

Cardiac Troponin I

A Marker With High Specificity for Cardiac Injury

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Background. Levels of MBCK can be increased in patients with skeletal muscle injury or renal failure in the absence of myocardial injury, causing diagnostic confusion. This study was designed to determine whether measurement of cardiac troponin I (cTnI), a myocardial regulatory protein with comparable sensitivity to MBCK, has sufficient specificity to clarify the etiology of MBCK elevations in patients with acute or chronic skeletal muscle disease or renal failure.

Methods and Results. Of the patients ($n=215$) studied, 37 had acute skeletal muscle injury, 10 had chronic muscle disease, nine were marathon runners, and 159 were chronic dialysis patients. Patients were evaluated clinically, by ECG, and by two-dimensional echocardiography. Total creatine kinase (normal, <170 IU/L) was determined spectrophotometrically, and cTnI (normal, <3.1 ng/mL) and MBCK (normal, <6.7 ng/mL) were determined with specific monoclonal antibodies. Values above the upper reference limit were considered "elevated." Elevations of total creatine kinase were common, and elevations of MBCK occurred in 59% of patients with acute muscle injury, 78% of patients with chronic muscle disease and marathon runners, and 3.8% of patients with chronic renal failure. Some of the patients were critically ill; five patients were found to have had myocardial infarctions and one had a myocardial contusion. cTnI was elevated only in these patients.

Conclusions. Elevations of cTnI are highly specific for myocardial injury. Use of cTnI should facilitate distinguishing whether elevations of MBCK are due to myocardial or skeletal muscle injury. (*Circulation* 1993;88:101-106)

KEY WORDS • cardiac troponin I • creatine kinase

Patients with elevations of total creatine kinase (CK) caused by skeletal muscle injury often manifest elevations of MBCK, which can cause diagnostic confusion.¹⁻⁴ These patients generally have chronic or severe acute skeletal muscle injury but also may be at risk for myocardial injury either directly as a consequence of the process affecting skeletal muscle or because of an independent cardiac abnormality. Increases in MBCK also occur in 5% of patients with chronic renal failure, probably as a consequence of skeletal myopathy.⁵ Determining whether elevations of MBCK reflect skeletal muscle or myocardial damage is essential for proper patient management but is often difficult. The percentage of MBCK with respect to total CK has poor sensitivity for the detection of myocardial damage; eg, individuals with autopsy-proven myocardial contusion often have a very low percentage (1%) of MBCK with respect to total CK, and noninvasive tests may not be as sensitive as enzyme determinations.⁶

Furthermore, the percentage of total CK composed of MBCK increases in regenerating skeletal muscle.⁷ Thus, a sensitive and highly specific marker of myocardial injury would be of substantial clinical value in patients with skeletal muscle disease.

Troponin I, C, and T form a complex that regulates the calcium-modulated interaction of actin and myosin in striated muscle. Troponin I from cardiac muscle and slow- and fast-twitch skeletal muscle are products of different genes with unique amino acid sequences.⁸⁻¹⁰ Thus, recently developed monoclonal antibodies to cardiac troponin I (cTnI) have no cross-reactivity with the skeletal muscle forms.¹¹ Furthermore, initial studies suggest that measurement of cTnI has sensitivity comparable to MBCK for the diagnosis of myocardial infarction, with elevations present for a longer period of time (up to at least 1 week).¹¹⁻¹³ Accordingly, a large cohort of patients with skeletal muscle injury were studied to determine whether increases of cTnI could be used to distinguish elevations of MBCK caused by skeletal muscle injury from those caused by acute myocardial injury.

Methods

Patients

A total of 215 subjects were studied. Fifty-six subjects had documented skeletal muscle injury: Thirty-seven had acute muscle injury (trauma, rhabdomyolysis, etc), 10 had chronic myopathy, and nine had acute muscle injury related to extreme exertion (ie, running a mara-

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TABLE 1. Clinical Characteristics of Patients Studied

	Acute muscle disease (n=37)	Chronic muscle disease (n=10)	Marathon runners (n=9)	Chronic renal failure (n=159)
Age (years, mean±SD)	38.8±13.9	27.1±15.4	41.1±16.0	60.6±1.5
Race				
White	14	6	9	34
Black	23	4		125
Sex				
Female	12	4	5	87
Male	25	6	4	72
Diagnoses	Trauma, 24 Rhabdomyolysis, 7 Other, 6	Polymyositis, 4 Duchenne's, 3 Idiopathic myopathy, 3		Hemodialysis, 145 Peritoneal dialysis, 14

thon). A cohort of patients with chronic renal failure requiring dialysis (n=159) was also evaluated. Acute muscle injury was defined by the presence of total CK activity >1700 IU/L. At this level in our laboratory, dilution is required, and the sample value is identified by the Barnes Hospital clinical laboratory computer. Patients with a plasma level of total CK >1700 IU/L have been found in other studies to have severe muscle injury.¹⁴ Patients with chronic skeletal myopathy and chronic renal failure were identified through their usual source of care at Barnes Hospital. Patients with acute and chronic muscle injury were excluded if before entering the study protocol they were known to have had a recent myocardial infarction, cardiomyopathy, left bundle branch block, or serious concomitant disease other than myopathy or if an adequate echocardiogram could not be obtained. Because it is frequently difficult to diagnose cardiac damage in such patients by noninvasive means, we anticipated that some patients with cardiac damage (myocardial infarction or contusion) as detected by echocardiography would be enrolled.^{15,16} Marathon runners consisted of four men and five women who participated in the 1991 Twin Cities Marathon, Minneapolis, Minn. None had a known cardiac abnormality and each had been running marathons for 5 to 10 years. All subjects gave informed consent. The protocol was approved by the Human Studies Committees of the Washington University School of Medicine and the Hennepin County Medical Center.

Clinical Evaluations

All patients except the marathon runners had a clinical evaluation (history, physical examination, and ECG review). Physicians performing the clinical examinations were blinded to the results of the echocardiograms and the levels of the molecular markers. Two-dimensional echocardiograms were performed on all patients with acute muscle injury and chronic myopathy as well as those chronic renal failure patients with elevations of either MBCK or cTnI. Echocardiograms were performed with a Hewlett-Packard 77600 ultrasound imaging system using either a 2.5- or 3.5-MHz transducer. Two-dimensional echocardiographic images were obtained in the parasternal short- and long-axis views, the apical two- and four-chamber views, and the subcostal view as recommended by the American Society of Echocardiography.¹⁷ All echocardiograms were

interpreted by a single physician expert in this technique who was blinded to clinical information (V.G.D.-R.). Patients with regional wall motion abnormalities on their initial echocardiogram had follow-up studies. Four patients had inadequate echocardiograms and were excluded from further analysis. When skeletal muscle injury is present, echocardiography is considered the method of choice to determine the presence or absence of concomitant cardiac injury.^{15,16} Accordingly, for this study, the presence of regional wall motion abnormalities detected by echocardiography was used as the "gold standard" for the presence of myocardial damage.

Evaluations of Molecular Markers

Blood was obtained for measurement of total CK, MBCK, and cTnI. Serial samples were obtained in all patients with acute muscle disease. Patients with chronic muscle disease and chronic renal failure had one sample obtained at the time of enrollment, whereas runners were sampled before the race and then on days 1, 2, 3, and 10 after the marathon.

Samples were processed as previously described for optimum preservation, stored at -70°C, then thawed once and assayed in batches; total CK, MBCK, and cTnI are stable when handled in this manner.^{11,18,19} Assays of CK, MBCK, and cTnI as well as decisions concerning which values were normal or abnormal were performed by individuals blinded to the clinical and echocardiographic data.

Total CK activity (normal, ≤220 IU/L; lower limit of detectability, 25 IU/L) was measured on an Olympus AU-5000 or a Flexigem centrifugal analyzer (Electro-Nucleonics, Inc) with a kinetic enzymatic method as previously described.¹⁹ Total CK activity for the marathon runners was performed on a Cobes Bio analyzer (normal, <170 IU/L) using a similar kinetic enzymatic method.

MBCK (normal, ≤6.7 ng/mL; lower limit of detection, 2.2 ng/mL) was measured in all samples with a commercially available immunoabsorbent assay (Stratus CK-MB, Baxter Dade, Miami, Fla) based on a monoclonal antibody that recognizes MBCK but neither BBCK nor MMCK isoenzymes.²⁰ MBCK was determined in the samples from the marathon runners by electrophoresis as previously described (normal, ≤11 IU/L).²¹

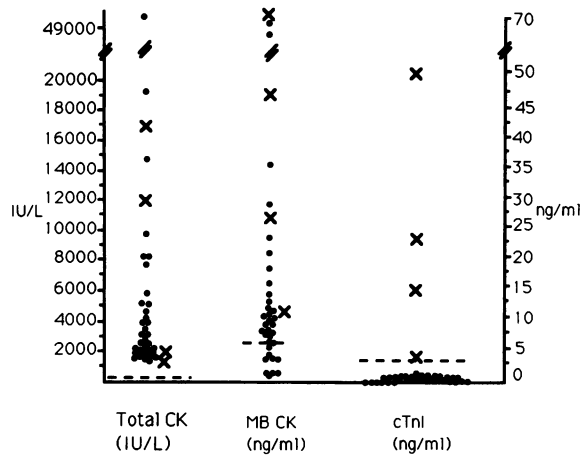


FIG 1. Graph of values of total creatine kinase (CK), MBCK, and cardiac troponin I (cTnI) in patients with acute muscle disease ($n=39$). Values for patients with acute myocardial injury are indicated by an "X." Dotted lines indicate the upper reference limit of the respective assay: cTnI (3.1 ng/mL), MBCK (6.7 ng/mL), and total CK (170 IU/L).

cTnI was assayed by an immunoassay that uses two cTnI-specific monoclonal antibodies with independent epitopes for cTnI.¹¹ The assay is similar to that previously described¹¹ except that a Stratus immunochemical analyzer was used, antibody 2F6.6 was used as the capture antibody, and the labeled Fab fragment of antibody 2B1.9 was conjugated to alkaline phosphatase. Levels of cTnI are undetectable in normal volunteers. Studies performed with this assay on samples of hospitalized patients without known cardiac disease have defined the upper limit of the reference range to be ≤ 3.1 ng/mL based on a 95% cutoff value by nonparametric analysis; the lower limit of detection is 1.5 ng/mL. The cTnI immunoassay has no detectable cross-reactivity with human skeletal muscle TnI.¹¹

Results

The clinical characteristics of the patients studied are tabulated in Table 1. Elevations of total and MBCK were common. By definition, all 37 patients with acute skeletal muscle disease had elevations of total CK (mean, $7731 \pm 10\,000$ IU/L). Twenty-four also had elevations of MBCK (mean, 22.7 ± 21.2 ng/mL). Only four of these patients had regional wall motion abnormalities consistent with acute cardiac injury (Fig 1). All patients with chronic muscle disease had marked elevations of total CK (mean, 4434 ± 4881 IU/L), and nine of 10 had elevations of MBCK (mean, 125.8 ± 254.4 ng/mL). Only one had a regional wall motion abnormality consistent with cardiac injury (Fig 2). Of the 159 patients with chronic renal failure, 27 had elevations of total CK (mean, 180 ± 165 IU/L) and seven had elevations of MBCK (8.1 ± 0.9 ng/mL). Only one of these patients had a regional wall motion abnormality (Fig 3). All marathon runners had elevations of total CK (mean peak, 1337 ± 1678 IU/L), and six of seven had elevations of MBCK (mean peak, 33 ± 35 ng/mL). The highest levels of both total CK and MBCK were present on the first post-race blood sample (Fig 4). Calculation of the percent of MBCK with respect to total CK did not

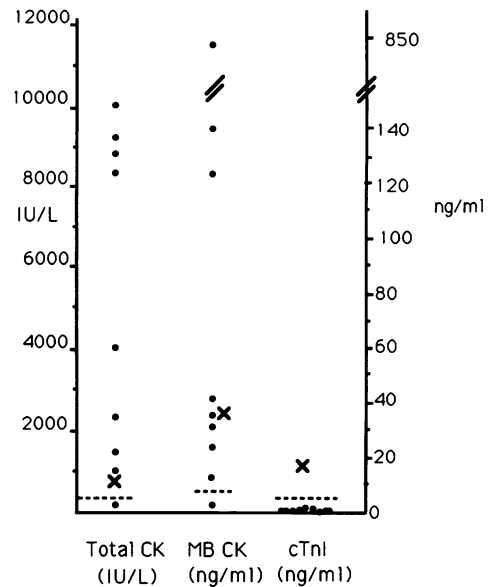


FIG 2. Graph of values of total creatine kinase (CK), MBCK, and cardiac troponin I (cTnI) in patients with chronic muscle disease ($n=10$). Values for patients with acute myocardial injury are indicated by an "X." Dotted lines indicate the upper reference limit of the respective assay: cTnI (3.1 ng/mL), MBCK (6.7 ng/mL), and total CK (170 IU/L).

distinguish whether elevations of MBCK were due to skeletal muscle injury or myocardial injury (Fig 5).

Levels of cTnI were elevated only in the six patients with regional wall motion abnormalities on their echocardiograms: four with acute muscle trauma, one with Duchenne's muscular dystrophy, and one with chronic renal failure. In addition to having segmental wall motion abnormalities, all had elevated levels of MBCK and ECG abnormalities consistent with ischemia. Of the four patients with acute muscle trauma and elevations in cTnI, three had a fixed area of akinesis on echocardiography in addition to ST-segment abnormalities; two developed new Q waves. The fourth, with anterior ST-segment abnormalities after severe blunt thoracic trauma, had transient anterior wall akinesis. The patient with Duchenne's muscular dystrophy developed new inferior wall hypokinesis (compared with an echocardiogram performed 1 week earlier) and a new inferior Q wave after an episode of chest pain, dyspnea, and inferior ST-segment abnormalities. The patient with chronic renal failure and an elevated level of cTnI had been admitted to the hospital for evaluation of anemia and was documented to have suffered an inferior myocardial infarction by history, ECG, and new inferior akinesis on echocardiogram.

No other patient had regional wall motion abnormalities detected by echocardiography or was suspected to have ischemia/infarction based on the clinical and ECG findings observed by the clinicians blinded to echocardiographic and cTnI data.

Discussion

Our data indicate that increases in cTnI do not occur despite severe acute and/or chronic muscle injury even when plasma levels of MBCK are increased unless concomitant cardiac injury is present. There was con-

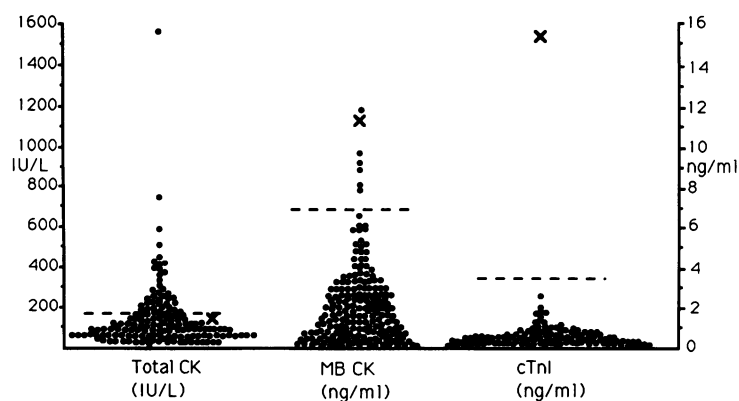


FIG 3. Graph of values of total creatine kinase (CK), MBCK, and cardiac troponin I (cTnI) in patients with chronic renal failure (n=159). Values for patients with acute myocardial injury are indicated by an "X." Dotted lines indicate the upper reference limit of the respective assay: cTnI (3.1 ng/ml), MBCK (6.7 ng/ml), and total CK (170 IU/L).

cordance between elevations of cTnI and the presence of echocardiographic wall motion abnormalities, suggesting that measurement of cTnI provides information comparable to echocardiography in clarifying the presence or absence of cardiac injury when elevations of MBCK occur. In no patient was cTnI elevated in the absence of echocardiographic abnormalities, and all patients with regional wall motion abnormalities on echocardiography had ECG abnormalities indicative of ischemia/infarction present in the same anatomic distribution. We cannot exclude the presence of cardiac injury in some patients who failed to manifest clinical, ECG, or echocardiographic abnormalities.

Consistent with previous studies,^{5,22,23} MBCK was elevated in 59% (22 of 37) of patients with acute muscle disease, 78% (seven of nine) of patients with chronic muscle disease, 78% (seven of nine) of the marathon runners, and 3.8% (six of 158) of chronic renal failure patients in the absence of clinical or echocardiographic evidence of myocardial injury. Calculation of the percentage of MBCK with respect to total CK (Fig 5) as suggested by others²⁴ did not differentiate skeletal muscle injury from myocardial injury.²⁵ The increased number of patients with elevations of MBCK as compared with cTnI could reflect a greater sensitivity of MBCK for myocardial injury. However, preliminary data indicate

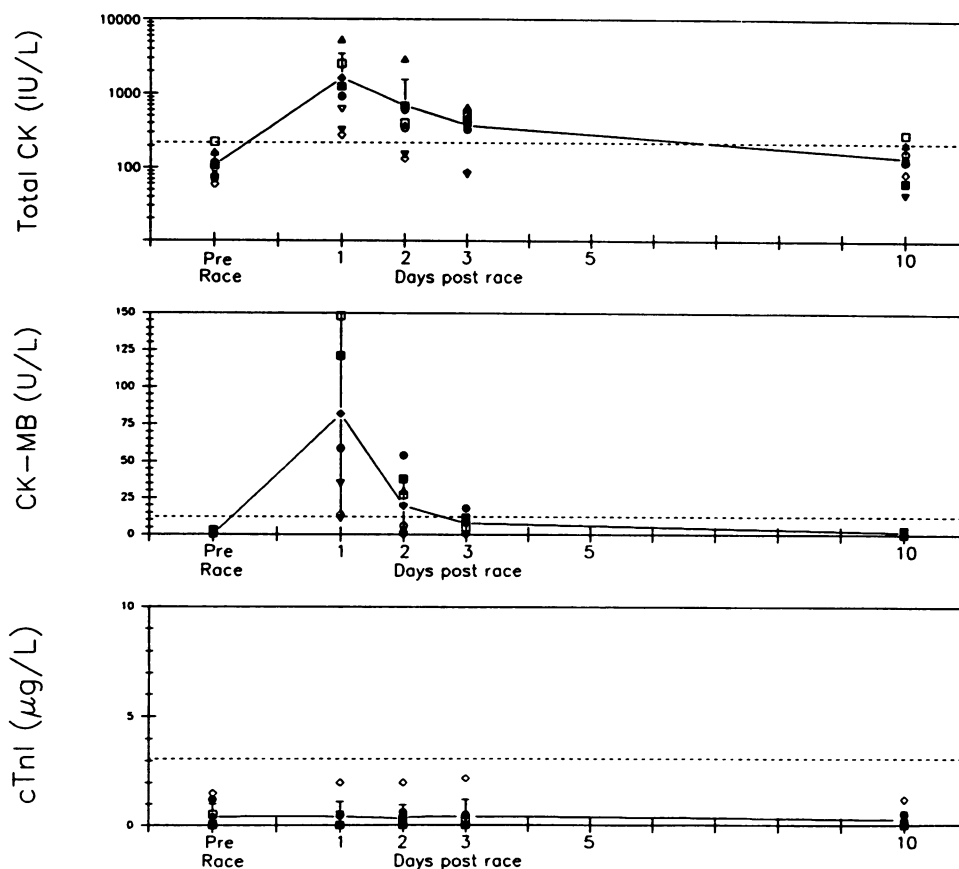


FIG 4. Graphs show values of total creatine kinase (CK), MBCK, and cardiac troponin I (cTnI) in marathon runners (n=9). Dotted lines indicate the upper reference limits of the respective assay: cTnI (3.1 ng/ml), MBCK (11 IU/L), and total CK (170 IU/L).

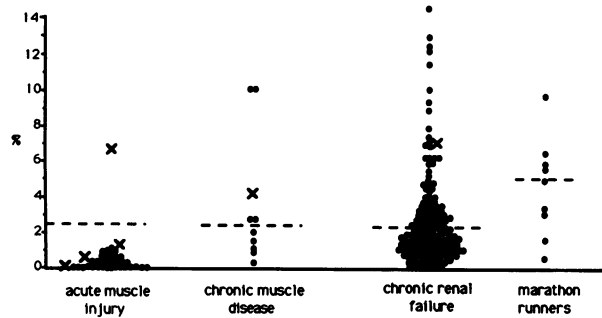


FIG 5. Graph shows percentage of MBCK with respect to total creatine kinase for all patients. Values for patients with acute myocardial injury are indicated by an "X." Dotted lines indicate the percentage cutoff proposed in previous studies, ie, 2.5 relative index using MBCK mass concentration and 5% using electrophoresis.^{23,24}

that measurement with this assay of cTnI is equally sensitive to MBCK for the detection of myocardial infarction.¹¹ More definitive studies to refine the relative sensitivity of MBCK and cTnI are needed. Studies by Cummins et al,^{12,13} using a polyclonal antibody-based radioimmunoassay for cTnI found that measurement of cTnI was equally sensitive to MBCK for the diagnosis of acute myocardial infarction. Therefore, we believe that discordance between elevations of cTnI and MBCK is due to the heightened specificity of cTnI for cardiac damage, supporting our contention that measurement of cTnI provided information comparable to that of the echocardiogram, the current diagnostic test of choice in these situations,^{15,16} for distinguishing those elevations of MBCK caused by skeletal injury alone from those associated with concomitant cardiac injury. Such an approach is likely to be more sensitive, more convenient, and more cost effective. This documentation of superior cardiac specificity in the setting of acute muscle injury is consistent with the studies of Cummins et al, who with an assay for cTnI with a 1% to 2% cross-reactivity with skeletal muscle troponin I found no elevations of cTnI in healthy canine skeletal muscle or in the blood of marathon runners.^{13,26} Whether the heightened specificity of cTnI will be useful in patients with unstable angina or other acute cardiac ischemic syndromes requires further study. Such studies also may define whether cytoplasmic enzymes such as MBCK are specific for necrosis, since it is unlikely that persistent release of cTnI, a structural protein, could occur in the absence of cell death.

The approach proposed appears to be effective in most groups known to manifest increases in MBCK in response to skeletal muscle injury. Our patients with acute skeletal muscle disease suffered from a broad spectrum of skeletal muscle insults. Many had sustained severe trauma, whereas others had toxic insults or rhabdomyolysis. The patients with chronic skeletal muscle disease were an equally diverse group, including patients with Duchenne's muscular dystrophy, polymyositis, and idiopathic myopathy. In addition, patients with renal failure, a subset of whom manifest increases in MBCK probably are due to chronic myopathy,⁵ and well-trained athletes (marathon runners) were included.²⁷ Although we excluded patients who were suspected by their physicians as having acute myocardial injury, the complex nature of

patients with severe skeletal muscle injury made this determination difficult. Therefore, we anticipated and were not surprised that some patients with acute myocardial injury were detected. We cannot exclude the possibility that other pathological processes might cause nonspecific elevations of cTnI, but given the concordance of our data with what is known of the biological response of MBCK and cTnI to skeletal muscle injury, this appears to be unlikely.

The improved specificity of cTnI compared with MBCK is consistent with differences in their developmental biology. During fetal and neonatal development, the B-subunit is the predominant CK species produced by skeletal muscle.²⁸ Suppression of B-subunit expression in skeletal muscle occurs during ontogeny so that adult skeletal muscle contains only small quantities of MBCK.² After skeletal muscle injury, there is an increased synthesis of B chains by skeletal muscle caused by re-expression of the previously suppressed B-subunit gene.⁷ The increased amount of MBCK in skeletal muscle subsequently results in increased plasma levels. For example, MBCK values of up to 50% of total CK can occur in patients with dermatomyositis.²⁹ A similar response has been observed for lactate dehydrogenase isoenzymes and myosin light chains. It appears that molecular markers expressed in skeletal muscle during fetal development are often re-expressed after muscle injury. As far as can be determined, skeletal muscle in experimental animals and humans does not express cTnI at any developmental stage or in response to any pathological stimuli.^{10,30,33} Thus, cTnI is not elevated in the plasma of patients with chronic muscle disease unless concomitant acute myocardial damage is present. This makes cTnI unique among molecular markers of myocardial necrosis.

Cardiac troponin T (cTnT) has been investigated extensively by others and has been found to be a sensitive marker of myocardial necrosis.³⁴⁻³⁶ However, its specificity has not been fully defined. cTnT is expressed in fetal and neonatal skeletal muscle in humans and experimental animals but is suppressed in healthy adult skeletal muscle.³⁷⁻³⁹ In rats, it is re-expressed in response to skeletal muscle injury.⁴⁰ Although cTnT is not found either in healthy adult skeletal muscle or in the plasma of athletes,^{37,41,42} because the troponin system is highly conserved across species, a similar response to skeletal muscle disease could occur in humans. This suggestion is supported by the recent observation of Kobayashi et al,⁴³ who have found increased plasma levels of cTnT in the absence of evidence of myocardial involvement in patients with polymyositis. A study similar to the one reported here would be necessary to evaluate the effect of other skeletal muscle processes and/or renal dysfunction on the specificity of cTnT. This issue of specificity is critical to the proper use and interpretation of the data of cTnI, cTnT, and other markers of myocardial injury that are elevated for prolonged periods of time. If specificity for myocardium is high, events can be attributed with a high degree of certainty to cardiac injury. However, if specificity is less robust, increases may occur because of release from skeletal muscle rather than myocardium and thus may be a marker of acute illness rather than cardiac injury.⁴⁴ This would be of particular concern when patients with more diverse underlying clinical problems are evaluated with these tests.

cTnI appears to be ideally suited for the detection of myocardial necrosis in these complex clinical situations. Its specificity for myocardium is high, yet its sensitivity for cardiac injury appears comparable to that of MBCK. Because we observed no elevations of cTnI in patients with acute or chronic muscle disease or renal failure except when evidence of cardiac injury was present, cTnI should be of value in determining whether elevations of MBCK are indicative of myocardial injury or are a consequence of skeletal muscle damage.

Acknowledgments

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