

From Creatine Kinase-MB to Troponin

The Adoption of a New Standard

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MAJOR perioperative cardiac events in patients undergoing noncardiac surgery continue to be a significant source of perioperative morbidity with ranges from 1.4% in relatively unselected patients¹ to 6% in patients older than 70 yr with cardiac disease.² Moreover, perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long-term morbidity and mortality associated with noncardiac surgery.^{3–6} The actual rate of PMI varies between studies in part because of the definition used and the method of surveillance. Part of the definition depends on the biomarkers (*e.g.*, creatine kinase [CK], lactate dehydrogenase, and troponin) used to define PMI. This article will review the evolution in the use of biomarkers and how more specific biomarkers have increased the rate of PMI detected.⁷

Definition of PMI

According to the traditional definition, at least two of the three criteria must be fulfilled to diagnose myocardial infarction (MI): (i) typical ischemic chest pain; (ii) increased serum concentration of CK-MB (myocardial band) isoenzyme; and (iii) typical electrocardiographic findings, including development of pathologic Q waves. The advent of sensitive and specific serologic biomarkers has resulted in a major shift in the classic paradigms for diagnosing infarction.

Devereaux *et al.*⁸ suggest that only 14% of patients experiencing a PMI will have chest pain and only 53% will have a clinical sign or symptom that may trigger a physician to consider

an MI. The large proportion of clinically unrecognized MIs can be explained by several factors present in the immediate postoperative period: analgesics, intubation and sedation, and a host of more common explanations for potential signs and symptoms, such as atelectasis, pneumonia, hypovolemia, and bleeding.

Electrocardiography

Electrocardiography plays a key role in the diagnostic workup of suspected MI. The changes in the ST-T waveforms and the Q waves potentially allow the clinician to date the event, to suggest the infarct-related artery, and to estimate the amount of myocardium at risk. Electrocardiography criteria for diagnosis of acute MI in the absence of left ventricular hypertrophy and left bundle branch block are ST elevation MI—new ST elevation at the J-point in two contiguous leads with the cutoff points: more than or equal to 0.2 mV in men or more than or equal to 0.15 mV in women in leads V₂–V₃ and/or more than or equal to 0.1 mV in other leads; non-ST elevation MI (ST depression and T-wave changes)—new horizontal or down-sloping ST depression more than or equal to 0.05 mV in two contiguous leads; and/or T inversion more than or equal to 0.1 mV in two contiguous leads with prominent R wave or R/S ratio more than 1.

However, the electrocardiogram by itself is often insufficient to diagnose acute myocardial ischemia or infarction because ST deviation may be observed in other conditions such as acute pericarditis, left ventricular hypertrophy, left bundle branch block, Brugada syndrome, and early repolarization patterns. Furthermore, in cardiomyopathy, for example, Q waves may occur due to myocardial fibrosis.⁹ A more complete review can be found elsewhere.¹⁰

Biochemical Markers—Evolution of the Tests Used for Biochemical Detection of Heart Damage

Measurement of cardiac markers in blood has been the mainstay for diagnosis of acute MI for nearly 50 yr.

A loss of cellular integrity of the sarcolemma results in the release of a number of proteins into the circulation that can be used as biochemical markers of acute myocardial necrosis. CK, SGOT (more recently known as AST), lactate dehydrogenase, myoglobin, and troponins are some of these markers.

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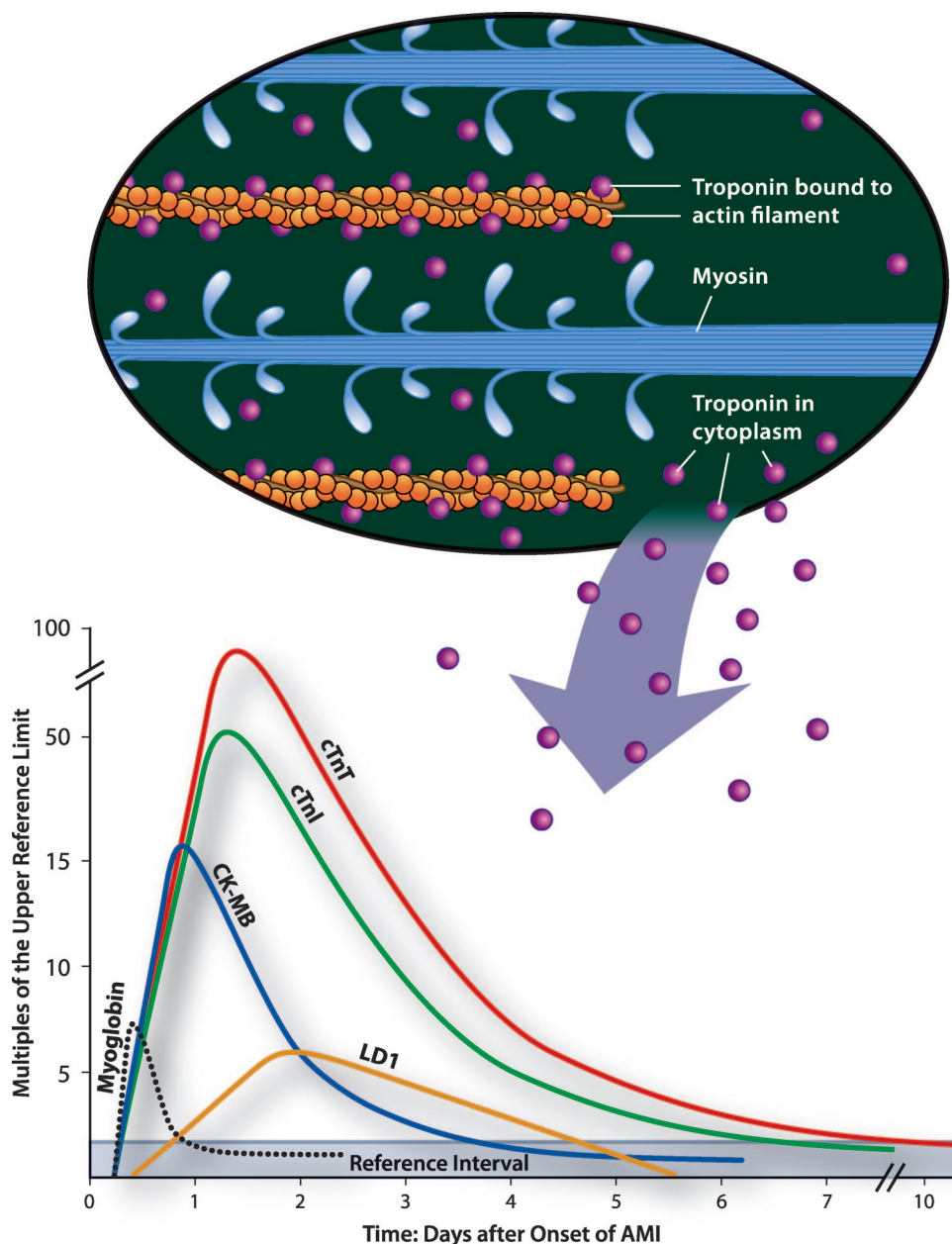


Fig. 1. Release of cardiac troponins in acute myocardial infarction. Top: a diagram of a cardiomyocyte that is in the process of releasing biomarkers. Most troponins exist as a tripartite complex of C, I, and T components that are bound to actin filaments, although a small amount of troponin is free in the cytoplasm. Bottom: the pattern of release of the different biomarkers based on time after an acute myocardial infarction (AMI) including myoglobin, creatine kinase (CK)-myocardial band (MB), lactate dehydrogenase (LD) 1, cardiac troponin I (cTnI), and cardiac troponin T (cTnT).

The timing of their appearance and disappearance in blood is mainly dependent on quantity of release, molecular size, and solubility (fig. 1). The first practical test used for biochemical detection of myocardial damage was the measurement of transaminases described in 1954.¹¹ Having wide tissue distribution, AST and lactate dehydrogenase are less specific for myocardial necrosis and offer no advantage over CK isoenzymes. Myoglobin, a heme-related protein abundant in cardiac and skeletal muscle, is an early marker of myocardial necrosis. It is detectable in the plasma 1–2 h after the onset of chest pain, with a peak at 3–8 h. With the availability of

assays for CK isoenzymes, these tests were gradually abandoned, at least for an early diagnosis of MI.

Creatine Kinase

CK is the enzyme responsible for catalyzing the transfer of high-energy phosphate from creatine phosphate to adenosine triphosphate. CK is known to rise within 4–8 h after an acute MI and to decline to normal levels within 3–4 days. In 1960, Dreyfus *et al.*¹² demonstrated markedly increased plasma CK activity in patients with MI. Total CK found in

the normal circulation varies tremendously, and CK is a well-recognized marker of rhabdomyolysis. The problem of multiple etiologies makes interpretation of CK release more difficult in the surgical population.

CK Isoenzymes

In 1966, van der Veen and Willebrands¹³ demonstrated that CK-MB is a highly specific marker of MI. In the 1970s, it became evident that CK-MB was to be the standard for the diagnostic and quantitative assessment of MI. CK isoenzyme analysis substantially increased the sensitivity of this test for the diagnosis of acute MI. However, other types of myocardial injury, such as myocarditis, trauma, and cardiac surgery, also cause the release of CK-MB.¹⁴

A variety of techniques were developed to further improve the sensitivity and rapidity of assaying for CK-MB. In the mid-1980s, the development of an antibody specific for CK-MB¹⁵ marked the beginning of the era of immunologic detection of biomarkers. This technique of mass assay offered the advantage of measuring protein concentration over enzymatic activity. With direct analysis of CK-MB irrespective of total activity, it was quickly recognized that the myocardium is not the only tissue containing large amounts of CK-MB as initially believed.¹⁶ CK-MB has been found in the small intestine, tongue, diaphragm, uterus, and prostate. Skeletal muscles also contain CK-MB in small amounts. In the surgical setting, the use of the CK-MB fraction is complicated by increased levels of both total CK and noncardiac CK-MB.

The shift from transaminases and dehydrogenases to isoenzymes of the latter and then to CK, CK-MB, and CK-MB mass improved test precision, resulting in greater sensitivity and specificity in the diagnosis of MI over time and better case classifications. However, these tests still did not allow the definite distinction of skeletal and cardiac muscle injuries. This lack of cardiospecificity accelerated the desire for a more specific test than CK-MB.

CK-MB was considered the benchmark for MI diagnosis from the 1980s through the late 1990s. The diagnostic sensitivity of both CK-MB (activity or mass) and the troponins markedly increases with time. Sampling to at least 10 h yields approximately 90% diagnostic sensitivity with either biomarker.¹⁷ In a meta-analysis by Balk *et al.*,¹⁸ CK-MB showed a rather low cumulative sensitivity of 79% and a cumulative specificity of 96% in emergency department patients. It could be argued, however, that inclusion of studies that mixed results of assays, different cutoff strategies, and less than ideal sampling almost certainly led to underestimation of diagnostic sensitivity. Wu and Lane¹⁹ limited inclusion to studies that used CK-MB mass assays in samples collected over the appropriate timeframe of 12–24 h after the onset of symptoms. Their meta-analysis reported a cumulative sensitivity of 97% and cumulative specificity of 90%.

Troponins

The cardiac troponins are regulatory proteins with both cytosolic and structural pools that are released because of

necrosis. The troponin complex is located on the thin filament of striated muscle and consists of three subunits: troponin T, a binding protein that attaches the troponin complex to tropomyosin; troponin I, which modulates the interaction of actin and myosin by acting as an inhibitor of actomyosin adenosine triphosphatase activity; and troponin C, the calcium-binding subunit of the troponin complex. The cardiac forms are designated cardiac troponin I (cTnI) and cardiac troponin T (cTnT). Cardiac troponin has nearly absolute myocardial tissue specificity and high clinical sensitivity.²⁰ Several large studies of patients with acute coronary syndrome support the clinical efficacy of troponin over the previous gold standard: the CK and its MB fraction.

Although there is only one assay for cTnT, there is a multiplicity of assays for cTnI with substantial heterogeneity of assay sensitivities.²¹ Manufacturers are now developing a new generation of high-sensitivity cTn assays that are more precise at low concentrations and measure cTn concentration at less than 1 ng/l. Of note, cTn assays are neither standardized nor harmonized. Different assays are composed of different antibody configurations recognizing different epitopes of cTnI, suggesting that specific assays may detect slightly different groups of patients, depending on the nature and timing of cTn release.²² The performance of assays and the release kinetics and plasma clearance of both troponin T and I have been described elsewhere.^{23–25} An increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population (upper reference limit). Detection of a rise and/or fall of troponin is essential to the diagnosis of acute MI. Blood samples for measurement of troponin should be drawn on first assessment and 6–9 h later. The above-mentioned discriminatory percentile is designated as the decision level for the diagnosis of MI and must be determined for each specific assay with appropriate quality control. It has also been recommended that optimal test reproducibility should be defined as less than or equal to 10% imprecision at the 99th percentile upper reference limit for each assay.

One of the biggest issues apart from the problem of selecting relevant reference subjects is the current practice of the Food and Drug Administration of approving assays based on higher receiver-operating characteristic-optimized cut-offs. In a recent issue of clinical chemistry, Apple²⁶ introduced his concept of a scorecard approach to decide which assays are acceptable for use in clinical practice. He proposed a two-tier system using both the 99th percentiles and imprecision values at the 99th percentile based on a young, healthy reference population that is diversified by sex, race, and ethnicity.

Studies Evaluating the Role of the Troponins for Diagnosis of PMI

The first major study to evaluate the perioperative use of cTnI was conducted by Adams *et al.*²⁷ The authors compared electrocardiogram, total CK, CK-MB, and cTnI with the gold standard (new akinesia or dyskinesia on postopera-

tive transthoracic echocardiography) for detection of perioperative infarction in 108 patients undergoing vascular or spine surgery. Blood samples were obtained every 6 h for at least the first 36 h after surgery. In this population, a PMI as defined by new abnormalities of wall motion was diagnosed in 8 patients (8%). The sensitivity of cTnI was 100% and that of CK-MB was 75%. The difference between the specificity of cTnI (99%) and that of CK-MB (81%) was significant ($P < 0.005$). Thus, these data did not establish the superior sensitivity of cTnI compared with CK-MB, only its superior specificity for the detection of perioperative infarction.

Lee *et al.*²⁸ evaluated the diagnostic performance of cTnT as a marker for myocardial injury in 1,175 patients aged 50 yr or older and undergoing major noncardiac surgery. CK-MB and electrocardiographic criteria were used to define acute MI. cTnT was measured in the recovery room after surgery and on the next two postoperative mornings. Acute MI was diagnosed in 17 patients (1.4%). cTnT increases occurred in 87% of patients with MI and in 16% of patients without MI, yielding a sensitivity of 87% and a specificity of 84%. The receiver-operating characteristic curves indicated that the two tests had similar diagnostic performance in detecting MI but that cTnT was superior for prediction of complications.

Metzler *et al.*²⁹ conducted a study with the aim of examining the perioperative pattern of changes in troponin. Blood sampling was performed daily from the day before surgery until the fifth postoperative day (POD) in 67 patients with cardiac risk undergoing elective noncardiac surgery. Eight of the 13 patients (12%) with increased cTnT concentrations had an adverse outcome. In seven patients, CK-MB and troponin increases were discordant. With a cTnT cutoff at 0.2 ng/ml, the positive and negative predictive values for adverse outcome were only 62% and 100%, respectively. By choosing a higher cutoff of 0.6 ng/ml, the positive and negative predictive values for adverse outcome were 88% and 98%.

Haggart *et al.*³⁰ compared the value of cTnI and CK/CK-MB ratios for detection of myocardial injury in 59 patients undergoing either emergency (24) or elective aortic surgery. More than half the patients undergoing emergency surgery and more than a quarter of those having elective surgery suffered myocardial necrosis as determined by detectable cTnI levels. This was accompanied by an increased CK-MB/CK ratio in less than one-fifth of patients.

The use of cTnI in diagnosing PMI in the setting of orthopedic surgery was evaluated by Jules-Elysee *et al.*³¹ in 85 patients with risk factors for coronary artery disease. In this population, cTnI seemed to be as sensitive as and more specific than the CK-MB index.

Martinez *et al.*³² evaluated surveillance strategies for the diagnosis of PMI using TnI in a cohort of 467 patients at high risk who required noncardiac surgery, with the goal of identifying the highest diagnostic yield. The diagnosis of myocardial injury was determined by biomarkers combined with either postoperative changes on 12-lead electrocardiogram or one of three clinical symptoms consistent with MI (chest pain, dyspnea, or requirement for hemodynamic sup-

port). The incidence of MI was 9.0% by the criterion of cTnI greater than or equal to 2.6 ng/ml, 19% by TnI greater than or equal to 1.5 ng/ml, 13% by CK-MB mass, and 2.8% by CK-MB ratio. The specificity of TnI greater than or equal to 2.6 ng/ml as an indicator of MI was 98%, and its positive predictive value was 85%. Using this cutoff, the strategy with the highest diagnostic yield was surveillance on PODs 1, 2, and 3.

Le Manach *et al.*³³ used cTnI surveillance after abdominal aortic surgery in 1,136 patients to better evaluate the incidence and timing of PMI (TnI ≥ 1.5 ng/ml) or myocardial damage (abnormal cTnI < 1.5 ng/ml). Abnormal cTnI concentrations were noted in 163 patients (14%), of whom 106 (9%) had myocardial damage and 57 (5%) had PMI. In 34 patients (3%), PMI was preceded by a prolonged (> 24 h) period of increased cTnI, and in 21 patients (2%) the increase in cTnI lasted less than 24 h. Abnormal but low postoperative cTnI was associated with increased mortality and could lead to MI. The authors concluded that they had identified two different types of PMI, early and delayed (fig. 2).

Studies Evaluating the Role of the Troponins for Both Diagnosis and Prognosis

The fact that, in the cohort studied by Lee *et al.*,²⁸ 90% of patients with cTnT increases did not have clinical complications during the perioperative follow-up raised the question whether these values were false-positive results or evidence of subclinical myocardial injury. To address this issue, Lopez-Jimenez *et al.*³⁴ collected 6-month follow-up data on a sub-cohort of 772 patients from the previous study. During the follow-up period, there were 19 (2.5%) major cardiac complications. A cTnT value more than 0.1 ng/ml was an independent correlate of cardiac events, whereas CK-MB was not correlated with postdischarge cardiac events.

Badner *et al.*³⁵ intensively monitored isoenzyme and electric activity of the heart for the first 7 postoperative days in 323 patients with ischemic heart disease, aged 50 yr or older, and undergoing noncardiac surgery. After surgery, patients had daily clinical assessments, electrocardiograms, and measurements of CK, CK-MB, and cTnT (not used in the first 92 patients) on the operative night, twice daily on PODs 1–4, and then daily on days 5–7. The criteria for PMI diagnosis were designed to require the presence of an indicator of high sensitivity (increased total CK) and at least two indicators of high specificity (increased CK-MB, increased cTnT, Q waves, or a positive result of a pyrophosphate scan). The authors observed a 6% incidence for PMI using these criteria. With 14 of 18 events occurring during the first postoperative night, they corroborated the finding that PMI is an early postoperative event in patients with known ischemic heart disease. Use of TnT increase as a sole criterion for the diagnosis of PMI would have nearly doubled the incidence and moved the peak of event occurrence to the first POD. Interestingly, 1-year follow-up suggested that patients with silent

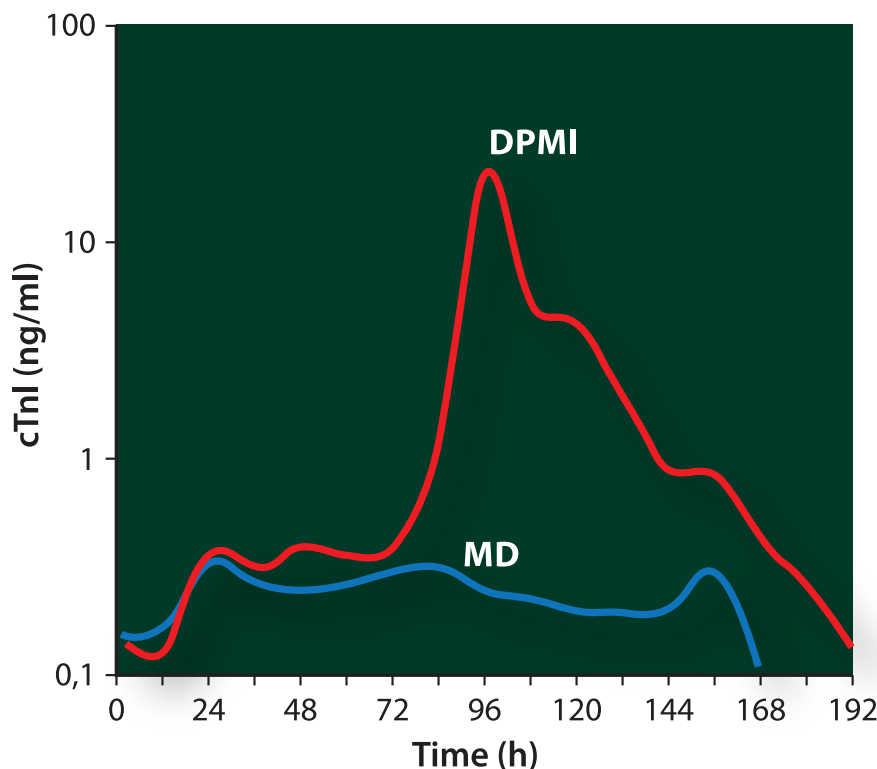


Fig. 2. Cardiac troponin I (cTnI) profiles over time of two representative patients with myocardial damage (MD) or delayed postoperative myocardial infarction (DPMI). Note that during the period of subinfarction MD in the patient with DPMI, the cTnI profile is similar to that of the patient with MD only. Log scale is used for cTnI values. Modified with permission from ANESTHESIOLOGY 2005; 102: 885–91.³³

PMIs have similar short-term outcomes as those with symptomatic PMIs.

Neill *et al.*³⁶ evaluated the changes in cardiac protein concentrations (CK-MB, cTnT, and cTnI) after vascular or major orthopedic surgery in 80 patients older than 45 yr. The authors compared these changes as markers of postoperative cardiac complications with the incidence of ambulatory electrocardiographic changes for silent myocardial ischemia. Eight patients (10%) had major and 21 patients (27%) had minor postoperative complications. Both cTnT and cTnI showed high specificity for major complications, 96% and 97% respectively, but sensitivity was only 43% for cTnT and 29% for cTnI. There were no associations between postoperative ischemia and cardiac protein concentrations. At 3-month follow-up, cTnT correlated best with complications.

The ideal discrimination value of cTnI between the “complicated and uncomplicated” patient groups was investigated by Godet *et al.*³⁷ in 329 patients undergoing infrarenal aortic surgery. cTnI was measured at recovery and on PODs 1–3. MI was defined as new Q wave or prolonged ST-T depression for more than 2 days. Thirteen patients (4%) developed 19 relevant cardiac complications (cardiac failure, MI, and cardiac death) in the postoperative period. A cTnI level greater than 0.54 ng/ml was correlated with the occurrence of postoperative cardiac complications in the period until discharge. That cutoff yielded a sensitivity of 75% and a specificity of 89%. Late cardiac complications occurring in the first year after aortic surgery were not correlated with cTnI.

Kim *et al.*³⁸ found that increased cTnI levels were associated with a significantly increased risk of PMI and 6-month mortality in a group of 229 patients after major vascular surgery. They further reported a dose–response relation between cTnI concentration and mortality.

Transition to the Use of Troponin

According to the new universal definition of MI, any of the following criteria meets the diagnosis for MI: detection of rise or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia; electrocardiogram changes indicative of new ischemia (new ST-T changes or new left bundle branch block); development of pathologic Q waves in the electrocardiogram; and imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.³⁹ However, it is important to keep in mind that nearly all the well-accepted studies of clinical risk stratification are based at least in part on diagnosis of PMI using adaptations of the World Health Organization definition, which requires any two of three criteria: ischemic symptoms, electrocardiographic changes, and increased CK-MB levels.

In summary, the available studies highlight the difficulty of using cardiac-specific troponin to distinguish myocardial damage from infarction. Commonly, troponin increase

alone is mistakenly equated with the diagnosis of MI. However, many conditions may be associated with increased troponin levels, including neurologic injury, brain death, hemorrhagic shock, cardiac trauma, sepsis, hypotension, renal insufficiency, pulmonary embolism, heart failure, and any other condition with increased ventricular wall stress.^{40–44} Furthermore, although recently any increase in troponin in the appropriate clinical setting had been considered indicative of myocardial necrosis rather than ischemia, results from the Protein Markers of Ischemia using Proteomic Testing—TIMI 35 study showed that transient stress-induced myocardial ischemia is associated with a quantifiable increase in circulating troponin that is detectable with a novel, ultrasensitive cTnI assay.⁴⁵ Another issue that remains to be addressed is use in terms of guiding aggressiveness of care. Even if we believe that there is value in perioperative surveillance looking for troponin leakage in the absence of other criteria for MI, the question remains whether early therapy could affect outcome in terms of morbidity and mortality either in the perioperative period or after discharge.

Future Directions

The new generation of hs cTn-assays has been shown to be superior to the standard troponin assays for early diagnosis of MI in two recently published studies.^{46,47} However, these studies did not assess the effect of the sensitive troponin assays on clinical management. Furthermore, it remains to be proven whether the results from a group of patients with a high pretest probability can be translated to postsurgical conditions.

Consistently performing better than traditional clinical risk scores and preoperative diagnostic tests, the natriuretic peptides clearly hold promise as a relatively cheap and noninvasive risk stratification tool, perhaps both pre- and postoperatively.⁴⁸

Hs C-reactive protein has been shown to be predictive of both immediate postoperative outcome⁴⁹ and significantly decreased overall survival⁵⁰ in the setting of coronary artery bypass surgery.

Another interesting approach may be the simultaneous measurement of multiple biomarkers. Goei *et al.* recently demonstrated that both hs C-reactive protein and NT-pro-brain natriuretic peptide have additional value in the prediction of postoperative cardiac events in vascular surgery patients to cardiac risk factors alone. The integrated use of both NT-pro-brain natriuretic peptide and hs C-reactive protein was able to improve cardiac risk stratification.⁵¹ Fellahi *et al.*⁵² assessed the multiple marker approach in cardiac surgery. Their recently published study showed that simultaneous measurement of cTnI, brain natriuretic peptide, and C-reactive protein improves the risk assessment of long-term adverse cardiac outcome after cardiac surgery.

Conclusion

The evidence to guide the rational use of perioperative cardiac monitoring, electrocardiograms, and troponins is limited,

and further evaluation regarding the optimal strategy is required. On the basis of the current evidence, in patients without documented coronary artery disease, surveillance should be restricted to those who develop perioperative signs of cardiovascular dysfunction. In patients with high or intermediate clinical risk who have known or suspected coronary artery disease and who are undergoing high- or intermediate-risk surgical procedures, serial 12-lead electrocardiograms should be obtained at baseline, immediately after the surgical procedure and on PODs 1 and 2. Consideration should be given to the use of cardiac-specific troponins for the first 4 days after surgery.

In light of all the areas of uncertainty concerning the clinical value of measuring troponin leakage, the 2007 update of the American College of Cardiology/American Heart Association Perioperative Evaluation Guidelines limited the recommendation for postoperative troponin measurement to patients with electrocardiographic changes or chest pain typical of acute coronary syndrome (level of evidence: C).⁵³ The European Society of Cardiology Guidelines for preoperative cardiac risk assessment and perioperative cardiac management in noncardiac surgery that were published in August 2009 do not recommend routine biomarker sampling to prevent cardiac events.⁵⁴

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