The clinical significance of cardiac troponins in medical practice

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Received 9 August 2010; accepted 9 October 2010
Available online 20 October 2010

Abstract  Troponins are regulatory proteins that form the cornerstone of muscle contraction. The amino acid sequences of cardiac troponins differentiate them from that of skeletal muscles, allowing for the development of monoclonal antibody-based assay of troponin I (TnI) and troponin T (TnT). Along with the patient history, physical examination and electrocardiography, the measurement of highly sensitive and specific cardiac troponin has supplanted the former gold standard biomarker (creatine kinase-MB) to detect myocardial damage and estimate the prognosis of patients with ischemic heart disease. The current guidelines for the diagnosis of non-ST segment elevation myocardial infarction are largely based on an elevated troponin level. The implementation of these new guidelines in clinical practice has led to a substantial increase in the frequency of myocardial infarction diagnosis.

Automated assays using cardiac-specific monoclonal antibodies to cardiac TnI and TnT are commercially available. They play a major role in the evaluation of myocardial injury and prediction of cardiovascular outcome in cardiac and non-cardiac causes.

In this review we discuss the clinical applications of cardiac troponins and the interpretation of elevated levels in the context of various clinical settings.

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1. Introduction

Cardiac muscle is similar to skeletal muscle which contains contractile proteins, but cardiac muscles are branched and interconnected and lack the end plates and have involuntary control. These contractile proteins compose of overlapping thick and thin filaments which slide past each other to produce muscle contraction in an active process requiring large amounts of oxygen which needs a rich capillary bed. The thick filament is composed of myosin which contains adenosine triphosphatase (ATPase) activity and forms cross-bridges with actin. The thin filament consists of actin, tropomyosin and troponin regulatory complex which includes: troponin C (TnC) that binds Ca^{2+} to initiate muscle contraction, troponin I (TnI) that...
inhibits actin-myosin coupling through the inhibition of ATPase activity, while troponin T (TnT) binds to tropomyosin and stabilizes the complex on the actin filament (Fig. 1) (Sacks, 1999; Hernandez et al., 2001).

Troponins are present in both skeletal and cardiac muscles, but amino acid sequences are dissimilar allowing differential detection by monoclonal antibody-based assay. The majority of cardiac troponin is bound to myofilaments and the remainder is free in the cytosol in comparison to CK-MB which is fully cytosolic. In myocyte damage, cytosolic pool is released first. Cytosolic pool for TnT is 6–8% of its total intracellular concentration while cytosolic pool for TnI is 2.8% (Alpert et al., 2000). Troponin has two peaks rendering it offers no advantage over CK-MB for early diagnosis of MI. CK-MB has a baseline value that may blunt the rapid rise and rapid clearance, while troponin has no baseline value and has a slow clearance and cross-reactivity of cardiac troponin with skeletal muscle is low (Neumayr et al., 2001).

Creatine kinase-MB isoform had been considered the reference standard for the diagnosis of acute myocardial injury in the past, but its utility was limited by lack of cardiac specificity and its rapid clearance.

The high sensitivity and specificity of cardiac troponin assays confer great impact in the early diagnosis and risk stratification in patients presenting with chest pain. The joint committee of the European Society of Cardiology and the American College of Cardiology issued the new criteria acknowledging that elevations of cardiac troponins are fundamental for the diagnosis of myocardial infarction (Uettwiller-Geiger et al., 2002).

Detection of cardiac troponin is not pathognomonic for acute coronary syndrome but rather suggests myocardial injury of any cause and may be found in non-coronary artery-related conditions (Roongsritong et al., 2004). In addition to their diagnostic value, elevated cardiac troponins have a strong correlation with adverse cardiovascular outcome whether coronary artery disease is present or not.

In this review article, we discuss the clinical applications of troponins in various clinical settings and their role in the diagnosis and prediction of outcome in cardiac and non-cardiac conditions.

1.1. Diagnostic value of cardiac troponins

Cardiac troponin monitoring for detection of myocardial injury has been designated the new standard for differentiating the diagnosis of unstable angina and non-ST elevation myocardial infarction (NSTEMI) in acute coronary syndrome (ACS) patients (Braunwald et al., 2000).

1.2. Acute myocardial infarction

Creatine kinase (CK)-MB was the gold standard marker of myocardial necrosis used in the evaluation of acute coronary syndromes (Roberts and Sobel, 1973). It is predominantly located in myocardial cells and constitutes 1–3% of the total CK found in skeletal muscle, and is also present in smaller quantities in other tissues, such as intestine, diaphragm, uterus, and prostate which limits its utility in clinical practice.

Recently, cardiac troponins have replaced the creatine kinase (CK)-MB for both diagnosis and risk stratification in myocardial necrosis.

The early release kinetics of cTnI and cTnT allows detection at 3–6 h after symptom onset during MI and may remain elevated for 7–14 days.

Previously, the diagnosis of myocardial infarction based on the MONICA criteria includes the presence of suggestive chest pain, pathological Q waves on electrocardiography and elevation of cardio-specific isoenzymes where creatinine kinase (CK)-MB is the gold standard marker (Tunstall-Pedoe et al., 1994), while the new definition of MI by ESC/ACC/AHA is more comprehensive and includes the clinical, electrocardiographic, biochemical, imaging and pathological features suggestive of myocardial necrosis (Alpert et al., 2000).

The recommended cut-off value for an elevated cardiac troponin is the 99th percentile of a control reference group at a precision level of ≤10% coefficient of variation (CV), which is a measure of precision and is defined as standard deviation/mean (Alpert et al., 2000).

Current generation troponin T assay meets the level of precision as specified in the ACC/ESC definition, while different manufacturers have used different antibodies raised against different epitopes on cardiac troponin I, and there is no standardisation between the different troponin I assays, which complicates their use. Thus at present, no troponin I assay meets the ACC/ESC criteria for diagnosis of MI (French and White, 2004).

Elevations of cTnI and cTnT are not sufficiently sensitive at presentation in the ED and must be measured serially over time to adequately exclude MI. Blood should be obtained for testing on hospital admission, at 6–9 h and again at 12–24 h if the earlier samples are negative and the clinical index of suspicion is high (Alpert et al., 2000; Bassand et al., 2007).

Troponin T has a short half-life of about 90 min, and persistent elevation on day 3 or 4 reflects degradation of the contractile elements which is a hallmark of irreversible cell injury (Katus et al., 1989). With this definition, the detection of even minor myocardial injury and the identification of a high-risk group of additional patients with acute coronary syndrome is, therefore, appropriately classified as myocardial infarction with early risk stratification and management (Omland et al., 2009). In addition to the diagnosis of MI the peak of troponin level may provide information about the infarct size (Steen et al., 2006).

1.3. Myocardial re-infarction

Detection of re-infarction is clinically important because it carries an incremental risk for the patient. Re-infarction may present special diagnostic difficulties, because an increase of cardiac troponin is long-lasting, and when cardiac troponin is persistently high, the timing of the initial myocardial damage is difficult to ascertain. If the first sample on presentation has a high cardiac troponin value, then for this reason a biomarker with a shorter time course, such as CK-MB or myoglobin, could be employed to clarify the timing of the infarct and to detect the re-infarction (Alpert et al., 2000).

The re-infarction is defined as recurrent symptoms occurring within 18 h of myocardial infarction, with chest pain lasting more than 30 min and more than a 2 mm ST segment
elevation or the presence of CK-MB rising above the upper limit of the reference range or more than 50% of the baseline value (French and White, 2004). Troponin I can also be used for detecting re-infarction which is demonstrated by re-elevation of cTnI after it reaches the plateau (Apple and Murakami, 2005).

2. Detection of peri-procedural myocardial infarction

2.1. Detection of MI after percutaneous coronary intervention (PCI)

Cardiac troponins are useful for the diagnosis of myocardial infarction and myocardial necrosis (Mair et al., 1991). They are more sensitive than CKMB for the detection of minor damage missed by conventional markers which are prognostically important (La Vecchia et al., 1996; Shyu et al., 1998; Harrington et al., 1995). The reported incidence of troponin T or I release after percutaneous coronary intervention (PCI) ranges between 13% and 44%, with the incidence higher after stenting (La Vecchia et al., 1996; Ravkilde et al., 1994; Karim et al., 1995; Saadeddin et al., 2001). Any elevation post-procedure is indicative of cardiac injury which raises the concern about potential problems arising from using overly sensitive tests to detect myocardial injury after PCI (Pierpoint and McFalls, 2000). However, the diagnosis of a procedure-related MI needs a three-fold increase from the normal baseline value.

2.2. Diagnosis of myocardial infarction after cardiac surgery

Perioperative MI after CABG, as defined by new Q waves on the post-operative ECG, occurs in 4–5% of patients and the cardiac markers are more common than Q waves, occurring in 62–90% of patients because most of the damage which occurs during CABG is sub-endocardial injury and the transmural infarction may require 5–10 times the upper limit of normal CK-MB. Therefore, for myocardial infarction after cardiac surgical procedures, a five-fold increase from the baseline in biomarkers is recommended, along with associated findings, such as new Q waves (Righetti et al., 1977).

As we know from literature, predisposing factors for perioperative myocardial infarction (PMI) in cardiac surgery patients include: incomplete revascularization, diffuse disease, inadequate myocardial protection during surgery, transient hypotension, left ventricular hypertrophy, prior PCI before CABG, recent MI less than one week, and emergency CABG (Van Lente et al., 1989). The guidelines state: Biomarker values more than five times the 99th percentile of the normal reference range during the first 72 h following CABG when associated with the appearance of new pathological Q-waves or new left bundle-branch block (LBBB), angiographically-documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium, should be considered as diagnostic of a CABG-related myocardial infarction (Adams et al., 1994).

Although creatine kinase MB exhibited the best diagnostic association with the presence of perioperative myocardial infarction, there is a poor correlation between changes in the cardiac biomarker activity and the ultimate evidence of post-CABG MI at autopsy (Thygesen et al., 2007).

Cardiac troponin levels are detectable in nearly all patients after CABG in the absence of a clinically documented MI. In spite of an excellent negative predictive value of cardiac troponins for the detection of myocardial injury after CABG, there is a degree of heterogeneity of optimal cut-off points for cTn measurement to predict the risk but a single cut-off point cannot be recommended to make a precise diagnosis of MI (Botha et al., 2004; Costa et al., 2001).

Carrier et al. (2000) illustrated the diagnostic value of troponin elevations in a study of 590 patients in whom a cTnT concentration > 3.4 μg/L at 24 h after CABG correlated best with a perioperative MI, as defined by new Q waves on the ECG and CK-MB > 100 IU/L within 48 h after surgery with high sensitivity and specificity and positive and negative predictive values exceeding 90%.

2.3. Diagnosis of MI after non-cardiac surgery

Perioperative ischemic events were mostly asymptomatic; they occur most commonly in the post-operative period and carry a high mortality rate (Mangano, 1990).

The lack of standardisation of the surgical procedures and variety of the related surgical risk creates different approaches for every medical institution for perioperative cardiac assessment. Many clinicians use electrocardiography, echocardiography and cardiac enzymes in their approach. However, uninterpretable ECGs in many perioperative conditions and low-sensitive transthoracic echocardiography in the diagnosis of new myocardial infarctions make those modalities insufficient in such conditions (Adams et al., 1994; Eisenberg et al., 1992).

The false positive elevation of CK-MB is more frequent than true elevation, therefore, limiting its diagnostic value and leading to putting a major weight on cardiac troponins, which are sensitive and specific if their level is interpreted in the context of a clinical condition and the incremental measurements taken rather than a single absolute value. Where the cardiac troponin I proved to be a very sensitive diagnostic tool, it was able to detect minor myocardial injury that was not detected by other traditional techniques. Interestingly, cTnT showed a strong positive predictive power for major in-hospital cardiac complications (Lee et al., 1996).

The importance of early diagnosis of perioperative MI implies rapid access to intensive care facilities for patients with acute myocardial infarction and significant reduction of the short-term mortality (Udvarhelyi et al., 1992).

Troponins are ideal for diagnosing perioperative MI after non-cardiac surgery. The same cut-off levels used to diagnose an acute MI should be used to detect perioperative injury in such patients.

2.4. Other causes of elevated cardiac troponin

Troponin elevations have been reported in a variety of clinical conditions other than coronary artery disease (Table 1). In a series of 21 subjects, Bakshi et al. (2002) reported tachycardia in 28%, pericarditis in 10%, heart failure in 5% and strenuous exercise in 10%. Elevated cardiac troponins have been used to detect structural heart disease, such as cardiomyopathies, myopericarditis, tachyarrhythmias, pulmonary embolism and high-dose chemotherapy due to minor myocardial injury in those conditions (Korff et al., 2006). In heart failure patients the elevated troponin levels occur in approximately 49% of the cases,
which is attributed to multiple mechanisms including excessive wall tension, sympathetic stimulation, and activation of rennin angiotensin aldosterone system, oxidative stress and inflammatory mediators release (Horwich et al., 2003; Jeremias and Gibson, 2005). While in critically ill patients, especially septic shock individuals, the troponin rise occurs in 50–85% and may indicate disease severity rather than ischemic events because several papers addressed this issue and noticed that the coronary blood flow and myocardial lactate extraction increase, while the oxygen availability to myocardium is preserved, and microvascular dysfunction and myocytotoxic effects of endotoxin, cytokines, reactive oxygen radicals and altered membrane permeability may have a role (Cunnion et al., 1986; Dhainaut et al., 1987; Lim et al., 2006a,b; Ammann et al., 2003; van Bockel et al.,2003). The central nervous system conditions the elevated troponin found in 27% of acute stroke and 20% of subarachnoid haemorrhage cases and this may be attributed to an imbalance in the autonomic nervous system resulting in an excess of sympathetic activity and an increased catecholamine effect on myocardial cells (Jeremias and Gibson, 2005; Lim et al., 2006a,b). Troponin elevation was observed in more than 53% of patients in the absence of clinical ischemia and was thought to be due to a silent myocardial injury, increased left ventricular mass or impaired renal troponin excretion (Jeremias and Gibson, 2005).

A false positive result was observed in several conditions ranging from 0.17% to 40%, and Bakshi et al. (2002) found no identifiable cause in 47% of patients with elevated troponin and normal coronaries. Common causes of false positive troponin include: heterophilic antibodies, rheumatoid factor, fibrin clots, micro-particles and analyzer malfunction. This error can be avoided by antibody blocking agents, use of clot activators, repeating the centrifugation, adding super serum and running quality-controlled samples after each maintenance check of the analyzer (Roongsritong et al., 2004; Beyne et al., 2000).

Table 1  Causes of elevated cardiac troponin levels.

<table>
<thead>
<tr>
<th>Coronary artery related</th>
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<tr>
<td>Atherosclerosis or emboli</td>
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<td>Coronary spasm</td>
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<tr>
<td>Coronary dissections</td>
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<tr>
<td>Post-coronary interventions</td>
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<tr>
<td>Myocardial injury or strain</td>
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<td>Myocarditis or myocardialitis</td>
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<tr>
<td>Tachyarrhythmias</td>
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<td>Toxic drugs (e.g., anthracyclines)</td>
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<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Cardiomyopathies (e.g., infiltrative diseases)</td>
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<td>Sepsis</td>
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<tr>
<td>Exercise</td>
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<tr>
<td>Pheochromocytoma</td>
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<tr>
<td>Traumas</td>
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<tr>
<td>Cardiac surgery</td>
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<tr>
<td>Chest trauma</td>
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<tr>
<td>Direct current defibrillations</td>
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<td>Radiofrequency ablations</td>
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<tr>
<td>False positive and laboratory errors</td>
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Patients with a low pre-test probability of CAD will most likely not derive any benefit from a treatment strategy aimed at coronary thrombosis (Jeremias and Gibson, 2005; Lim et al., 2006b).

2.4.1. Prognostic value of elevated cardiac troponins
Cardiac troponins play a major role in predicting the cardiac events in several situations where their elevated levels are frequently observed.

2.4.2. Cardiac troponins in acute coronary syndrome
Troponin positivity in patients with acute coronary syndrome implies a significantly worse prognosis and indicates a response with a significant reduction of death or non-fatal myocardial infarction to glycoprotein IIb/IIIa inhibitors. Elevated troponin levels may point to an increased prevalence of significant coronary disease, multi-vascular coronary disease, visible thrombus, suboptimal coronary flow or reduced left ventricular systolic function (Anonymous, 1997; Rao et al., 2003).

In a CAPTURE trial, as late as 5 days’ randomization to abciximab led to a 60% reduction of death and non-fatal myocardial infarction (Anonymous, 1997). A PRISM study showed that patients with elevated troponin at a mean of 8.4 h after symptoms started had death or MI in 4.3% compared to 13% in those with positive troponin and had not received tirofiban (Anonymous, 1998). While in a PARAGON-B trial sub-study, patients with a cardiac troponin T of more than 0.1 ng/ml within 24 h of symptom onset were given Lamifiban which led to a 42% relative reduction of death or MI at 30 days compared to those with negative troponins (Newby et al., 2001).

TACTIC-TIMI 18 sub-study reported around 4% of patients who satisfied the criteria for acute coronary syndrome and had positive cardiac troponin had no angiographic flow limiting epicardial coronary disease which might suggest a false positive troponin test, but the 6 months death, myocardial infarction and re-hospitalization were significantly higher in troponin-positive patients than those with no significant coronary artery disease and negative troponin (Wong et al., 2002).

Interestingly, it was found that even in patients presenting to emergency departments without chest pain, an elevated cardiac troponin was significantly associated with death and myocardial infarction at one year (Swinkels et al., 2006). On the other hand, positive troponin T in stable coronary artery disease predicts the incidence of cardiovascular death and heart failure but not myocardial infarction (Omland et al., 2009), while the role of elevated troponins in patients without acute coronary syndrome still debated the data from recent study that showed higher mortality (Wong et al., 2007).

2.4.3. Cardiac troponins and prediction of post-percutaneous coronary intervention (PCI) events:
As many as 48% of coronary angioplasty patients have detectable troponin levels post-PCI (Cantor et al., 2002).

Multiple studies showed that minor troponin elevations post-successful coronary angioplasty were not associated with any adverse clinical outcome during the long-term follow up (Garbarz et al., 1999).

In contrast, studies evaluating the long-term follow up of patients with creatine phosphokinase (CK-MB) elevation after
PCI suggested that post-procedural enzyme elevation is associated with a worse clinical outcome (Harrington et al., 1995; Abdelmeguid et al., 1996).

On reviewing literature, many data suggest that there is probably no association between minor myocardial injury occurring after successful angioplasties and late adverse cardiac events, particularly if CK-MB is negative (Okmen et al., 2006).

An observational study from the Mayo Clinic found that the pre-procedural cardiac troponin T elevation is a more powerful predictor of post-PCI cardiac events than post-procedural levels (Prasad et al., 2008).

A meta-analysis of 15,581 patients in twenty studies was performed by Nienhuis MB and colleagues found troponin elevation in 32.9% of the patients and a 1.1% higher mortality compared with the non-troponin elevated group (Nienhuis et al., 2008). A recent meta-analysis of fifteen studies with a total of 7578 patients found 15% of them fill the new guidelines definition of MI with increased cardiac events up to 18 months (Testa et al., 2009).

Many conflicting data in this issue make the need for randomized trials instead of small or observational studies to resolve these variations in the results.

2.4.4. Cardiac troponins and coronary bypass grafting (CABG)

Almost all patients undergoing cardiac surgery will have detectable cardiac troponins. The level of rise of troponins parallels the level of injury occurred during that surgery. It is, therefore, useful to remember a time course of cardiac troponin elevation in those with perioperative myocardial infarction, which peaks 8–16 h post-surgery (Katus et al., 1991).

Whether the patients had preoperatively-elevated readings of troponins is an important factor to consider when analyzing post-operative levels. Collectively, higher levels of troponin after surgery imply a worse outcome compared to those with undetectable or low level troponins (Force et al., 1990).

Pre-operative elevation of cardiac troponin in more than 0.1 ng/ml within 24 h before cardiac surgery is the strongest predictor of morbidity, mortality and a longer hospital stay (Swaanenburg et al., 1998; Espinoza et al., 1974; Jain, 1992; Muehlschlegel et al., 2009).

Pre-operative elevation of cardiac troponin T in more than 0.02 ng/ml identifies a sub-group of patients with a longer intensive care unit stay and higher in-hospital morbidity (Hamm et al., 1992).

After elective open heart surgery, a single measurement of cardiac troponin T of more than 0.46 mg/l at 48 h after cardiac surgery was an independent predictor of both short-term and long-term mortality and morbidity (Lehrke et al., 2004).

The negative predictive value of cardiac troponin T below 3.9 mg/l at 24 h of open cardiac surgery is more than 90% (Bonnefoy et al., 1998).

2.4.5. Cardiac troponins and heart failure

The usefulness of cardiac troponins in prognosis of acute heart failure trials is limited by the fact that serial (rather than one) estimations of cardiac troponins are needed to rule out the possibility of acute myocardial infarction. However, after multivariate adjustment, there was a significant persistent dose-response relationship between cardiac troponin and mortality, i.e., the higher the level of troponin, the higher the mortality.

In patients with chronic heart failure, the fate of high cardiac troponin is unknown in view of scanty data.

In heart failure patients, elevated troponin is associated with the risk of death and re-hospitalization regardless of underlying cause and the three-year survival is about 29% (Setsuta et al., 1999; Perna et al., 2002).

2.4.6. Cardiac troponins and renal failure

Cardiac troponin T is detectable in the blood of patients with chronic kidney disease whether or not dialyzed. This is a true detection and is not cross-reactivity with skeletal troponin.

An elevated cardiac troponin T more than 0.1 mg/l is strongly associated with all cause mortality in haemodialyzed patients as shown in many trials (McLaurin et al., 1997; Dierkes et al., 2000; Gabr et al., 2004).

In renal failure elevated cardiac troponin is associated with a two- to five-fold increase in mortality but reduced its sensitivity and specificity in suspected CAD (Apple et al., 2002; Goldmann et al., 2001; Van Lente et al., 1999).

2.4.7. Cardiac troponins in non-cardiac patients in intensive care units

Critically ill patients who require staying in an intensive care unit are a heterogeneous group of patients who are ill for a variety of heterogeneous diseases. Thus, estimation of cardiac troponins and their significance in these patients are heterogeneous (Guest et al., 1995).

The prevalence of raised cardiac troponins in an ICU generally ranges between 15% and 70% and the majority of these critically ill patients (about 70%) are not having flow-limiting coronary artery disease, as demonstrated by stress echocardiography or autopsy (Ammann et al., 2003).

Forty-two percent of patients needing to be transferred to ICU are troponin positive but myocardial infarction could be documented only in 50% of them. On the other hand, around 12% of patients in ICU will have a rise in their cardiac troponin, and 75% of them will meet the criteria for myocardial infarction (Lim et al., 2006b).

Cardiac patients with known coronary artery disease, who have been admitted for a medical reason and became critically ill, will have a significantly higher in-hospital mortality if they have a high cardiac troponin level (Kollef et al., 1997).

Among critically ill medical patients, the clinical deterioration of cardiac dysfunction is an independent predictor of a significantly higher mortality, but an isolated elevation of cardiac troponin is not (King et al., 2005; Favory and Néviere, 2006; Keller et al., 2009).

The higher mortality noted in those critically ill ICU patients with elevated cardiac troponin is due to the fact that they are sicker (Keller et al., 2009).

3. Conclusion

Troponins are highly sensitive and specific cardiac markers which play a major role in the diagnosis and risk stratification of coronary artery disease and the interpretation of their results should be in the clinical context. On the other hand, the elevation of troponin levels in the absence of coronary artery disease is of little diagnostic value but may be helpful in anticipating the outcome but does not dictate which type of management is appropriate.
Elevated troponin in patients with coronary artery disease who presented with acute coronary syndrome may indicate high risk and predict the benefit from aggressive therapy, while non-thrombotic causes derive no benefit from aggressive therapy in low-risk patients.

References


