and indicated that cTnI-positive patients had a poorer functional class, ventricular function, and prognosis. In a study conducted by the same group in 1999, the researchers indicated that they had observed cTnI-positivity in 10 of 34 CHF patients with a mean cTnI value of 0.7±0.3 ng/mL. The authors also reported that cTnI-positive patients had a significantly lower EF (20±5% versus 26±7%) compared with cTnI-negative patients, and a negative but statistically insignificant correlation was found between cTnI and EF.[20]

In their research examining 44 patients and 22 healthy individuals, Balcı et al.[21] studied 8 cTnT-positive patients with low LVEF and indicated that troponin positivity may be a useful measure of LVEF.

In 1999, Missov et al.[12] evaluated 33 patients with CHF and 47 healthy individuals, and they reported a statistically significant cTnT level (0.140±0.043 ng/mL) in the patient group when compared with the control group (0.002±0.0001 ng/mL), and that the level of cTnT was parallel to the severity of HF (EF=45%: 0.163±0.05 ng/mL; EF >45%: 0.07±0.001 ng/mL).

In our study, a quantitative method was used to measure cTnI in 50 congestive heart failure patients and 20 control cases. The mean cTnI level was 0.084±0.07 ng/mL in the patient group and 0.018±0.012 ng/mL in the control group, with a statistically significant intergroup difference. Our result was consistent with literature data.[13, 19, 22]

The patients were divided into 3 subgroups according to NYHA functional capacity (II-IV), and a comparison of the cTnI level revealed that the troponin level was statistically significantly greater as functional capacity decreased.

The mean cTnI value was 0.047±0.016 ng/mL in Group A,

Table 3. General characteristics of the subgroups

	Group A	Group B	Group C	p (A-B)	p (B-C)	p (A-C)
Age (years)	59.7±7.7	65.7±7.4	66±35.2	0.18	0.78	0.02
CK-MB (U/L)	14±4.5	16.1±4.2	16.7±2.3	0.13	0.66	0.11
cTnI (ng/mL)	0.047±0.016	0.080±0.048	0.175±0.1	0.005	0.001	0.0001
EF (%)	38.6±3.5	30.9±4.6	22.8±3.3	0.004	0.0001	0.0001

CK-MB: Creatinine kinase myocardial band; cTnI: Cardiac troponin I; EF: Ejection fraction.

with a functional capacity of Class II, and 22.8±3.3 ng/mL in Group C, with a functional capacity of Class IV. These findings showed that cTnI was a successful predictor of the severity of HF.

There was no significant difference in the CK-MB level between the patient and control groups or between Groups A, B, and C.

These findings were consistent with the results of other studies in the literature indicating that CK-MB was insufficient to demonstrate myocyte damage or the severity of HF.

There was a statistically significant difference between groups when the EF values of the patient and control groups (32.4±6.9 versus 60.9±4.3) were compared, as well as those of Groups A, B, and C. When linear regression analysis was performed to investigate the relationship between EF and cTnI, an inverse relationship was found between EF and cTnI (r: -0.66; p=0.0001).

As the EF value decreased, namely, as heart failure was further aggravated, the level of cTnI increased. This result was consistent with the results of the study reported by Missov et al., and a smaller scale study by La Vecchia et al. demonstrating that cTnI values increased according to the severity of heart failure.

None of our patients had findings of acute myocardial infarction or ischemia. The CK and CK-MB levels often used in the detection of myocardial damage were not significantly different from those of the control group.

Patients with acute ischemic syndrome, in whom elevated cTnI values may be detected for up to 30 days after a myocardial infarction, and those with systemic conditions that could lead to cTnI elevation were not included in the present study. In addition, the method we used to determine the level of cTnI is specific to the heart muscle. Therefore, it would be appropriate to accept that the detected cTnI levels were secondary to myocardial damage.

Our results indicated that as functional capacity and EF decreased, the cTnI level increased categorically and with statistical significance. Linear regression also demonstrated the presence of a strong correlation between EF and cTnI, suggesting that measurement of cTnI may be valuable in the evaluation and diagnosis of HF. The fact that patients with overt ischemic components and those with non-cardiac diseases that may cause troponin elevation were not included in this study make this interpretation and the results obtained even more meaningful.

Recent studies have suggested that as a result of evolving spectrometric analytical methods and the use of modified cTnI proteoforms, there are promising developments concerning the diagnosis of HF.[23]

Furthermore, in a recent meta-analysis related to the use of high-sensitivity cardiac troponins in new onset HF, it was suggested that troponins may be very effective in demonstrating and predicting the risk of the development of HF.[24]

There is current medical literature indicating that cardiac troponins may be used successfully for the risk stratification of cardiovascular mortality.[25] It has also been suggested that cTnT may play a role in the prognostic evaluation of patients with congenital heart diseases,[26] and that it might be used as a predictor of cardiac mortality in patients with non-ischemic LV dysfunction.[27] At the same time, the importance of the prospective Caerphilley study, which emphasized the potential usefulness of troponins and B-type natriuretic factor (BNP) as a screening tools in the identification of patients with a high risk of developing HF in the future among individuals without cardiovascular disease should be kept in mind.[28]

A recent study suggested that hsTnT alone could significantly contribute to the risk assessment details provided by the BNP value in the determination of a prognosis in anemic HF patients with reduced EF.[29]

The research and the literature clearly indicate the importance of cardiac markers in terms of current medical applications and the intense interest in exploring them. Though contrary views have been advocated in some studies, there is potential for the greater use of troponins in the follow-up and treatment of patients with different types of heart disease.[30] Troponins may also have a role in risk stratification or diagnosis of patients with preserved EF.[31]

Dilatation of the LV and thinning of the LV wall are generally expected with the progression of HF. In vitro and in vivo studies have also reported endothelial cell apoptosis in HF patients.[32, 33] Apoptosis, coronary ischemia, decreased coronary reserve, and increased end-diastolic pressure caused for subendocardial ischemia, vasoconstrictive neurohormonal factors, and cytokine activation lead to the loss of cardiac myocytes.[34–40]

In our study, cTnI values increased with the severity of HF may be explained by, a sympathetic discharge that also increased parallel with the severity of HF, acceleration of the apoptotic cycle, and increased end-diastolic pressure caused for disruption of the coronary reserve, the increase in subendocardial ischemia and related myocyte loss.

Conclusion

This investigation of the relationship between EF, functional capacity, and cTnI indicated that increased levels of cTnI were associated with lower EF and decreased functional capacity.

This result suggests that cTnI can be used successfully in the assessment of the severity of HF. Whether troponins, which may contribute to the diagnosis of heart failure in patients with low ejection fraction, will continue to do so in individuals with preserved ejection fraction, it seems to continue to be the subject of new studies using advanced technologies.

Disclosures

Ethics Committee Approval: Şişli Etfal Training and Research Hospital, 2003.

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Conflict of Interest: None declared.

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