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Biomarkers

Elevation of Cardiac Troponin T, But Not Cardiac Troponin I, in Patients With Neuromuscular Diseases

Implications for the Diagnosis of Myocardial Infarction

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Objectives This study sought to determine the clinical and biological significance of elevated cardiac troponin T (cTnT) in patients with neuromuscular diseases.

Background Practice guidelines regard cTnT and cardiac troponin I (cTnI) as equally sensitive and specific for the diagnosis of myocardial injury. Although cTnI is unique to myocardium, cTnT can be re-expressed in skeletal muscle in response to injury. The commercial cTnT assay is claimed to be cardiac specific.

Methods Fifty-two patients with 20 different types of acquired and inherited neuromuscular diseases underwent full clinical assessment, cardiac investigations, and measurements of serum cTnT, cTnI, creatine kinase (CK), creatine kinase myocardial band (CK-MB), and N-terminal pro-B–type natriuretic peptide (NT-proBNP).

Results Serial measurements (265 samples) in 25 initially hospitalized patients taken during a mean of 2.4 years showed persistent elevation of cTnT (median: 0.08 μg/l; interquartile range: 0.06 to 0.14 μg/l), CK (582 U/l; 303 to 3,662 U/l), and CK-MB (24 μg/l; 8 to 34 μg/l). In contrast, cTnI, measured using 2 sensitive assays, was persistently normal throughout the study in 22 patients. Electrocardiograms (ECGs) and echocardiograms were normal in 16 and 17 patients, respectively, and no serial changes were observed. Therapeutic interventions in patients with reversible myopathies normalized cTnT, CK, and CK-MB in unison. Single measurements in 27 ambulatory patients showed elevated CK (953 U/l; 562 to 1,320 U/l), CK-MB (18 μg/l; 11 to 28 μg/l), and cTnT (0.03 μg/l; 0.02 to 0.05 μg/l) in 21, 22, and 18 patients respectively. cTnI was abnormal in only 1 patient. NT-proBNP (41 pg/ml; 35 to 97 pg/ml) was normal in all but 2 patients. ECGs were normal in 15 patients. No patients with elevated cTnT, but with normal cTnI, had any cardiovascular events in either group during follow-up.

Conclusions Patients with a wide spectrum of neuromuscular diseases commonly have persistent elevation of cTnT and CK-MB in the absence of clinical and cTnI evidence of myocardial injury. Re-expressed cTnT in diseased skeletal muscle appears to be the source of the elevated cTnT detected in the circulation of these patients. (J Am Coll Cardiol 2014;63:2411–20) © 2014 by the American College of Cardiology Foundation

Troponin is a regulatory protein complex located on the thin filament of striated muscles. It consists of 3 subunits: C, I, and T. Troponins I and T have 3 isoforms, each controlled by different genes; 1 is cardiac and the other 2 are slow skeletal and fast skeletal isoforms. Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) have become the biomarkers of choice for the diagnosis of acute myocardial infarction (AMI), superceding the creatine kinase myocardial band (CK-MB) (1–3). Elevation of either marker in the circulation is generally interpreted as indicative of myocardial necrosis. The third edition of the universal definition of myocardial infarction (4), endorsed by the European Society of Cardiology, the American Heart Association, the American College of Cardiology Foundation, and the World Heart Federation, re-emphasizes the preeminent diagnostic role of cardiac troponins and makes no distinction between cTnT and cTnI. Similarly, the recent American College of Cardiology Foundation recommendations on the interpretation of elevated cardiac troponins assume that the 2 biomarkers have equivalent diagnostic accuracy for myocardial injury (5).

Our clinical experience with patients with neuromuscular diseases led us to question the cardiac specificity of the commercial cTnT immunoassay. We observed that these patients commonly have elevated cTnT without any clinically apparent evidence of myocardial injury. Although

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Abbreviations and Acronyms

AMI = acute myocardial infarction
BMD = Becker muscular dystrophy
CK = creatine kinase
CK-MB = creatine kinase myocardial band
cTnI = cardiac troponin I
cTnT = cardiac troponin T
DMD = Duchenne muscular dystrophy
ECG = electrocardiogram
FA = Friedreich ataxia
hs-cTnT = high-sensitivity cardiac troponin T
IBM = inclusion body myositis
LGMD = limb girdle muscular dystrophy
MG = myasthenia gravis
MyoD = myotonic dystrophy
NT-proBNP = N-terminal pro-B–type natriuretic peptide

cTnT and cTnI are both absent in healthy adult skeletal muscle, cTnT, but not cTnI, is present in fetal skeletal muscle (6–9). When skeletal muscle is injured, it repairs itself by regeneration, a process that recapitulates embryonic myogenesis (10,11). Regenerating skeletal muscle thus re-expresses fetal isoforms of cTnT (12–15) and also CK-MB (16–18). In contrast, cTnI has not been shown to be expressed in skeletal muscle at any point of development (6). One study reported the mRNA, but not the protein, of cTnI in the skeletal muscle of patients with Duchenne muscular dystrophy (DMD) (19). It is not known whether these biological differences have any significant clinical implications. We studied the behavior of cTnT and cTnI in the circulation of patients with several different types of inherited and acquired neuromuscular diseases. We use the term "neuromuscular disease" to cover both primary myopathies and muscle diseases secondary to nerve disorders.

Methods

Patients. The study started in 2005 when we observed persistent elevation of cTnT and CK in patients with skeletal muscle diseases. The first group consisted of 25 hospitalized patients (ages 58 ± 17 years; range: 17 to 87 years) admitted urgently to Wirral University Teaching Hospital under the care of 1 cardiologist (D.R.). The hospital uses both cTnT and CK routinely for the assessment of patients suspected of having acute coronary syndromes.

Of these 25 patients, 13 had previously established diagnoses of neuromuscular diseases (3 facioscapulo humeral muscle dystrophy, 2 polymyositis, 2 motor neurone disease, 2 paroxysmal rhabdomyolysis, 1 inclusion body myositis [IBM], 1 muscle sarcoma, 1 myotonic dystrophy [MyoD], 1 periodic hypokalemic paralysis). The other 12 patients received new diagnoses of skeletal myopathies (3 statin-induced, 2 alcohol-induced, 1 inflammatory, 1 hypothyroid, 1 cocaine-induced, and 4 subclinical, presumed inflammatory) during the course of this study.

To validate the findings in the hospitalized group, we studied a second group consisting of 27 unselected ambulatory patients with different types of neuromuscular diseases under routine follow-up in either a neuromuscular (n = 19) or cardiology (n = 8) outpatient clinic. The clinical characteristics of these 2 groups of patients are shown in Table 1.

All patients underwent full clinical assessment and routine blood tests consisting of full blood count, electrolytes, renal function, liver function, and thyroid function. Cardiac investigations in hospitalized patients comprised serial ECGs, echocardiograms, and when clinically indicated, cardiac catheterization studies (coronary angiography, left ventriculography, and pressure measurements). Serial measurements of serum CK, CK-MB, cTnT, cTnI, and N-terminal pro-B–type natriuretic peptide (NT-proBNP) were performed while in hospital and also after discharge to the outpatient clinic. ECG and echocardiography were also repeated in the clinic at 4 to 6 monthly intervals. Ambulatory patients had single measurements of these biomakers in addition to ECGs and echocardiograms. The study was approved by the local research ethics committee, and patients gave written informed consent.

Cardiac troponin immunoassays. Roche Diagnostics (Indiana, Indianapolis) is the sole manufacturer of cTnT assays. Serum cTnT was measured initially using the standard third- and fourth-generation assays, and subsequently by the high-sensitivity (hs-cTnT) assay when it became commercially available. The standard assay has a limit of detection of 0.01 μg/l, a 99th percentile of <0.01 μg/l, and a coefficient of variation of 10% at 0.03 μg/l. The corresponding values for the hs-cTnT assay are 0.005, 0.014, and 0.013 μg/l (20).

Serum cTnI was measured using 2 immunoassays, Siemens cTnI-Ultra (Siemens Corporation, Washington, DC) and Roche troponin I. The cTnI-Ultra assay has a limit of detection of 0.006 μg/l, a 99th percentile of 0.04 μg/l, and a 10% coefficient of variation at 0.03 μg/l. The corresponding values for the Roche I assay are 0.10, 0.16, and 0.30 μg/l, as obtained from the manufacturer's package insert.

To ascertain that the cTnI-Ultra assay is at least as sensitive as the conventional cTnT assay for the detection of relatively minor myocardial injury, serum samples with low concentrations of cTnT (median cTnT 0.14 μg/l; interquartile range 0.06 to 0.33) from 32 randomly selected patients with unequivocal AMI were analyzed. cTnI-Ultra was elevated (>0.04 μg/l) in 31 patients. One patient with cTnT of 0.03 μg/l had a cTnI-Ultra of 0.02 μg/l. Regression analysis yielded the following relationship: cTnI-Ultra = 13.32 cTnT − 0.70 ($r = 0.89$, $p < 0.0001$).

Serum CK-MB and NT-proBNP concentrations were measured using Roche Diagnostics immunoassays. CK was considered normal if <170 U/l in women and <200 U/l in men.

All assays were performed according to the manufacturers' instructions by experienced laboratory personnel blinded to the study.

Statistical analysis. Continuous variables are reported as medians with interquartile ranges or as means with SDs.

Results

Hospitalized patients (n = 25). Table 2 summarizes the clinical presentation and results of investigations of the