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Cardiac Troponin T in Patients With Clinically Suspected Myocarditis

BERNWARD LAUER, MD, CHRISTOPH NIEDERAU, MD,* UWE KÜHL, MD,†
MIRA SCHANNWELL, MD,‡ MATTHIAS PAUSCHINGER, MD,†
BODO-ECKHARD STRAUER, MD, FACC,‡ HEINZ-PETER SCHULTHEISS, MD†

Leipzig, Dusseldorf and Berlin, Germany

Objectives. **The present study investigated whether myocyte injury can be assessed sensitively by measurement of serum levels of cardiac troponin T (cTnT) in patients with clinically suspected myocarditis and whether cTnT levels may predict the results of histologic and immunohistologic analysis of endomyocardial biopsy specimens.**

Background. **Conventionally used laboratory variables often fail to show myocyte injury in patients with clinically suspected myocarditis, possibly because of a low extent of myocardial injury in these patients. Sensitive variables for myocyte injury have not yet been investigated.**

Methods. **Eighty patients with clinically suspected myocarditis were screened for creatine kinase (CK) activity, MB isoform of CK (CK-MB) activity and cTnT. Endomyocardial biopsy specimens were examined histologically and immunohistologically.**

Results. **cTnT was elevated in 28 of 80 patients with clinically suspected myocarditis, CK in 4 and CK-MB in 1. Histologic analysis alone of the endomyocardial biopsy specimen revealed evidence of myocarditis in only five patients, all with elevated cTnT levels. Twenty-three of 28 patients with elevated cTnT levels had histologically negative findings for myocarditis. Additional immunohistologic analysis revealed evidence of myocarditis in 26 (93%) of 28 patients with elevated cTnT levels and in 23 (44%) of 52 patients with normal cTnT levels. Mean cTnT levels were higher in patients with myocarditis proved histologically or immunohistologically, or both, than in patients without myocarditis (0.59 ± 1.68 vs. 0.04 ± 0.05, $p < 0.001$).**

Conclusions. **Measurement of serum levels of cTnT provides evidence of myocyte injury in patients with clinically suspected myocarditis more sensitively than does conventional determination of cardiac enzyme levels. Myocardial cell damage may be present even in the absence of histologic signs of myocarditis. Additional immunohistologic analysis often shows lymphocytic infiltrates in these patients. Elevated levels of cTnT are highly predictive for myocarditis in this group.**

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In patients with clinically suspected myocarditis, laboratory variables conventionally used to detect myocardial cell damage, such as creatine kinase (CK) and creatine kinase MB isoform (CK-MB) levels, are often within the normal range, partly because they are present in normal serum and a small amount of myocardial necrosis does not lead to increases that exceed the normal range. Therefore, the definitive diagnosis of myocarditis has to be established by the demonstration of myocytolysis and lymphocytic infiltrates in endomyocardial biopsy specimens (1–4). For clinical and also economic reasons it would be desirable to find a noninvasive screening variable to determine in patients with clinically suspected myocarditis whether myocardial cell damage is present and endomyocardial biopsy should be performed. Recently, a new and very sensitive assay has been developed to detect cardiac troponin T (cTnT) in the serum (5). CTnT is unique to cardiac tissue (6,7). Using monoclonal antibodies specific for the cardiac isoform of troponin T, a highly specific one-step double-monoclonal sandwich assay has been established that shows very low cross-reactivity with skeletal troponin T (8). In healthy volunteers, levels of circulating cTnT are nearly always below the detection limit of the assay (9). In patients with unstable angina pectoris, measurement of cTnT has proved to be more sensitive than measurement of CK levels for the diagnosis of myocardial injury, and increased serum levels of cTnT can be used as a prognostic factor in these patients (10). The present study investigates whether measurement of serum levels of cTnT can sensitively provide evidence of myocardial cell damage in patients with clinically suspected myocarditis and whether increased levels of cTnT correlate with histologic and immunohistologic findings in endomyocardial biopsy specimens.

From the Herzzentrum Leipzig, Universitätsklinik für Kardiologie, Leipzig; *Diabetes-Forschungsinstitut, Universität Düsseldorf, Dusseldorf; †Universitätsklinikum Benjamin Franklin, Abteilung Kardiologie, Berlin; and ‡Medizinische Klinik und Poliklinik B, Abteilung für Kardiologie, Pneumologie und Angiologie, Dusseldorf, Germany.

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Address for correspondence: Dr. Bernward Lauer, Herzzentrum Leipzig, University Hospital, Department of Cardiology, Russenstrasse 19, D-04289 Leipzig, Germany. E-mail: e.und.b.lauer@t-online.de.

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Abbreviations and Acronyms

CK	=	creatine kinase
CK-MB	=	MB isoform of creatine kinase
cTnT	=	cardiac troponin T
cTnT+ patients	=	patients with elevated serum levels of cardiac troponin T
cTnT− patients	=	patients without elevated serum levels of cardiac troponin T
MHC	=	major histocompatibility complex

Methods

Patient selection. Eighty patients with clinically suspected myocarditis were enrolled in the study (52 men, 28 women [mean age 49 ± 14 years, range 12 to 85]). The diagnosis of myocarditis was suspected because of the patients' history and symptoms and the clinical investigation. The patients were examined by using invasive and noninvasive techniques including physical examination, routine laboratory tests, electrocardiography, exercise electrocardiography, echocardiography, right and left heart catheterization, coronary angiography, left ventriculography and right heart myocardial biopsy.

Analysis of endomyocardial biopsy specimens. Endomyocardial biopsy specimens were taken transvenously through the femoral approach from the right heart side of the intraventricular septum. From each patient, several specimens (at least five) were analyzed. Analysis was performed in blinded fashion by persons unaware of patient data and history. The endomyocardial specimens were examined histologically according to the Dallas criteria (1) and, additionally, immunohistologic methods were applied (4,11). The histologic sections were analyzed by light microscopy for evidence of myocardial necrosis, interstitial fibrosis and the presence of lymphocytic infiltrates (1). As the histologic evaluation of myocardial biopsy specimens is known to be difficult and affected by many problems (2,3,12) including high interobserver variability (13) and sampling error (14), the biopsy specimens were therefore examined additionally with immunohistologic techniques using various monoclonal antibodies. Antibodies directed against surface antigens of human lymphocytes (CD3, CD4, CD8) were used to detect and quantitate lymphocytic cells in myocardial tissue (4,11,15–18). Cell numbers are expressed as the mean value of ≥10 counted high power fields (magnification ×400), each equivalent to 0.28 mm^3. Additionally, using antibodies against the major histocompatibility complex (MHC) antigens, the expression of MHC I and II antigens was analyzed. With these techniques, the diagnostic accuracy in the biopsy specimens could be increased (18) and the interobserver variability minimized (4,11).

The biopsy specimens were classified as showing "acute myocarditis" when histologic sections of the specimens revealed lymphocytic infiltrates in the neighborhood of myocardial necrosis (1). *Borderline myocarditis* was diagnosed when lymphocytic infiltrates were present in histologic sections without myocyte necrosis (1). When the immunohistologic examination revealed >2.0 lymphocytes/high power field (equivalent to >7.0 cells/mm^3) (19) and increased expression of MHC I and II antigens, the biopsy specimen was considered to show a generalized activated inflammatory process of the myocardium and was therefore classified as showing *lymphocytic myocarditis*. When neither the histologic nor the immunohistologic analysis revealed myocytolysis or lymphocytic infiltrates, the biopsy specimens were classified as showing *no myocarditis.*

Measurement of cTnT, CK and CK-MB. Blood samples were drawn at admission into tubes with no preservatives and centrifuged at 2,000 × *g* for 15 min. Serum was stored at −70°C, thawed once and assayed in batches. All assays were performed in blinded fashion by a staff member who was unaware of patient data and history. CTnT was measured with a one-step double-monoclonal sandwich immunoassay (Boehringer Mannheim, Mannheim, Germany) using two different monoclonal antibodies specific for cTnT that recognize different epitopes. The lower detection limit of the assay is stated by the manufacturer as 0.04 ng/ml, although some investigators (20) have shown the limit to be 0.015 ng/ml. The reference range for cTnT is 0 to 0.1 ng/ml as stated by the manufacturer; therefore, in the present study, levels >0.1 ng/ml were considered elevated. CK and CK-MB activity levels were measured by using routine laboratory assay (upper reference limit 80 U/liter for CK activity and 10 U/liter for CK-MB activity (21,22).

Statistical analysis. All results were expressed as mean value ± SD, except when stated otherwise. CTnT values of the groups with and without myocarditis were analyzed with the Mann-Whitney *U* test. Nominal or ordinal values were compared by Fisher exact test (two-tailed) or chi-square test. Continuous variables were analyzed by unpaired *t* test. Correlation between lymphocyte density and cTnT levels in patients with myocarditis was calculated by using the Spearman rank correlation. A p value < 0.05 was considered to indicate statistical significance.

Results

Levels of cTnT in patients with clinically suspected myocarditis. The serum cTnT levels of 80 patients with clinically suspected myocarditis are shown in Figure 1. Elevated levels of cTnT could be detected in 28 (35%) of 80 serum samples; cTnT levels were undetectable or <0.1 ng/ml in 52 (65%) serum samples.

Among patients with elevated cTnT levels (cTnT+ patients), myocarditis was diagnosed (histologically or immunohistologically, or both) in 26 patients (93%); in 2 patients (7%) the endomyocardial biopsy specimen was negative for myocarditis (Fig. 1). In patients with normal cTnT levels (cTnT− patients), evidence (histologic or immunohistologic, or both) for myocarditis in the biopsy specimen was found in 23 patients (44%); in 29 patients (56%), the specimens showed no sign of myocarditis. Mean cTnT levels were higher in patients with histologically or immunohistologically proved myocarditis than in patients without myocarditis (0.59 ± 1.68 vs. 0.04 ± 0.05,

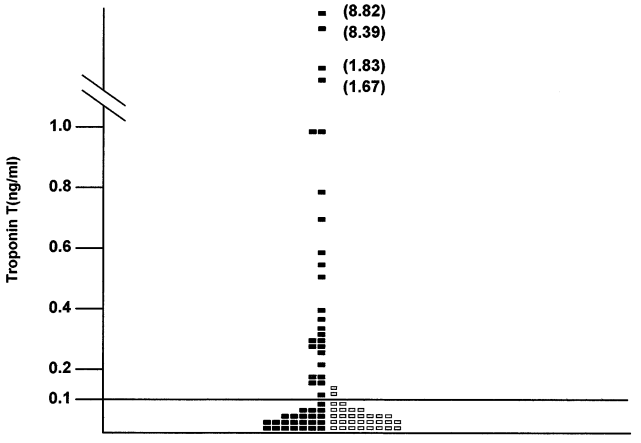

Figure 1. Serum levels of cTnT in 80 patients with clinically suspected myocarditis. **Solid squares** = patients with histologically or immunohistologically diagnosed myocarditis; **open squares** = patients whose endomyocardial biopsy failed to show evidence of myocarditis; **horizontal line** = threshold for elevated cTnT levels.

$p < 0.001$). The sensitivity of the cTnT assay for the detection of myocarditis (histologically or immunohistologically, or both) was 53%, the specificity 94%, the positive predictive value 93%, the negative predictive value 56% and the effectiveness 69%.

Histologic and immunohistologic analysis of endomyocardial biopsy specimens. Separate histologic and immunohistologic analyses of the endomyocardial biopsy specimens are shown in Table 1. Histologically, evidence for acute myocarditis was present in 1 (1.2%) of 80 patients, and evidence for borderline myocarditis in 4 (5%) of 80 patients. In 75 (94%) of 80 patients histologic examination of the endomyocardial biopsy specimen did not demonstrate evidence for myocarditis. All five patients with histologically diagnosed acute or borderline myocarditis had elevated serum levels of cTnT (Table 1). However, elevated cTnT levels were also found in 23 (31%) of the 75 patients, in whom histologic analysis of the biopsy specimen was negative for myocarditis. All cTnT− patients had normal findings on histologic analysis of the biopsy specimens. The sensitivity of the cTnT assay for the histologic detection of myocarditis was 100%, the specificity 69%, the positive predictive value 18%, the negative predictive value 100% and the effectiveness 71%.

Immunohistologic analysis of the endomyocardial biopsy specimen showed lymphocytic myocarditis in 49 patients (61%) and revealed no evidence for myocarditis in 31 patients (39%) (Table 1). All patients in whom histologic study showed evidence for acute or borderline myocarditis were also considered to have lymphocytic myocarditis by immunohistologic analysis. Among the 28 cTnT+ patients, immunohistologic analysis of the endomyocardial biopsy specimens showed lymphocytic myocarditis in 26 patients (93%) and no myocarditis in 2 (7%). Among the 52 CTnT− patients, immunohistologic evidence of lymphocytic myocarditis was found in 44% (23 patients) whereas 56% (29 patients) had no evidence for myocarditis (Table 1). The sensitivity of the cTnT assay for the immunohistologic detection of myocarditis was 53%, the specificity 94%, the positive predictive value 93%, the negative predictive value 56% and the effectiveness 69%.

Table 1. Histologic and Immunohistologic Findings in 80 Patients With Clinically Suspected Myocarditis With and Without Elevated Levels of Cardiac Troponin T

	cTnT+ (n = 28)	cTnT− (n = 52)
Histologic findings		
Acute myocarditis (n = 1)	1 (1.25%)	0 (0%)
Borderline myocarditis (n = 4)	4 (6%)	0 (0%)
No myocarditis (n = 75)	23 (29%)	52 (65%)
Immunohistologic findings		
Lymphocytic myocarditis (n = 49)	26 (32.5%)	23 (29%)
No myocarditis (n = 31)	2 (2.5%)	29 (36%)

Data presented are number (%) of the total group of 80 patients. cTnT+ = elevated cardiac troponin T; cTnt− = no elevated cardiac troponin T.

Clinical data of patients with myocarditis. The clinical data and the results of diagnostic procedures of the patients with myocarditis in the cTnT+ and cTnT− groups are given in Table 2. The number of patients with recent onset of symptoms (<1 month) was greater in cTnT+ than in cTnT− in patients ($p < 0.030$). The frequency of the various clinical symptoms was equal in both groups. CK levels were elevated in four cTnT+ patients (maximal level 682 U/liter); CK-MB levels were elevated in one cTnT+ patient (68 U/liter). In cTnT− patients, CK and CK-MB were always within the normal range ($p = 0.112$ and 1.000, respectively). These levels exclude extensive skeletal muscle injury in the study patients. Impaired renal function (creatinine >1.2 mg/dl) was found in five cTnT+ patients and four cTnT− patients ($p < 0.763$). CTnT+ and cTnT− patients did not differ in the frequency of atrial fibrillation, premature supraventricular beats, premature ventricular beats, bundle branch block or ST segment alterations, as analyzed by electrocardiography and Holter electrocardiography. Echocardiography disclosed disturbed left ventricular function in ~50% of patients in both groups; pericardial effusion was present more often in cTnT+ patients ($p < 0.024$). Hemodynamic variables at rest during ventriculography (ejection fraction, end-diastolic volume, end-systolic volume, stroke volume) were not different between cTnT+ and cTnT− patients. The number of lymphocytes detected immunohistologically was not different between cTnT+ and cTnT− patients. There was no correlation between lymphocyte density and cTnT levels (correlation coefficient [r] = 0.0858, $p < 0.575$).

Discussion

Significance of cTnT, CK and CK-MB in Patients With Clinically Suspected Myocarditis. The present study shows that measurement of serum levels of cTnT can often provide evidence of ongoing myocardial cell damage in patients with clinically suspected myocarditis when conventionally used laboratory variables such as CK or CK-MB are within the normal

Table 2. Clinical Data of 49 Patients With Myocarditis With and Without Elevated Levels of Cardiac Troponin T

	cTnT+ (n = 26)	cTnT− (n = 23)	p Value
Age (yr)	52 ± 17 (12–86)	44 ± 12 (22–60)	0.065
Male/female	19/7	17/6	0.811
Symptoms			
Duration <1 mo	11	3	0.030
Duration >1 mo	15	20	0.030
Angina pectoris	11	10	0.934
Dyspnea	18	19	0.333
Palpitation or pulse irregularities	7	6	0.947
Others	0		0.096
NYHA class			
I	5	1	0.194
II	10	9	0.961
III	5	7	0.363
IV	6	6	0.807
Mean ± SD	2.46 ± 1.07	2.78 ± 0.90	0.265
Laboratory findings			
CK >70 U/liter	4	0	0.112
CK-MB >10 U/liter	1	0	1.000
Creatinine >1.2 mg/dl	5	4	0.762
Electrocardiographic changes			
Absolute arrhythmia	12	6	0.146
Premature supraventricular beats	11	6	0.234
Premature ventricular beats	19	20	0.299
Atrioventricular block	4	6	0.482
Bundle branch block	11	6	0.234
ST segment changes	15	18	0.143
Echocardiographic changes			
Left ventricular dysfunction	14	19	0.132
Pericardial effusion	6	0	0.024
Left ventriculographic variables	(n = 14)	(n = 18)	
Ejection fraction	55 ± 22 (22–85)	49 ± 19 (18–73)	0.474
Stroke volume	121 ± 73 (61–312)	111 ± 37 (65–198)	0.621
Stroke volume index	65 ± 44 (33–199)	58 ± 19 (36–94)	0.585
End-diastolic volume	238 ± 127 (104–466)	251 ± 113 (137–625)	0.759
End-diastolic volume index	127 ± 74 (60–296)	132 ± 56 (70–308)	0.820
End-systolic volume	117 ± 90 (25–335)	140 ± 118 (49–515)	0.550
End-systolic volume index	62 ± 49 (11–184)	73 ± 59 (27–253)	0.567
Immunohistologic analysis			
Lymphocytes/high power field	7.4 ± 10.0	5.7 ± 6.8	0.497

Data presented are mean value ± SD (range) or number of patients. CK = creatine kinase; CK-MB = MB isoform of creatine kinase; NYHA class = New York Heart Association functional class; other abbreviations as in Table 1.

range. Among patients with histologically or immunohistologically diagnosed myocarditis, cTnT levels were elevated in 53%, whereas CK and CK-MB levels were increased in only 8% and 2%, respectively. As the half-life of cTnT in the serum is ~2 h (23), the elevated levels of cTnT reflect truly ongoing myocardial cell damage rather than merely recent myocyte injury. These results demonstrate a higher sensitivity of the cTnT assay for the detection of myocardial cell damage than that of other cardiac enzyme determinations (23,24).

As part of the troponin complex, Troponin T is a 37-kDa protein (25) that is responsible for the binding of the troponin complex to tropomyosin (26). Several isoforms of troponin T have been described, including a specific cardiac isoform that is normally not expressed in other tissues (6,7). CTnT is normally hardly detectable in the serum of healthy persons (9). Elevated serum levels of cTnT are found to be a sensitive and specific indicator for myocardial cell damage (8). In patients with acute myocardial infarction, measurement of cTnT levels provides better diagnostic efficiency for the detection of myocardial cell necrosis than that of other conventionally used cardiac enzyme measurements (23). In unstable angina pectoris, elevated serum levels of cTnT are a more sensitive than CK as a marker for myocardial cell damage, and such findings may be used as a prognostic indicator in these patients (10). Serum levels of cTnT can be used as a sensitive and specific test for the detection of perioperative myocardial infarction in patients

undergoing coronary artery bypass surgery (27), to detect occlusions of small side branch arteries during percutaneous coronary angioplasty (24) and to show myocardial involvement in patients with polymyositis/dermatomyositis (28).

cTnT and results of endomyocardial biopsy. When elevated cTnT levels were detected in patients with clinically suspected myocarditis, histologic and immunohistologic analysis of the endomyocardial biopsy specimen showed evidence of myocarditis in 93%. Thus, elevated cTnT levels were highly predictive for myocarditis in these patients. In two cTnT+ patients the endomyocardial biopsy did not reveal evidence for myocarditis. Possibly because of sampling error the lymphocytic infiltrates may have escaped histologic and immunohistologic detection in these patients (14). However, antimyosin scintigraphy with monoclonal antibodies against the cardiac myosin heavy chain showed that in some patients the radiopharmacon is not evenly distributed over the myocardium. This finding indicates a more focal nature of the disease in these patients (29–31). Because the endomyocardial biopsy specimens in our study patients were always taken from the right heart side of the interventricular septum, a focal myocarditic process in other regions of the heart might have been missed in these specimens. Nevertheless, ongoing myocardial damage in these patients could lead to increased serum levels of cTnT. Finally, other causes of myocyte injury, such as subendocardial ischemia in acutely dilated cardiomyopathy or toxins, cannot be ruled out as the source of elevated cTnT levels.

Evidence of myocarditis was also found in 48% of cTnT− patients, indicating a lower extent of myocardial damage in these patients. cTnT− patients had a longer duration of symptoms before they underwent measurement of cTnT levels and endomyocardial biopsy. It cannot be ruled out that in the course of the disease, autoantibodies against cTnT may have developed that might have interfered with the ELISA method employed to quantify circulating cTnT. In contrast, it is possible that cTnT+ patients had a more active inflammatory process than cTnT− patients, and that this greater activity led to increased myocardial damage; however, the extent of lymphocytic infiltrates was not different between cTnT+ and cTnT− patients. Another possible explanation is that the difference in cTnT levels may be due to different pathogenetic mechanisms of the disease in patients with myocarditis. With the use of in-situ hybridization or the polymerase chain reaction, viral ribonucleic acid (RNA) has been detected in the myocardium of some patients with myocarditis (32,33). In these patients the viral infection is discussed as the pathogenetic mechanism of their myocardial inflammation. Other studies (34–38) detected autoantibodies against various cardiac structures in patients with myocarditis.

Histologic and immunohistologic analysis of endomyocardial biopsy specimens. In the present study, histologic examination alone of the biopsy specimen revealed acute or borderline myocarditis in 6.3% of patients with clinically suspected myocarditis. In the Myocarditis Treatment Trial (39), acute myocarditis was diagnosed histologically in 10% of patients with clinically suspected myocarditis. However, histologic analysis of the biopsy specimen was negative in 21 of 26 cTnT+ patients, indicating ongoing myocyte damage. These observations indicate that histologic analysis of the biopsy specimen according to the Dallas criteria (1) may be a rather insensitive diagnostic procedure for the detection of myocarditis.

The Dallas classification for the diagnosis of acute myocarditis was initially established for various reasons by a group of outstanding pathologists. The goals were 1) to produce a morphologic definition of myocarditis, 2) to develop histologic criteria for the diagnosis of myocarditis, 3) to establish a simple reproducible working classification, 4) to outline the problems and pitfalls of establishing the diagnosis of myocarditis, 5) to assess the applicability and reproducibility of the classification system itself, and 6) to make this information available to other pathologists and clinicians (1,2). However, as these pathologists have emphasized, the Dallas criteria were not meant to establish a definite diagnosis of myocarditis and should not be misunderstood and misinterpreted as a "conditio sine qua non" of this diagnosis (2). Therefore, the present study used the Dallas criteria (13) and additionally immunohistologic techniques for the detection of lymphocytic infiltrates (11,15–18) and an increased expression of MHC I and II antigens. With these techniques, the diagnostic accuracy could be increased (18) and the interobserver variability minimized (11). Immunohistologic analysis revealed lymphocytic infiltrates and increased expression of MHC I and II antigens in 93% of cTnT+ patients with clinically suspected myocarditis. This finding indicates that immunohistologic analysis may be a better diagnostic tool than histologic examination alone for the detection of myocarditis associated with myocardial cell damage. We believe that the immunohistologic detection of lymphocytes in the myocardium together with increased expression of MHC I and II antigens as a marker for an activated immunologic process allows the classification of these patients as having lymphocytic myocarditis even in the absence of histologically detectable myocyte necrosis.

The present results show that measurement of serum levels of cTnT can provide evidence of myocardial cell damage in patients with clinically suspected myocarditis more effectively than can conventionally used cardiac enzyme determinations. Myocardial cell damage may be present even in the absence of histologic evidence of myocarditis. In these patients, additional immunohistologic analysis of the endomyocardial biopsy specimen often reveals lymphocytic infiltrates and an increased expression of human leukocyte antigens (HLA) antigens indicating myocardial inflammation. In patients with clinically suspected myocarditis, elevated cTnT levels are highly predictive for myocarditis.

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