Abstract

Background: Although measurements of serum creatine kinase levels, as well as myoglobin levels, has been used for screening patients with acute coronary syndrome (ACS), the specificity of both is low. Measurement of cardiac troponin levels is now extensively used for the diagnosis of ACS because of their superior cardiac specificity. However, troponin levels are reportedly elevated not only in patients with ACS but also in those with the other diseases.

Methods and Results: The clinical characteristics of 1,023 patients (mean age: 63.5 ±16.3 years; males: 665, females: 358) whose serum cardiac troponin I (cTnI) levels had been measured at the initial visit to the emergency room of Toyota Memorial Hospital between April 2004 and March 2005 were retrospectively analyzed. A positive elevation of cTnI was defined as cTnI ≧0.03ng/ml. There were 432 patients (42.2%) with positive cTnI levels. The cTnI levels (8.48±2.64ng/ml) in patients with acute myocardial infarction (AMI) were greater than those (0.25±0.07ng/ml) in patients with unstable angina pectoris (AP), as well as those (0.04±0.01ng/ml) in patients with stable AP. In terms of the diagnosis of AMI, the sensitivity was high enough (94.6%), but its specificity was relatively low (61.9%). Furthermore, the differentiation between AMI and unstable AP by the cTnI values alone was impossible. The cTnI levels were elevated in patients with a variety of diseases other than ACS, including heart failure, cardiomyopathies, myocarditis, renal failure, tachyarrhythmias, and pulmonary embolism.

Conclusions: Elevations of the cTnI level is frequently observed in patients in the emergency room with common diseases other than ACS.

Key Words: Acute coronary syndrome; Cardiac troponin I; Emergency room

Introduction

In the clinical condition of myocardial damage, including acute myocardial infarction (AMI), cardiac troponins T (cTnT) and I (cTnI) are currently used as sensitive and specific laboratory markers of cardiac injury.[1-3] Traditionally, the diagnosis of AMI has been based on the combination of chest symptoms, electrocardiographic (ECG) abnormalities and elevations in serum cardiac biomarkers of myocardial damage. However, symptoms are often nonspecific, especially in older patients. Furthermore, it is impossible to diagnose AMI and anginal attack accurately by ECG changes alone in patients with Wolff-Parkinson-White (WPW) syndrome or complete left bundle branch block (CLBBB).

The troponin complex is made up of 3 discrete proteins. Both cTnI and cTnT are myocardial regulatory proteins that control the calcium-mediated interaction of actin and myosin.[4] Cardiac TnI is somewhat smaller than cTnT (23.5 vs. 33 kDa). Both proteins have cytosolic and structural pools, with most existing in the latter.[2, 5] The early troponin release during AMI is thought to stem from the cytosolic pool, and the subsequent gradual release is prolonged with degradation of the actin and myosin filaments in the damaged myocardium. Because the cardiac forms of both proteins come from specific genes, both are likely to be unique to the heart. In contrast, cTnC exists not only myocardium but also in skeletal muscles, resulting in poor cardiac specificity. Although cTnT is principally cardiac-specific protein, it should be noted that it is also expressed to minor extent in skeletal muscles. However, several studies have failed to find any trace of cTnI outside of the heart at any stage of neonatal development.

Because of their superior specificity compared with that of creatine

kinase-MB and other markers, the troponins are the preferred markers for the diagnosis of myocardial injury. The use of cTnI or cTnT for myocardial infarction diagnosis was highly recommended by a consensus statement of the European Society of Cardiology and the American College of Cardiology (ACC) in 2000.[3] Subsequently, the measurement of cTnI or cTnT was given a class I recommendation by a task force of the ACC and the American Heart Association in 2004.[6]

Among patients with a high pretest probability of acute coronary syndrome (ACS), the diagnostic and prognostic value of measuring cardiac troponin levels have been demonstrated. However, a number of investigators have shown that a variety of diseases, including sepsis, atrial fibrillation, heart failure, pulmonary embolism (PE), myocarditis, renal failure, subarachnoid hemorrhage, blunt cardiac injury and myocardial damage due to high-dose chemotherapy, can be associated with an elevated troponin level.[7-13] Accordingly, we sought to clarify the clinical significance of elevated plasma levels of troponin I in patients at the first visit to the emergency room (ER).

Methods

Study Population

We retrospectively analyzed the clinical characteristics of 1,023 consecutive patients (mean age: 63.5±16.3 years, range: 18-98 years; males: 665, females: 358) whose serum cTnI levels were measured during their initial visit to the ER of Toyota Memorial Hospital between April 2004 and March 2005. Cardiologists made the clinical diagnosis. Patients were grouped as having AMI, unstable angina pectoris (UAP), stable AP, heart failure, heart failure with renal failure, renal failure, PE, cardiomyopathy, myocarditis, paroxysmal atrial fibrillation (PAF), and paroxysmal supraventricular tachycardia. AMI was diagnosed on the basis of chest pain persisting > 30 min, ST-segment elevation of ≧0.2 mV in ≧2 contiguous leads on a standard 12-lead ECG, and serial elevation of serum creatine kinase level to more than twice the upper limit of normal. UAP was defined as chest pain at rest with documented transient ST depression or elevation of ≧0.1 mV in at least 2 ECG leads. The last spontaneous attack was required to have occurred within the 24h prior to visiting the ER. Stable AP was defined as typical exertional chest discomfort associated with ST-segment depression ≧0.1 mV on exercise test, and ≧70% narrowing of major coronary arteries. Patients with stable AP had not experienced any acute events or worsening of symptoms during the previous 6 months. PE was diagnosed by CT angiography, as well as by echocardiographic findings. Cardiomyopathy was diagnosed on the basis of echocardiographic findings. All patients with cardiomyopathy underwent coronary angiography for diagnosis and no coronary artery disease was observed. Therefore, no

patient with ischemic cardiomyopathy was present in this group. Myocarditis was diagnosed by clinical findings, including atypical chest pain, fever, transient ST-T changes in ECG with elevations of cardiac enzymes and transient LV wall swelling on echocardiography. The institutional ethics committee approved the study design.

Measurements of cTnI

We used chemiluminescent enzyme immunoassay (Access 2; Beckman Coulter, Chaska, Brea, CA, USA) for measurement of cTnI levels following the manufacturer's protocol. We had access to various instruments and methods with different generations of antibodies. To date, there is no a standard protocol for the troponin assay. We analyzed the detection sensitivity, 20% coefficient of value (CV) value and 10% CV value. The results were 0.01ng/ml, 0.03ng/ml and 0.06ng/ml, respectively. We also used 0.03ng/ml as the cutoff value for a positive diagnosis; that is, a positive elevation of cTnI level was defined as cTnI $\geqq$0.03ng/ml.

Statistical Analysis

Values are expressed as means$\pm$SEM. Multiple comparisons were analyzed by 1-way analysis of variance followed by Fisher's test. A level of $p < 0.05$ was considered statistically significant.

Results

There were 432 patients (42.2%) with positive cTnI levels (≧0.03ng/ml). The average values and the standard errors are summarized in Table 1.

ACS

The sensitivity of cTnI levels for detecting AMI was high enough at 94.6% (70/74), but its specificity was relatively low (61.9%). The average cTnI level in patients with AMI was 8.48±2.64ng/ml, which was the greatest value among the groups (Table 1, Fig 1). In all ACS patients a cTnI level > 3ng/ml was caused by AMI (Fig 2). However, the variation in cTnI values in patients with AMI was extremely large, compared with that in patients with other underlying diseases. The cTnI values in patients with UAP were also high, but significantly lower than those in patients with AMI ($P<0.001$). Among 48 patients with UAP, 37 (77.1%) had positive results. Although the cTnI levels in patients with stable AP were relatively low, 7 patients (63.6%) had a positive test (Fig 3). Importantly, the cTnI levels in patients with UAP were not significantly greater than those in patients with stable AP ($P=0.954$). In fact, the cTnI values of the 3 groups of coronary artery diseases were intermingled, especially in the range of < 0.2ng/ml.

Heart failure, Cardiomyopathy and Myocarditis

In patients with heart failure, the average of cTnI level was 1.32±0.36ng/ml.

Furthermore, patients with both heart failure and renal failure also had high cTnI levels (0.97±0.39ng/ml) (Fig 4). The elevation of cTnI level was relatively small (0.06± 0.01ng/ml) in patients with renal failure alone. In patients with cardiomyopathy and myocarditis, the cTnI levels were 1.74±1.02ng/ml and 2.27±1.09ng/ml, respectively.

Miscellaneous Diseases

The distribution of cTnI values is shown in Fig 5. The cTnI values were mildly elevated in patients with PAF (0.15±0.08ng/ml) or paroxysmal supraventricular tachycardia (0.13±0.06ng/ml). In patients with PE, the cTnI value was substantially elevated (0.35±0.27ng/ml) with a large variation.

Discussion

The present study demonstrated that cTnI values are elevated in patients with diseases other than ACS, including heart failure, cardiomyopathies, tachyarrythmias, renal failure, and PE. It is very important to know whether the cTnI values are elevated or within normal values for the various diseases encountered in the ER.

ACS

In this study, we confirmed that the measuring the cTnI level was useful for detecting ACS. The sensitivity of cTnI for detecting AMI was 94.6%, as a number of investigators have previously reported. However, the variance of the cTnI values was remarkably large, which appears to be related to many factors including the time from onset to the time of measurement, the extent of collateral flow development, the site responsible, etc. We observed 4 cases of negative cTnI test and blood was sampled less than 3h after the onset of AMI symptoms in all 4 cases. We also had a few positive cTnI patients whose blood was sampled even less than 3h after onset. It has been reported that a significant elevation of cTnI level can be detected 3 - 4h after the onset of symptoms of AMI.[14] On the other hand, the cTnI values in patients with UAP were much lower than those in patients with AMI, and the sensitivity of cTnI was also low. As shown in Fig 1, patients with a remarkable elevation of the cTnI level, such as greater than 3ng/ml, are highly suggestive of AMI, whereas the differentiation of AMI from UAP is impossible in patients with values less than 1ng/ml, as indicated in Fig 2 and 3. Cardiac troponins can be released into the bloodstream by 2 major mechanisms

in cases of ACS. One mechanism is myocardial necrosis, and the other is increased membrane permeability resulting from severe ischemia. It is strongly suggested that the former is the case with AMI and the latter occurs in cases of UAP. Because the elevation of serum cTnI values can last until 1 week after onset, measurement can play a role in late diagnosis of AMI, especially in asymptomatic patients with diabetes mellitus, or those for whom ECG diagnosis may be impossible or difficult, such as patients with WPW syndrome, CLBBB, ventricular pacing, or digitalis effects.

Heart failure, Cardiomyopathy and Myocarditis

In the present study, many patients with heart failure, cardiomyopathy or myocarditis had positive cTnI values. It should be kept in mind that cTnI values in patients with heart failure appear to be higher than those in patients with UAP. The broad range of cTnI values in patients with heart failure may be explained by many factors, including the magnitude of left ventricular hypertrophy (LVH), and concomitant coronary artery diseases. The extent of the troponin values in patients with myocarditis appeared to be greater than that in patients with cardiomyopathy, which may reflect the disease process (acute vs chronic). Sato et al[15] analyzed the cTnT values in patients with dilated cardiomyopathy (DCM) before and after β-blockers therapy and classified them into 3 groups. negative cTnT both before and after the therapy; positive cTnT before and negative after the therapy; and positive cTnT both before and after the therapy. The prognosis of the patients of the 3rd group whose cTnT values were persistently positive was significantly worse than that of the other 2 groups. Accordingly, the measurement of cardiac troponins is useful for predicting which patients have ongoing myocardial

injury with poor prognosis. Furthermore, experimental studies in DCM hamsters suggest the usefulness of measuring cardiac troponins to detect the natural history of cardiac injury.[16, 17] In that study, cTnT peaked at the age of 8 weeks, when the left ventricular ejection fraction decreased abruptly.

In the present study, cTnI levels in patients with heart failure and in those with both heart failure and renal failure tended to be higher than that in those with renal failure alone. Elevated cTnI levels in patients with renal failure have been reported. Because coronary artery disease is highly prevalent in patients with end-stage renal disease, accurate interpretation of serum cTnI levels is very important. Although the exact mechanisms underlying the serum troponin levels are unclear, possible reasons include LVH, endothelial dysfunction, loss of integrity with leakage of the free cytosolic troponin pool, stretch-mediated troponin release, and impaired renal excretion.[18] In renal failure patients with repeated heart failure, the measurement of cTnI levels during the stable phase in the absence of heart failure can be useful for the diagnosis of ACS and the severity of cardiac injury during the subsequent heart failure.

Miscellaneous Diseases

The elevation of the cTnI levels was reconfirmed in patients with tachyarrythmias, as previous reported. Tachycardia alone was implicated as the cause of troponin elevations in a small case series.[19] In the current study, the extent of elevation in patients with paroxysmal supraventricular tachycardia was similar to that in patients with PAF. In fact, the values were within normal limits in some patients, and elevated in others. LVH leading to subendocardial ischemia was more prominent in the former

rather than the latter cases. However, our results were derived from a limited number of patients, whose heart rates and time intervals from onset to measurement were completely different. Therefore, a more detailed large-scaled study should be conducted.

Clinical Significance of cTnI Level at the First Visit to ER

Very recently, Wallance et al reported the prevalence of cTnT elevations in the general population according to stored samples from 3,557 participants in the population-based Dallas Heart Study.[20] Their data strongly suggested that normal individuals have very low cTnT levels. Actually, only 0.7% of participants have cTnT values $\geqq$0.01 ng/ml, which is the 99% percentile of the reference range. In contrast, in the current study we observed a higher prevalence of cTnI elevation defined as $\geqq$0.03 ng/ml in patients during their first visit to the ER. The usefulness of measuring the cTnI level for diagnosis ACS was confirmed. Importantly, we demonstrated more patients with positive cTnI without ACS in the clinical setting of the ER. Cardiac troponin release into the systemic circulation in the absence of myocardial necrosis can occur in conditions that produce cardiomyocyte membrane permeability. One of the mechanisms of such release is demand ischemia, which refers to a mismatch between myocardial oxygen demand and supply. Increased myocardial demand can be induced by conditions such as tachycardia, changes in cardiac loading conditions, increased in cardiac output to accommodate increased systemic oxygen consumption, and myocardial depression. On the other hand, diminished myocardial oxygen supply can be caused by reduced coronary perfusion secondary to both tachycardia and lower perfusion pressure. As an example, tachycardia and elevated left ventricular filling pressures and elevated tumor

necrosis factor-alpha are very common features of heart failure. These forces combine to create the mismatch in myocardial oxygen supply and demand. A similar scenario occurs in other diseases including renal failure and sepsis.

Among patients with a high pretest probability of ACS, such as those with typical chest pain, the diagnostic value of the troponins is invariable. However, in patients with a low pretest probability of ACS, which is very common in Japanese ERs, the elevation in cTnI level may be nonspecific and divert attention from the diverse underlying clinical problems. Therefore, a comprehensive understanding of the characteristics of cTnI release may prevent unnecessary cardiac evaluation, including cardiac catheterization.

Conclusions

Elevations of the cTnI level are frequently observed in patients presenting in the ER with common diseases other than ACS. The extent of the elevation should be interpreted with caution, considering the etiology of the underlying diseases and the time interval from onset of symptoms to blood sampling.

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Table 1 Age, cTnI value, and Its Sensitivity in Each Group of Patients in ER

Group	Age (years)	cTnI (ng/ml)	Sensitivity (%)
Acute Myocardial Infarction (AMI, n=74)	68.6 ± 1.4 [g, h, j, k]	8.48 ± 2.64 [b, c, d, e, f, g, i, j, k]	94.6
Unstable Angina Pectoris (UAP, n=48)	65.9 ± 1.4 [g, h, j]	0.25 ± 0.07	77.1
Stable Angina Pectoris (SAP, n=11)	67.0 ± 3.9 [h, j]	0.04 ± 0.01	63.6
Heart Failure (HF, n=79)	75.3 ± 1.7 [a, b, e, g, h, i, j, k]	1.32 ± 0.36	89.9
Heart Failure + Renal Failure (HF+RF, n=27)	65.9 ± 2.7 [g, h, j]	0.97 ± 0.39	88.9
Renal Failure (RF, n=13)	78.2 ± 2.7 [a, b, e, g, h, i, j, k]	0.06 ± 0.01	84.6
Cardiomyopathy (CM, n=13)	56.1 ± 7.6	1.74 ± 1.02	76.9
Myocarditis (MC, n=5)	47.0 ± 14.8	2.27 ± 1.09	80.0
Paroxysmal Atrial Fibrillation (PAF, n=23)	64.6 ± 1.9 [h]	0.15 ± 0.08	60.9
Paroxysmal Supraventricular Tachycardia (PSVT, n=8)	53.5 ± 7.4	0.13 ± 0.06	87.5
Pulmonary Embolism (PE, n=10)	57.5 ± 5.4	0.35 ± 0.27	70.0

Values are means ± SEM.

[a]$p<0.05$ vs. AMI; [b]$p<0.05$ vs. UAP; [c]$p<0.05$ vs. SAP; [d]$p<0.05$ vs. HF; [e]$p<0.05$ vs. HF+RF; [f]$p<0.05$ vs. RF;

[g]$p<0.05$ vs. CM; [h]$p<0.05$ vs. MC; [i]$p<0.05$ vs. PAF; [j]$p<0.05$ vs. PSVT; [k]$p<0.05$ vs. PE.

Figure Legends

Fig. 1 The distribution of cardiac troponin I (cTnI) levels in patients with acute coronary syndrome. AMI, acute myocardial infarction; UAP, unstable angina pectoris; SAP, stable angina pectoris.

Fig. 2 The magnified distribution of cardiac troponin I (cTnI) levels in patients with acute coronary syndrome in the range of cTnI levels less than 12ng/ml. AMI, acute myocardial infarction; UAP, unstable angina pectoris; SAP, stable angina pectoris.

Fig. 3 The magnified distribution of cardiac troponin I (cTnI) levels in patients with acute coronary syndrome in the range of cTnI levels less than 0.4ng/ml. AMI, acute myocardial infarction; UAP, unstable angina pectoris; SAP, stable angina pectoris.

Fig. 4 The distribution of cardiac troponin I (cTnI) levels in patients with heart failure, cardiomyopathy and myocarditis. HF, heart failure; RF, renal failure; CM, cardiomyopathy; MC, myocarditis.

Fig. 5 The distribution of cardiac troponin I (cTnI) levels in patients with miscellaneous diseases. PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; PE, pulmonary embolism.