Serum Cardiac Troponin T, But Not Troponin I, Is Elevated in Idiopathic Inflammatory Myopathies

ROHIT AGGARWAL, DOROTA LEBIEDZ-ODROBINA, ALPANA SINHA, AUGUSTINE MANADAN, and JOHN P. CASE

ABSTRACT. ***Objective.*** To study the association of serum cardiac troponin T (cTnT) and cardiac troponin I (cTnI) with creatine kinase (CK) in patients with idiopathic inflammatory myopathies (IIM).

Methods. We performed a retrospective study on patients with IIM followed by the rheumatology service of a county hospital from 2004 to 2008. Patients with myocardial ischemia and/or with renal failure were excluded. Clinical data including electromyogram, muscle biopsy, and CK, cTnT and cTnI were recorded. Patients who had simultaneous analysis of CK and cardiac troponin (cTnT or cTnI) levels were studied. CK levels were correlated with cTnT and cTnI by chi-square test and Spearman correlation.

Results. We identified 49 patients with IIM (69 observations) who satisfied our inclusion criteria. The primary diagnosis was polymyositis in 23, dermatomyositis in 16, and myositis associated with connective tissue disease in 10 patients. There were 33/49 women with average age 45.8 years. Twenty-eight patients with IIM had simultaneous CK and cTnT values assayed. Of those patients, 18/23 with elevated CK also had elevated cTnT, and 5/5 patients with normal CK levels had normal cTnT levels ($p = 0.005$). In 41 patients with IIM who had simultaneous CK and cTnI levels assayed, only 1/29 with elevated CK had elevated cTnI, and 12/12 patients with normal CK had normal cTnI ($p = 0.5$). CK correlated strongly with the cTnT ($r = 0.62$, $p = 0.001$) but did not correlate with cTnI.

Conclusion. Elevated cTnT, but not cTnI, was highly associated with CK in patients with IIM despite the absence of myocardial ischemia. (First Release Oct 15 2009; J Rheumatol 2009;36:2711–14; doi:10.3899/ jrheum.090562)

Key Indexing Terms:
INFLAMMATORY MYOPATHIES CREATINE KINASE CARDIAC TROPONIN

Polymyositis (PM), dermatomyositis (DM), and myositis associated with connective tissue disease (CTD) are among the acquired idiopathic inflammatory myopathies (IIM) that affect adults. The muscle enzyme creatine kinase (CK) is increased in these patients because of ongoing muscle destruction and regeneration[1,2]. Although adult skeletal muscle typically contains only the CK-MM form, the expression of CK-MB, normally restricted to the myocardium, is increased during chronic skeleton muscle regeneration in patients with IIM[3-6]. This leads to detectable serum CK-MB concentrations and an increased CK-MB/total CK ratio. Therefore in these disorders the CK-MB or the CK-MB/total CK ratio do not imply myocardial damage and are unreliable in the diagnosis of myocardial infarction[7]. Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are thought to be highly specific markers of the myocardial infarction[8,9], even in the absence of typical clinical symptoms or electrocardiographic (EKG) changes[10,11]. Recent case reports in patients with IIM have shown an increase of cTnT in the apparent absence of myocardial infarction[12-14]. Interpreting the elevated cTnT in these patients as myocardial damage resulted in negative and therefore potentially unnecessary investigations for ischemic myocardial disease. One pathological study suggested that cTnT and not cTnI may be expressed in regenerating skeletal muscles of patients with muscle disease[15,16]. Potentially, cTnI may therefore be a more useful cardiac marker than cTnT in patients with IIM in the diagnosis or exclusion of myocardial damage. We tested the hypothesis that cTnT, but not cTnI, is elevated in active myositis and investigated their correlations with the muscle enzymes CK and CK-MB.

MATERIALS AND METHODS

We performed a retrospective study of patients treated for IIM over a 44-month period at the rheumatology clinic of the John H. Stroger, Jr. Hospital of Cook County, Chicago, from January 2004 to August 2008. All study patients fulfilled the Bohan and Peter classification criteria for definite or probable PM, DM, or myositis associated with CTD[17]. At our institution, the laboratory performed cTnI as the cardiac ischemia marker until August 2006, and thereafter performed cTnT instead. Patients with clinical evidence of myocardial ischemia or infarction were excluded, as were patients with renal failure, as cardiac troponins are generally elevated in

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these patients. Evidence of myocardial damage was assessed from available clinical data including clinical examination, EKG, echocardiogram, or left-heart catheterization. Renal failure was defined as serum creatine > 1.5 mg/dl.

Records were also reviewed for the following information: demographics, clinical data, and laboratory data including CK, CK-MB, cTnT, cTnI, electromyograms, and muscle and/or skin biopsy. Since patients may have had several recordings of CK and cardiac troponins (cTnT and cTnI) during one or more outpatient visits or hospital admissions, we recorded only the first simultaneous recording of CK and cTnT and/or of CK and cTnI on or following the diagnosis of IIM.

Assays. Standard third-generation immunoassays were used for cTnT measurements. Concentrations of cTnT were measured by an Elecsys troponin T immunoassay (Roche Diagnostics, Indianapolis, IN, USA). It employs 2 monoclonal antibodies specifically directed against human cardiac troponin T[18]. Concentrations of cTnT > 0.02 ng/ml were considered abnormally elevated according to manufacturer's instructions. cTnI was measured using the Immulite cTnI assay (chemiluminescent immunometric assay; Diagnostic Products Corp., Los Angeles, CA, USA), according to the manufacturer's instructions. It uses a monoclonal antibody immobilized on beads and a goat polyclonal antibody[19]. Concentrations of cTnI > 0.5 ng/ml were considered abnormally elevated. CK levels were measured using a standard immunoassay using a CK-NAC reagent. CK concentrations > 165 U/l were considered to be abnormally elevated. CK-MB was measured using the Elecsys CK-MB immunoassay (Roche), which employs 2 different monoclonal antibodies directed against human CK-MB. CK-MB concentration > 6.7 ng/ml was considered abnormally elevated according to the manufacturer's instructions.

The study was approved by the hospital institutional review board.

Statistics. Patients were dichotomized into 2 groups: patients with elevated and those with normal CK levels. Patients were further divided into groups according to their cardiac enzyme levels: patients with elevated cTnT level, patients with elevated cTnI level, and patients with normal cTnT and normal cTnI levels. The categorical data thus obtained were studied in 2×2 tables, using the chi-square test (Fisher exact test when necessary) to compare CK levels with cTnT levels and CK levels with cTnI levels. CK and CK-MB levels were correlated with cTnT and cTnI level, respectively, using Spearman correlation given the nonparametric nature of the data.

RESULTS

After the exclusion of 2 patients (one with myocardial infarction, one with renal failure), we identified 49 patients (69 observations) with IIM who met study criteria. There were 34 women and 16 men, with average age 45.8 (SD 16.7) years. Mean age at diagnosis was 23.6 (SD 8.8) years with 9.3 (SD 6.5) years of followup. The primary diagnosis was DM in 16 patients, PM in 23 patients, and myositis associated with CTD in 10 patients. Simultaneous CK and cTnT were checked in 28 patients and CK and cTnI in 41 patients.

CK and cTnT correlation. CK levels were significantly associated with cTnT levels (p = 0.005). Of 28 patients in whom simultaneous CK and cTnT were measured, there were 23 patients with elevated CK (mean CK levels 1340.9 ± 2732.1 mg/dl) and 5 patients with normal CK. cTnT was elevated in 18/23 patients with elevated CK, and cTnT was normal in 5/5 patients with normal CK levels (p = 0.005). The mean level of cTnT in patients with elevated CK levels was 0.76 ng/ml (SD 0.12), whereas in patients with normal CK levels, cTnT levels were all below 0.02 ng/ml. The CK level showed strong correlation with the level of cTnT elevation (rho = 0.62, p = 0.001; Figure 1). All patients with elevated cTnT had high CK-MB levels and 12/18 had elevated CK-MB ratio. A strong correlation was observed between CK-MB levels and cTnT levels (rho = 0.56, p = 0.005).

CK and cTnI correlation. CK levels were not associated with cTnI levels (p > 0.5). Of 41 patients in whom simultaneous CK and cTnI levels were assayed, there were 29 with elevated CK and 12 with normal CK. cTnI was elevated in only 1/29 patients with elevated CK, and was normal in 12/12 patients with normal CK. Almost all patients (28/29) with elevated CK had normal cTnI, thus demonstrating no association between CK and cTnI (p > 0.5). The CK level showed no correlation with the cTnI level (rho = 0.06, p > 0.5). In the single patient in whom cTnI and CK were elevated, myocarditis related to severe refractory PM with low left ventricular function was diagnosed. Ninety-seven percent (28/29) of patients with elevated CK had elevated CK-MB and 76% (22/29) had an elevated CK-MB ratio. CK-MB showed no correlation with cTnI (rho = 0.15, p > 0.5).

DISCUSSION

Determinations of cardiac troponins are well established, highly sensitive, and in most clinical situations, specific markers for myocardial infarction. However, we observed that cTnT, but not cTnI, is elevated in IIM and that cTnT is correlated with total CK. cTnT is therefore not a specific marker of myocardial damage in these patients. Our finding is supported by several case reports of elevated cTnT in patients with myopathies with no evidence of cardiac involvement[12-14]. Patients in these studies as well as several patients in our study underwent unnecessary, extensive cardiac evaluations. One observational report showed that cTnT was elevated in 41% of patients with inflammatory muscle disease[20]. The major limitations of previous reports on elevated cTnT in myopathies are their small sample size,

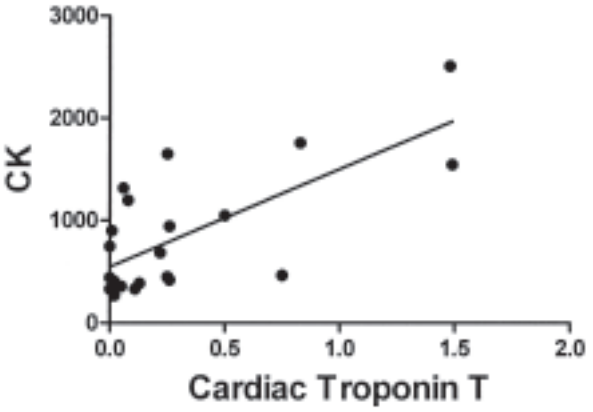

Figure 1. Correlation of creatine kinase (CK, mg/dl) with cardiac troponin T (cTnT, ng/ml).

lack of correlation data, and lack of comparisons with IIM patients with normal levels of CK.

It could be argued that, rather than representing a false-positive elevation in IIM, cTnT actually reveals an unappreciated ischemic or inflammatory cardiomyopathy in patients with IIM. We believe that this explanation is unlikely, however, because patients in our study had no clinical, electrocardiographic, echocardiographic, or angiographic evidence of myocarditis or coronary artery disease even after a median followup of 24.5 months; cTnT levels became undetectable on followup as CK levels normalized; there is no evidence that either cTnT or cTnI is significantly more sensitive than the other for myocardial damage; and because as many as 18 out of 28 patients (64%) in whom cTnT was checked had elevated cTnT, whereas clinically significant myocardial disease is regarded as uncommon[21], and even in the single published autopsy study the rate of myocarditis or coronary artery disease was only 30%[22].

A second potential reason to explain cTnT elevations in patients with IIM without evidence of myocardial muscle injury is cross-reactivity of the commercial cTnT immunoassay with skeletal troponin. However, our institution used third-generation troponin T assays, which are reportedly highly specific for cardiac enzymes and do not cross-react with normal adult skeletal troponin[23]. Finally, a third possibility is the expression of cTnT in regenerating skeletal muscle. We believe that this is the best explanation for the elevated cTnT seen in our IIM patients with elevated CK. Bodor, *et al* showed that skeletal muscle biopsy samples of 8/13 patients with PM and all patients (6/6) with Duchenne muscle dystrophy as well as all fetal skeleton muscle samples from therapeutic abortions were positive for cTnT by immunohistochemistry, whereas only 1/6 normal adult human sample showed (minimal) expression of cTnT[16]. No expression of cTnI was seen in skeletal muscle samples from patients with muscle disease or normal healthy adults or in the aborted fetus[15]. In an observational study, cTnI was not elevated in patients with IIM without clinical evidence of myocardial damage[24]. Similarly, the expression of cTnT mRNA and not cTnI mRNA in muscle biopsy specimens of patients with muscle disease (Duchenne muscle dystrophy) was described by Ricchiuti, *et al*[25]. These studies provide evidence that cTnT is not 100% cardiac-specific, but may be expressed in regenerating skeletal muscle as seen in myopathies as diverse as PM and Duchenne muscle dystrophy. Since cTnT is expressed in fetal skeletal muscle, it is possible that adults lose the expression of cTnT in skeletal muscle but not in cardiac muscle during development, but regain expression of it in skeletal muscle regeneration after severe injury in various muscle diseases. In this respect, cTnT may resemble the B subunit of CK-MB, as both are early developmental forms expressed in all muscles[26].

Our study had a few limitations. First, it was a retrospective study. Second, clinically asymptomatic patients were not routinely evaluated by echocardiography and cardiac angiography for myocarditis or non-ST elevation myocardial infarction. Both myocarditis and coronary artery disease are generally considered not common in patients with IIM[21,22,27,28], although systematic studies of the heart in IIM patients from older literature may not be reliable[21,22]. Given the limited state of knowledge at present, myocarditis and coronary artery disease do not easily explain the cTnT elevation seen in 78% of the patients in our series, all of whom were asymptomatic for myocardial disease.

Our results showed that cTnT was highly associated with CK elevation in IIM, whereas cTnI was not associated with CK elevation. cTnI is the preferred test to evaluate for the presence or absence of myocardial damage in patients with IIM. cTnT may misleadingly suggest the presence of coronary damage, as it is routinely elevated when the CK is elevated. cTnT may prove to be a marker for muscle regeneration in IIM and to be clinically useful in this regard, but further study is needed.

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