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REDEFINING MYOCARDIAL INFARCTION FOR THE 21ST CENTURY

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INTRODUCTION

By defining an object or a concept, we gain control over it. Medical education consists in large part of learning a series of definitions that carry with them the power to communicate with one's colleagues. This process of definition and hence control continues indefinitely throughout a medical career. Defining a disease is a process that enables clinicians and clinical scientists to label patients—a process known as "making a diagnosis". Labeling a patient with a specific diagnosis has important implications for that individual with respect to his/her relationship to the medical community and to the rest of society. For example, when a patient is given a diagnosis of myocardial infarction, this simple step changes that individual's ability to perform certain jobs, e.g., airline pilot; or, it may make this patient eligible to participate in a variety of clinical experiments aimed at improving either the diagnostic or the therapeutic aspects of myocardial infarction. Unfortunately, clinicians and clinical scientists often define the same disease differently. Thus, characteristics used to define a disease in one country may be interpreted differently by physicians in another nation thus rendering comparisons of this particular disease between countries difficult if not impossible. Similarly, one study may define a disease in a manner that is different from the definition employed in another clinical trial. This makes it very difficult to compare the results of different pharmacological, interventional and epidemiological studies that employ patients with a specific disease. Moreover, public health statistics and insurance company data may also employ differing definitions of a particular disease such as myocardial infarction, thereby making comparisons of results very difficult.

Diagnosis of Myocardial Infarction

Such diagnostic confusion is the case with myocardial infarction. Attempts in the past to arrive at a standardized definition of this entity

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have failed, often because of evolving diagnostic technology and/or complexity or confusion in the suggested definition. In an attempt to alleviate some of this confusion and arrive at an internationally acceptable definition of myocardial infarction, the American College of Cardiology and the European Society of Cardiology completed a two year consensus process during the year 2000. A joint task force of these two international organizations sought to define myocardial infarction in a universally acceptable manner. The consensus process led to a document that went through an extensive editorial process before it was published simultaneously in the European Heart Journal and the Journal of the American College of Cardiology (September, 2000). Additional refinements of this definition are currently being implemented with a new committee (including representation from the World Heart Federation and the World Health Organization) scheduled to begin meeting in September of 2003.

Myocardial infarction can be defined from a number of different perspectives related to clinical, pathological, electrocardiographic, biochemical, and epidemiological aspects of the disease. Changes in the definition of myocardial infarction can have major social and psychological implications. Initially, the task force studied the original WHO definition of myocardial infarction stemming from work done during the 1960's and 70's (1).

It became clear early in the deliberations of the task force that the new definition of myocardial infarction needed to be linked to a number of qualifying prognostic factors related to the infarct in question. Such qualifications referred to the size of the infarct, the amount of surviving, functional left ventricular myocardium, the circumstances under which the infarct occurred, e.g., during PTCA/stent placement or spontaneously, and the timing of the episode of myocardial necrosis in question in relation to the time of observation, i.e., was the infarct new or old? Each of these factors carried with it important prognostic implications. Thus, it was decided that it would be insufficient for the clinician to know merely the volume of myocardium infarcted during the period of observation. The new definition for myocardial infarction that was eventually accepted was as follows:

Either of the following two criteria satisfies the diagnosis for an acute or evolving myocardial infarction:

(1) typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of myocardial necrosis with at least one of the following:
   (a) ischemic symptoms;
   (b) development of pathologic Q waves on the ECG;

(c) development of ECG changes of ischemia (ST segment elevation or depression);
(d) coronary artery intervention, e.g., angioplasty;
(2) pathological findings of an acute myocardial infarction.

Criteria for established myocardial infarction—

(1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember any symptoms. Biochemical markers of myocardial necrosis may have normalized.
(2) Pathologic findings of a healed or healing myocardial infarct (1).

Clinical Presentation

Symptoms suggestive of myocardial ischemia/necrosis include chest, epigastric, arm, wrist, or jaw discomfort with exertion or at rest. Discomfort associated with myocardial necrosis usually lasts at least 20 minutes. Symptoms associated with myocardial necrosis can also include nausea, vomiting, dyspnea, dizziness, and/or syncope. Occasionally, myocardial necrosis develops in the absence of symptoms.

Pathology

Myocardial infarction is defined pathologically as myocardial cell death secondary to prolonged ischemia. It can be recognized by an experienced observer following a careful histological examination. After the onset of myocardial ischemia, cell death is not immediate, requiring a finite period of time (as little as 15–20 minutes) to develop. Thereafter, approximately 6 hours must pass before the pathologist can identify myocardial necrosis by standard macroscopic or light microscopic techniques. Complete necrosis of all cells within an ischemic myocardial zone usually requires 4 to 6 hours (1).

Electrocardiography

Electrocardiographic signs of ischemia and non-ST segment elevation infarction may be identical, i.e., ST segment depression. The ECG findings are more specific with respect to ST segment elevation infarction. ECG changes indicative of myocardial ischemia that may progress to infarction include: patients with new or presumed new ST segment elevation at the J point in two or more contiguous leads with the elevation equal to or more than 0.2 mV in leads V1, V2, or V3 and equal to or more than 0.1 mV in other leads. Patients with ST depression or T wave inversion should also have these changes in two or more

contiguous leads. An established myocardial infarction by ECG is defined by an ECG pattern demonstrating a QR pattern in leads V1–V3 that is at least 30 msec in duration and/or an abnormal Q wave (1 mm in depth) in any two contiguous leads involving leads I, II, aVL, aVF, or V4–V6. These findings are only valid in the absence of QRS confounders such as left bundle branch block or WPW syndrome. Not all patients who develop myocardial necrosis have an abnormal ECG. Thus, a normal ECG does NOT rule-out myocardial infarction since the new sensitive biomarkers detect very small quantities of myocardial necrosis in a range where ECG abnormalities may not be present (1).

Biochemical Markers

Because blood biomakers have become the "gold standard" for the diagnosis of myocardial infarction, these entities will be discussed more extensively. The diagnosis of myocardial infarction has been based historically on the combination of symptoms, ECG changes and biochemical markers. Lactate dehydrogenase (LDH), serum glutamate oxaloacetate transaminase (SGOT), and creatine kinase (CK) were the original markers used to confirm MI. Greater biochemical sophistication led to assays for creatine kinase subforms/isoforms, which were more specific for myocardial cells. Ongoing efforts to improve diagnostic accuracy for myocardial injury have involved a number of newer more specific myocardial biomarkers, e.g., troponin.

Creatine Kinase

Before the advent of the troponin assays, creatine kinase and its CKMB fraction were the gold standards for diagnosing myocardial infarction. Creatine kinase is abundant in many tissues and its presence in striated muscle and brain makes it a less specific marker for myocardial injury (1). Isoenzymes of CK are dimers composed of two M subunits, two B subunits, or one M and one B subunit. Approximately 15–30% of CK in the myocardium is of the CKMB type compared with 1–3% in normal striated skeletal muscle. The determination that CKMB was an isoenzyme more specific to myocardium made it the marker of choice in the past. CK isoform analysis has a sensitivity of 92%, and, until recently, this assay was the gold standard for early, rapid diagnosis of AMI to assist in emergency room triage (1,2). Unfortunately, electrophoretic assays can be of limited reliability because a number of proteins and other macromolecules can interfere with the assay. Naturally fluorescing compounds such as bilirubin, benzodiazepines, antidepressants, pyridoxine, and aspirin can and do produce artifacts in these assays. Patients

with renal failure also have artifactual bands that migrate with the CKMB isoenzyme in electrophoretic assays.

Immunochemical assays using monoclonal antibodies to measure CKMB mass are more reliable, sensitive, and specific, displacing the previous methods. Increases in plasma levels usually occur 6 to 12 hours after the onset of infarction, peaking at 24 hours, and returning to baseline after 36 to 72 hours. CKMB tends to peak and clear more quickly than does total CK. Traditionally, most studies have used a CKMB mass limit of >7 ng/ml as the cutoff for diagnosing AMI (2). Unfortunately, there are a number of situations where CKMB levels in the blood are elevated without a clear relationship to cardiac injury, e.g., extensive skeletal muscle injury.

Efforts to identify a percentage of CKMB to total CK values that might differentiate muscle injury from myocardial injury have been largely unsuccessful (3). Patients with hypothyroidism and renal failure also have elevated CK and CKMB blood levels. Cross reactivity of certain forms of alkaline phosphatase and of other macro kinases (antibody bound to CK isoform or CK aggregates) also results in false positive diagnoses of myocardial infarction. Lastly, heterophilic antibodies such as rheumatoid factor interfere with the CKMB assay thereby resulting in false positive identification of myocardial necrosis.

Myoglobin

Myoglobin is a protein present in all cardiac and skeletal muscle cells. Myoglobin is rapidly released into the circulation after cellular injury. Following myocardial necrosis, serum myoglobin levels rise in 1–2 hours, peaking at 6–7 hours and returning to baseline by 24 hours. However, the sensitivity of this test for myocardial necrosis is low but the negative predictive value is high, making it a useful test for rapid triage of chest pain patients in the emergency room. Unfortunately, myoglobin is not cardiac specific and is increased in patients with trauma, skeletal muscle injury, a variety of chronic disease states and renal failure. Its rapid kinetics and renal clearance make frequent, early testing essential for detection. With a sensitivity of 39% and a positive predictive value of only 43%, myoglobin testing alone is not recommended for the diagnosis of myocardial necrosis. Myoglobin can be used together with other biomarkers for the early detection of myocardial injury.

Troponin

Cardiac troponins are regulatory proteins tightly complexed to the contractile apparatus of myocardial cells (4). Different troponin iso-

forms are produced by separate genes in different types of muscle cells. Cardiac troponins are therefore unique and completely specific to myocardium. There is a very small pool of cytosolic troponin present in myocardial cells, accounting for a relatively rapid release of this biomarker following myocardial cellular injury. Troponin is an ideal marker for myocardial injury because there are extremely low levels of this molecule circulating in the blood of normal people. In addition, marked changes in blood levels occur following small quantities of myocardial cellular injury, and these changes are easily measured and identified as abnormal. Two cardiac specific forms of troponin can be isolated and assayed: troponin T and troponin I. Troponin levels begin to rise at 3 to 12 hours after injury, peaking at 12 to 24 hours. Troponin T remains elevated for 8 to 21 days and troponin I remains elevated for 7 to 14 days.

The initial assay for troponin T had a nonspecific second antibody that resulted in false elevations. The assay was also abnormal in patients with polymyositis and no evidence of cardiac injury (5). Unfortunately, multiple assays from multiple companies are available for troponin I (6). Moreover, different assays utilize antibodies to a number of different epitopes or sites on the troponin I molecule thereby complicating the accuracy of the assays (7,8). Interference with these assays has also been noted from fibrin strands, heterophilic antibodies, phosphorylation, and the level of oxidation/reduction of the troponin molecule. Despite more technical assay problems, troponin I determinations (9), have turned out to be more specific than troponin T measurements for defining myocardial injury (10,11) with no spurious elevations related to muscle injury, renal failure, malignancy or sepsis, as seen with troponin I. The specimen collection process affects troponin assays. Heparinized tubes are the most reliable for collecting blood that will be used for troponin determination since clots interfere with the assay as do EDTA and citrate (12).

Despite these problems, the sensitivity and specificity of the assays for both troponins are greater than that for CK or CKMB for the detection of myocardial cell injury. Point-of-care qualitative testing is available for both forms of troponin, but the assay for troponin T has been more uniform and reliable (13,14,15).

Renal Failure and Troponin

Elevations in CKMB are commonly noted in patients with renal failure but turn out to be rather nonspecific for the diagnosis of myocardial injury. Elevated values in these patients fail to demonstrate

the typical rise and fall seen with myocardial infarction. Elevations in CKMB in renal failure patients are thought to be due to low levels of muscle breakdown as well as failure to clear CKMB in the kidneys. The frequent occurrence of chest pain in patients undergoing dialysis creates an important diagnostic dilemma.

Initially, it was hoped that troponin assays would eliminate the problem of false positive diagnoses of myocardial injury in renal failure patients (16). Thus far, the study results have been mixed (17). Elevations of troponin T occur more frequently in dialysis patients than do elevations in troponin I. Patients with diabetes undergoing dialysis are also more likely to have elevated troponin T values; they are also more likely to have coronary atherosclerosis. Persistently elevated troponin values in patients with renal failure have negative prognostic implications. The exact mechanism of such elevations is not yet clarified. Clearly, there are a number of issues yet to be resolved in the use of troponins to assess dialysis patients. However, it is clear that elevated troponin values in patients with renal failure portend a more complicated course than when blood troponin values are normal.

Troponin Assays and Percutaneous Coronary Intervention

Cardiac enzyme determinations have been used to assess post-interventional risk of adverse events since the mid-1990s. In the absence of Q-wave myocardial infarction, the level of enzymatic elevation that can be deemed totally benign has been controversial. Data from the Cleveland Clinic regarding angioplasty and directional atherectomy (18), showed that CKMB elevations twice the upper limit of normal or more were associated with higher cardiac death rates and higher cardiac event rates during the first 12 to 24 months following the procedure. Procedural complications such as distal arterial embolism, no reflow following successful angioplasty, side branch compromise and dissection were all associated with greater likelihood of CKMB elevation. Pooled data from several large trials showed consistent correlations between CKMB elevations and increased mortality at 6-month follow-up (19). Evaluation of the extent of coronary disease in patients with CKMB elevation revealed a greater plaque burden and more thrombus-containing lesions in patients with elevated CKMB values, suggesting that more extensive atherosclerotic coronary artery disease might be the explanation for the increased CKMB values and the worsened outcomes (20). In a study of interventional procedures on vein grafts, the 1 year mortality correlated incrementally with CKMB elevations from greater than 1 to greater than 5 times the upper limit of normal (21).

Coronary arterial stenting has reduced procedural complication rates associated with angioplasty. Data from the Washington Hospital Center involving a large cohort of patients undergoing coronary stenting demonstrated that minor CKMB elevations from 1 to 5 times normal were not associated with adverse clinical events or increased late mortality. However, elevations of greater than 5 times normal were associated with worse outcomes (22). Troponin elevations were not good predictors of adverse clinical events unless there was concordant CKMB elevation (23,24). In patients admitted with acute coronary syndromes and elevated troponin I values, re-elevation of troponin I above the admission level following a stenting procedure was associated with a higher in-hospital mortality and a higher 6 month cumulative mortality compared with patients without troponin I re-elevation (25). CKMB re-elevation had no prognostic value in this study. It seems clear that small elevations in biomarkers following an interventional procedure do represent small quantities of acute myocardial necrosis. Whether these minor infarcts portend a worsened prognosis depends on a multiplicity of factors (see below).

While there are no clear recommendations at the present time regarding the routine evaluation of cardiac biomarkers post-intervention, it seems prudent to suggest that determinations of these markers seems reasonable (26). If elevated values are noted, patients should be monitored more closely than if normal troponin values were observed.

Coronary Bypass Surgery (CABG)

Perioperative myocardial infarction is associated with a high risk of both early and late mortality post-CABG. Traditionally, the diagnosis of perioperative myocardial infarction has been based on the finding of new Q waves on the ECG along with segmental wall motion abnormalities on echocardiography. The skeletal muscle injury associated with sternotomy coupled with myocardial ischemia induced by surgery made interpretation of CK isoenzymes difficult. CKMB cutoff for the diagnosis of perioperative MI in the literature ranges from 5 times the upper limit of normal to 10 times the upper limit of normal. Lack of specificity for irreversible myocardial injury makes the use of this enzyme less than optimal for the diagnosis of myocardial ischemic injury.

The advent of troponin assays provided hope for a more specific and sensitive marker that might facilitate the identification of those patients with perioperative MI and its consequent risks. One study (27) identified a clear cutoff for perioperative patients: no patient with a

troponin I level of less than 40 ng/ml had a cardiac event at follow-up, and all but one of the patients with a level greater than 60 ng/ml had a cardiac event. Hence, the negative predictive value of a level below 40 ng/ml was 100% and the positive predictive value of a level greater than 60 ng/ml was 95%. Peak troponin I levels correlated strongly with new wall motion abnormalities, the development of Q waves on the ECG, arrhythmias, prolonged intubation, and re operation. Using a different troponin I assay and a strict definition for perioperative MI based on Q waves, Bonnefoy and colleagues found less impressive results (28): there was little difference between troponin I, troponin T, and CKMB for predicting adverse events even though there was a trend for troponin I to be a better discriminator. At a cutoff of 5 ng/ml, troponin I had a positive predictive value of only 53% with a negative predictive value of 98%, sensitivity of 91% and specificity of 82%. Another study of perioperative myocardial injury noted that troponin T levels correlated best with perioperative MI with a cutoff of greater than 3.9 ng/ml (29). The positive predictive value of this cutoff point was 41% with a negative predictive value of 99%.

Given the variations in assay sensitivities, no clear recommendations can be made at this time regarding the use of troponins to identify perioperative infarction. Clearly, troponins are invariably elevated following cardiac surgery as a result of minor trauma sustained before, during, and after the operation. The degree of troponin elevation in uncomplicated bypass tends to be relatively minor. However, identification of a clear cutoff point that would enable the physician to diagnose clinically important myocardial necrosis is still beyond our current abilities. On-going studies should enable us to make the diagnosis of perioperative infarction in the near future with the aid of sensitive and specific biomarkers.

Imaging

Imaging techniques are useful for ruling out myocardial ischemia/infarction in the emergency room, for identifying non-ischemic causes of chest discomfort, for defining post-infarction prognosis, and for identifying post-infarct complications such as ventricular septal rupture or mitral regurgitation. Neither echocardiography nor radionuclide techniques can distinguish ischemia from infarction. The positive predictive value of either of these two techniques for defining myocardial infarction is approximately 50%. Indeed, biomarkers are more sensitive, more specific and considerably less costly when compared with echocardiography or radionuclide techniques (1). However, imag-

ing techniques yield valuable information concerning complications of myocardial infarction as well as prognosis. Discussions are currently on-going concerning further revisions in the diagnostic criteria for myocardial infarction that would enable the finding of an abnormal imaging study in conjunction with elevated blood biomarker levels or electrocardiographic Q waves to be designated as a myocardial infarct.

Implications of the Revised Definition of Acute Myocardial Infarction

The use of cardiac biomarkers seeks to clarify diagnosis of the various subdivisions of "acute coronary syndromes". This relatively new term, acute coronary syndrome, speaks to shifts in our understanding of unstable coronary artery disease that has occurred over the past 20 years. While we previously spoke of acute myocardial infarction or unstable angina or even intermediate syndrome, we now recognize a continuum of disease that in its mildest form is stable angina, passing through unstable angina to non-Q-wave myocardial infarction, and ultimately reaching the most severe form of acute coronary syndrome, ST elevation myocardial infarction. With the advent of the new biomarkers such as troponin, it is now clear that patients with the previously identified syndrome of "unstable angina" were a mixed population ranging from individuals with pure myocardial ischemia to patients with mixed myocardial ischemia and myocardial necrosis. The troponin assay has enabled clinicians to identify a group of unstable coronary artery disease patients with normal or near normal ECGs and normal CKMB levels but minor elevations in blood troponin values. These latter individuals have suffered very small myocardial infarcts. In a number of studies, up to 33% of patients who were previously said to have had unstable angina are noted to have small elevations in blood troponin values and hence small quantities of infracted myocardium (30). The move to redefine myocardial infarction (1,31,32,33,34,35) to include this population was driven by the clear finding in innumerable studies that patients with elevated troponin values had cardiac event rates and mortality similar to that of patients who met the traditional criteria for acute MI (36,37,38,39,40,41,42,43). For example, data from the TIMI IIIB study revealed a 3.7% mortality rate for patients with troponin I levels $\geq$0.4 ng/ml compared to a mortality of 1% for individuals with troponin I $<$0.4 ng/ml. There was an almost linear correlation between increasing troponin I levels and increasing mortality, even in those patients who had a normal serum CKMB. A meta-analysis by Ottani (41) of 18,982 patients with acute

coronary syndromes found that individuals with non-ST-elevation chest pain who manifested an elevated troponin value had a mortality rate of 5.9% at 30 days compared with a 1.3% rate in similar patients with normal troponin values. The overall risk of death or MI at 30 days was 3.5 times higher in the elevated troponin group.

The use of troponin assays has clearly improved diagnostic accuracy in patients with acute coronary syndromes (Table 1). In addition, the improved sensitivity of troponin assays has helped to identify a population at high risk, a population previously under diagnosed and under treated. Newer therapies, specifically targeting this high-risk population, such as glycoprotein IIb/IIIa antagonists and low molecular weight heparin, have already shown survival benefit in this group of patients. Current studies also imply that a more aggressive, interventional approach is indicated in these patients.

Risk Stratification Following Acute Myocardial Infarction

The prognosis of patients with acute myocardial infarction has been thoroughly studied since coronary care units were first developed in

TABLE 1
Diagnostic Sensitivity and Specificity of Markers for Myocardial Infarction Based on Time From Onset of Chest Pain

Early Diagnosis	Late Diagnosis						
Marker	2h	4h	6h	10h	14h	18h	22h
CK-CKMB sub forms							
Sensitivity	21.1	46.4	91.5	96.2	90.6	80.9	53.1
Specificity	90.5	88.9	89.0	90.2	90.0	89.9	92.2
Myoglobin							
Sensitivity	26.3	−42.9	78.7	86.5	62.3	57.5	42.9
Specificity	87.3	89.4	89.4	90.2	88.3	88.8	91.3
Troponin T							
Sensitivity	10.5	35.7	61.7	86.5	84.9	78.7	85.7
Specificity	98.4	98.3	96.1	96.4	96.1	95.7	94.6
Troponin I							
Sensitivity	15.8	35.7	57.5	92.3	90.6	95.7	89.8
Specificity	96.8	94.2	94.3	94.6	92.2	93.4	94.2
Total CK-CKMB activity							
Sensitivity	21.1	40.7	74.5	96.2	98.1	97.9	89.8
Specificity	100.0	98.8	97.5	97.5	96.1	96.9	96.2
Total CK-CKMB mass							
Sensitivity	15.8	39.3	66.0	90.4	90.5	95.7	95.7
Specificity	99.2	98.8	100.0	99.6	98.9	99.6	99.1

Values are percentages.

the early 1960s. In general, the smaller the infarct, the more left ventricular myocardium that is preserved and the better is the prognosis. However, even very small infarcts such as those identified by means of the highly sensitive and specific troponin assays will still increase short and long-term mortality when acute coronary syndrome patients are compared. Elevated troponin values are not the only criteria on which prognosis should be based.

Consider the following two examples: In the first case, a 50 year old male presents with 30 minutes of substernal chest pain; his ECG is normal. A cardiac catheterization reveals single vessel coronary artery disease and normal left ventricular ejection fraction. His stenosed coronary artery is successfully dilated and a coronary stent is placed thereby eliminating all residual coronary arterial stenosis. Following the procedure, the patient develops a small infarct defined by an elevated blood troponin level. Clearly, if this patient corrects his coronary risk factors, his prognosis is excellent. Compare the prognosis of this first patient with that of an 80 year old man who comes to the hospital following 6 hours of severe substernal chest pain; again, the ECG is normal. The blood troponin value is modestly elevated to the same level as that noted in the first patient. However, cardiac catheterization of the second patient reveals severe, diffuse, three vessel coronary artery disease and a left ventricular ejection fraction of 20%. It is quite clear that the short and long-term prognosis is much worse for the second patient as compared with the first patient. Although both of these patients had suffered small infarcts that were diagnosed from their clinical history together with small elevations in blood troponin levels, their prognoses are quite different. Therefore, it is essential that the clinician pay attention to multiple factors when assessing a patient with an acute coronary syndrome. An elevated blood troponin level is an important prognostic factor but it is not the only prognostic factor to be considered.

Epidemiology

With the use of new sensitive biomarkers of myocardial necrosis, the incidence and prevalence of myocardial infarction is altered, thereby creating considerable consternation for students of epidemiology. Indeed, it will be difficult to compare current and future public health statistics dealing with acute myocardial infarction with data from earlier eras. Therefore, it is essential that a number of clinical centers continue to measure the new biomarkers as well as traditional enzymes and older

definitions of myocardial infarction so as to ascertain the magnitude of change engendered by the use of the new biomarkers (1).

Social And Public Policy

Changing the criteria for diagnosing myocardial infarction will have important effects on individual patients and on society in general. For example, a patient who formerly would have been told that he/she had had an episode of unstable angina might now be told that they had suffered a myocardial infarct, albeit a small one. Public health statistics, insurance calculations, disability applications, etc. will also be altered. It is important that educational efforts be sustained in order to inform both patients and healthcare regulatory agencies concerning the new definition of myocardial infarction. Moreover, the small nature of many of the newly diagnosed infarcts should be stressed.

CONCLUSIONS

The role of accurate biomarkers in the diagnosis of acute coronary syndromes has increased considerably in the past decade. The World Health Organization previously defined acute myocardial infarction from a combination of at least two of three components: symptoms consistent with myocardial ischemia, diagnostic ECG changes, and an enzyme pattern with classic rise and fall. Measurement of creatine kinase and its MB fraction by various assays were the gold standard for the diagnosis of myocardial necrosis until the new biomarker assays became available. Troponins are the most specific and sensitive biomarkers for identifying myocardial injury and their increasing utilization have resulted in a broadening of the definition of acute myocardial infarction. Previously, the traditional definition of myocardial necrosis failed to identify patients with small quantities of myocardial necrosis. Newer markers, such as troponin, now identify these patients as a subgroup at high risk for subsequent cardiac death or events. Newer therapeutic interventions including invasive strategies have been shown to improve outcomes in this high risk subgroup. The increased specificity of the troponin assays has reduced the number of patients who undergo extensive, expensive, and invasive evaluations for noncardiac chest pain syndromes.

The new cardiac biomarkers have improved triage in emergency rooms, enhanced diagnostic accuracy for myocardial ischemia, reduced inappropriate testing, and identified a previously unrecognized high-risk population of patients within those individuals who present with an acute coronary syndrome. Unfortunately, even with heightened

specificity and sensitivity, no assay is totally accurate and no assay by itself enables the clinician to perform a completely accurate risk assessment.

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DISCUSSION

Mitch, Galveston: I was wondering how you defined people with renal insufficiency. With renal insufficiency, the blood level of troponins might be artificially high with even a small release of troponin.

Alpert, Tucson: Yes, the whole question of patients with renal insufficiency is very interesting because at least with some troponin assays, particularly with the earlier assays and somewhat with the more recent assays, there are elevations in troponin that are persistent. These patients don't have the appropriate symptoms or EKG changes and so forth of an acute coronary syndrome. Their troponin is elevated and it never goes down. And interestingly enough, there have now been two large series (a particularly good one from the University of Minnesota) that point out that patients with renal failure, who have elevated troponin have a worse prognosis compared to patients who don't have elevated troponins. So it's telling us something about the uremic interaction with the myocardium. Perhaps these patients have an increased rate of myocardial apoptosis or some such thing, but we wouldn't want to stamp them as having myocardial infarction. Often in a clinical setting this can be a problem, because these patients may have atypical chest pain. In patients with renal failure, you need to look very much more carefully at the whole clinical picture.

Wolf, Boston: Joe, I wonder how the new definition has changed your management of patients? As a GP, if somebody now comes in and has a typical story or atypical EKG do you rely only on troponin level in your discussion about further evaluation?

Alpert: That's a very important point, Marshall. As you know, the emergency room physicians these days are absolutely terrified about chest pain patients, and they would like to admit everybody that even walks by the hospital complaining of chest pain. And so that leads to a big problem for the CCU service and the cardiologists in that there's a poor signal to noise ratio since most of these people don't have ischemic heart disease or at least don't have active ischemic heart disease. So one immediate factor here is that people who have negative troponins can often be sent home very quickly from the hospital and later referred for an exercise test or further evaluation without worrying that they are going to drop dead as soon as they get out of the hospital. This has led, of course, as you know, to rapid chest diagnostic protocols in hospitals and even in chest pain units that enables us to move folks out of the hospital faster as opposed to holding them for a day or two. Another point is that any patient with an elevated troponin usually finds their way to the catheterization laboratory because a number of large clinical trials have demonstrated that the invasive route seems to be a better way to keep these folks alive down the road than the non-invasive route.

Wolf: Are you saying that somebody with prolonged chest pain with a negative troponin you would send home without an exercise test?

Alpert: No, I'm not saying that. What I am saying is that somebody who you see who has fluky chest pain, of which there are many, many individuals who come into the hospital and have a negative troponin test. I'm perfectly happy to send these patients home without an exercise test. Now clearly if they said to me: "I have two hours of crushing substernal chest pain," and I also see EKG changes, but no bump in their troponin, clearly, we aren't sending that patient home.

Wolf: Thank you.

Ende, Philadelphia: What about the role of the hand-held echocardiogram in the emergency room for triage decisions?

Alpert: Well in fact Dr. Kaul will later be talking about some of these things. He has published data that shows that using the echocardiogram in the emergency room, or in fact doing treadmills or nuclear tests in the emergency is very helpful in sorting out people in whom the chest pain is non-cardiac. Thus, if you have normal wall motion by echo or normal perfusion by one of the perfusion scans or normal electrographic exercise test in those patients, it's perfectly safe to send those patients out immediately. You don't even have to follow up with finishing troponins. And a number of hospitals have demonstrated that that's very effective strategy. However, you need a really good person looking at these tests to make sure they are negative. It isn't something that the emergency room doc can have a quick look at and decide, "oh this looks ok." It really needs somebody who is very knowledgeable to look at it.

Weisfeldt, Baltimore: Your comments are very insightful, and really I think provide a great guide. In dilated cardiomyopathy there are increasing numbers of studies that show that there is a small troponin leaks from time to time that have prognostic significance. Do you think that represents myocardial infarction going on in these patients? Or that we are now getting down to the sensitivity of assay that actually detects the apoptosis as part of generalized cardiomyopathy?

Alpert: It's a wonderful questions, and one that got a great deal of discussion, both during the consensus conference and subsequently. I don't know yet if we are identifying myocardial apoptosis with the troponin test, but we may be seeing inflammatory myocardial injury or even, as you know, myocardial necrosis secondary to markedly increased wall stress in very dilated cardiomyopathies. These patients may actually be having little ischemic injuries. The answer to your questions is that we don't know yet exactly what kind of injury we're seeing. But I think as the assays get better in third generation troponin assays, the sensitivity will continue to get better, and we will be able

to discriminate at some point very, very tiny injuries maybe approximately the level of apoptosis injuries. As you know I mentioned before to Bill Mitch's question that when a patient has an elevated troponin and has renal failure, their prognosis is worsened over the next several years. The same is true of a heart failure patient, for example a patient with a dilated cardiomyopathy of a non-ischemic ideology. When they have a elevated troponin, they're prognosis is also worse compared to a patient who doesn't have the elevated troponin. So there's no question it means something. It means that there is ongoing injury. Now whether it's ischemic injury, and therefore meets the definition of myocardial infarction, or whether it's an inflammatory injury or a structural injury related to the dilatation, I don't think we know yet. I think we're going to hear a lot more about that as people collect more information in that area.

Colwell, Charleston: It seems to me that this might have a major impact on the planning of cardiovascular clinical trials. For instance, planners would wonder about the change in the event rate if myocardial infarction is the primary event. With ongoing trials, changing the definition in the middle of the stream would create problems. My question is: What impact do you think this would have in contributing to an increase in the diagnosis of myocardial infarction in a primary prevention trial?

Alpert: Your question is of course right on the mark. And in fact led us to come up with this new definition. And the reason was that if you look at most of the trials, most of the coronary care unit trials in the last ten years that have tested 2B3A blockers, low molecular heparin, etc., in fact, they usually look at so called major coronary events. And the major coronary events are usually recurrent myocardial infarction or readmission for very severe ischemia requiring bypass or angioplasty. Well, it turns out that in most of these trials the major component in that triple event is myocardial infarction, reinfarction or a second infarction. And consequently, that is the major factor that drives the statistical significance of these trials. The problem is that you look from trial, to trial to trial, people are using different definitions. So I can't compare trial A to B because the major end point that was used to determine statistical significance isn't the same in the two different trials. So the hope here is that we would get every trialist, and we actually had meetings with the FDA to try to get the FDA onboard here, to say "hey you have got to use this definition in your trial" so that at least from here on in every trial we will use the same definition so 10 years from now we can compare a trial then to now. So your point is very important, and in fact is the central tenant leading to a uniform world wide definition. One final point, we are in the second round of this now. We tried the last time to WHO and the World Heart Federation involved without success. This time they are going to be on board and the next couple of years we're going to tweak the definition a little bit.