Biochemical markers of cardiac damage: what is current, what is redundant?*

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BACKGROUND

The evaluation of patients with chest pain is one of the most challenging and difficult problems an emergency physician faces (1). Seven million patients access the emergency medical service system or present directly to emergency departments in the United States each year with a chief complaint of chest pain. Although the majority of cases are of benign etiology, there are several potential life-threatening causes, primary among which is ischemic heart disease (2).

From the pathophysiological point of view, acute coronary syndromes have a common mechanism: the atherosclerotic plaque ruptures and a mural or occlusive thrombus forms, impairing or interrupting the perfusion of myocardial tissue. Large plaque ulceration can lead to total occlusion of a coronary artery resulting in acute myocardial infarction (AMI), but also smaller nonocclusive plaques may produce minor injury associated with irreversible damage in clinically defined unstable angina patients (3). Nevertheless, for much of the past three decades, acute ischemic heart disease has been regarded as a binary phenomenon, AMI or non-AMI, using World Health Organization (WHO) recommendations that include fulfillment of at least two of the three well-known diagnostic criteria: a history of acute, severe, and prolonged chest pain, presence of significant changes in electrocardiogram (ECG), and abnormal elevation of traditional enzyme activities in serum (4). In particular, the WHO definition of 'abnormal' enzymes for the diagnosis of AMI is a rise to at least twice the upper reference limit of either total creatine kinase (CK) and its MB isoenzyme or total CK and one of aspartate aminotransferase or lactic dehydrogenase within 72 h of onset of acute event (5).

Unfortunately, chest pain is an unreliable indicator, and unless ST elevations are found at presentation, the ECG can be inconclusive in 40 to 65% of cases. The imperfect sensitivity and specificity of the traditional enzymatic markers for the detection of myocardial injury is also well known (6). In this context, the risk of misdiagnosis is relatively high. During the last 20 years, several studies estimated that 2 to 8% of patients with AMI are inadvertently sent home from emergency departments because of the diagnostic limitations of the ECG and of measurements of classic enzymes (7). In these patients, the risk-adjusted mortality is double that of those who are admitted (8). Litigation against emergency physicians for a missed AMI accounts for 10% of all successful lawsuits, but 20 to 30% of all money paid in United States (9). The opposite side of the coin is overtreatment. Here a patient who has not suffered from an infarction is kept in the hospital emergency room for a prolonged stay or is admitted for observation in the intensive care unit. These hours or days in the hospital can cost an istitution a tremendous amount of money-money that is hard to come by in this age of cost-containment.

Therefore, with increasing economic pressures on health care, physicians, health plans, and medical centers are interested in improving the efficiency of care for patients

with acute chest pain. This renewed interest reinforces the need for a better diagnostic approach to patients with suspected coronary syndrome and, consequently, the need for a new standard definition of AMI and of risk determination (10). Of course, the ECG remains the cornerstone for the early diagnosis of acute ischemia, showing ST segment change within seconds of the ischemia insult, but there is an urgent need to redefine the WHO biochemical criterion of the triad. This need stems from the findings of several trials using highly sensitive and specific markers of heart muscle damage that are not themselves enzymes, such as cardiac troponins: the phenomenon of the detection of an increase of these markers in the blood of patients with chest pain, but who do not fulfill the current criteria for the diagnosis of infarction, requires a re-evaluation of the biochemical diagnostic criteria (11). We should be going forward to something more accurate and workable for general use involving these new markers of myocardial injury.

THE DIAGNOSTIC STRATEGY

An important point concerns the selection of the most appropriate strategy for the use of new markers and the suggested sample frequency in patients without electrocardiographic evidence of AMI at hospital admission. In fact, the excitement of new applications in the use of biomarkers to improve routine patient care can be offset by angst regarding the appropriate selection and utilization of currently available and new assays.

To meet the clinical requirements a marker ideally should be: 1. Highly cardiac-specific to allow reliable diagnosis of myocardial damage in the presence of skeletal muscle injury; 2. Highly sensitive: the marker should detect even small myocardial damage; 3. Suitable for early as well as late diagnosis; and 4. Measurable with a rapid, easy to perform, and cost-effective assay (6). As currently there is no single marker that meets all of these criteria, a multi-analyte diagnostic approach has probably the most merit. In particular, it is suggested as optimal the use of a combination of two biochemical markers to enable detection of infarction in patients who present early and late: an early marker (reliably increased in blood within 6 h after onset of symptoms), and a definitive marker (increased in blood after 6-12 h but with high sensitivity and specificity for myocardial injury, and with abnormal concentrations measurable in blood for several days after onset) (11,12).

Currently, myoglobin is the marker that most effectively fits the role as an early marker (13). Myoglobin measurement can now be performed in real time and it is time to reappraise the role of this marker for early detection of AMI. The alternative to myoglobin would be the measurement of CK-MB isoforms or heart fatty acid-binding protein. However, as recently demonstrated in a systematic review of literature, measurement of myoglobin has the merit of a robust scientific evidence, with almost 30 studies recently published on the use of this protein as an early sensitive marker for excluding infarction (14). Myoglobin is detectable in blood as early as 2-3 h after onset. Its concentration appears to peak quickly, reaching the maximum level between 6 and 12 h after the onset of symptoms. It then falls to normal levels over the next 24 h, rapidly cleared from the serum by the kidneys. Myoglobin is not cardiac specific, and patients with renal failure, skeletal muscle injury, or trauma can have abnormal concentrations in the absence of AMI. But, despite this limitation, myoglobin has potential utility as test for excluding early AMI in patients presenting to the emergency department with chest pain. The negative predictive value of this marker for excluding early infarction 4 h after patient admission is virtually 100% (15).

Cardiac troponins are regarded as the most cardiac-specific of currently available biochemical markers for the diagnosis of myocardial injury. Troponin appears in the serum 4 to 12 h after symptoms onset and remains abnormal for 4 to 10 days. The cardiac specificity and duration of elevation after infarction make troponin an ideal replacement for traditional lactate dehydrogenase isoenzymes to diagnose an infarction with a delayed presentation. Furthermore, due to its cardiospecificity, troponin testing should mandatorily replace CK-MB in any setting where the specificity of CK-MB is in doubt, as in any cause of acute or chronic muscle injury (16). Possibly, the only significant drawback of troponins is the insufficient clinical sensitivity in the early stages of infarction (14). An additional important challenge for which cardiac troponin could assist is in early risk stratification of patients with acute coronary syndrome and without frank infarction, with the aim to identify

the subgroup of patients who have a high risk for developing severe cardiac events, thus offering prognostic information to the clinician unavailable by other biochemical investigations (17).

Coming to the sampling protocol for detection of infarction using these two biochemical markers, the timing and the frequency showed in Table I is recommended. Using this protocol, the negative predictive value for myoglobin, using upper reference limit as diagnostic threshold, is approximately 100% 4 h after admission. This potential for 100% predictability in excluding early infarction can be very helpful in the rapid triage of patients presenting with acute chest pain. Alternatively, a single positive result for troponin would trigger a diagnosis of myocardial necrosis and triage of the patient to the appropriate level of care, without the need for necessary completing the sequence of blood samples at every time point.

The question of whether zero time in the protocol should be assigned to the onset of chest pain or presentation to the emergency department is debatable. Patients with large infarcts tend to have a clear-cut start to the symptoms and to present early, but these are not the patients in whom there is any doubt about the need for admission. In the patients with no electrocardiographic changes and possible small myocardial damage, the symptoms may have a stuttering start and undergo a waxing and waning time course which mirrors the waxing and waning myocardial ischemia. So, it is not uncommon for these patients to report multiple episodes of chest pain over the hours and days prior to admission. Studying a consecutive series of about 250 patients with infarction, Bholasingh et al. (18) recently showed an inaccurate estimation of time interval between onset of symptoms and admission in about 15% of them. Therefore, the suggestion is that, for routine clinical practice, blood collections should be referenced relative to the time of presentation to the hospital: the use of the recommended early and late marker combination will permit infarct timing in any case.

Zaninotto et al. recently documented the high clinical performance of the two-marker approach, showing that the combination of myoglobin and troponin significantly improves the clinical predictive values of standard CK-MB alone irrespective of the disease prevalence (19). This two-marker approach results especially useful in those hospitals attempting to triage patients between emergency department holding areas and inpatient beds. The diagnostic information provided can significantly influence subsequent management, reducing length of stay and hence patient episode cost (Table II) (20). For those hospitals who do not have an area for rapid rule out of chest pain patients, and therefore patient triage decisions are not made within the first few hours after admission, the use of an early marker is probably unnecessary (6). The key issue is indeed whether a

Table 1
Proposed diagnostic strategy and recommended sampling frequency for detection of acute myocardial damage by biochemical markers

Marker	Sample frequency			
	Admission	+4h	+8h	+12h or next morning
Early	x	x	(x)	
Troponin	x	x	x	x

(x) indicates optional determination

Table 2
Impact of the use of two-marker protocol on the outcome of patients with suspected acute myocardial infarction (AMI) [adapted from Caragher et al. (20)]

Group	n	Length of stay (days)	N. of ordered procedures	Total costs	Laboratory costs
		AMI negative patients			
Control*	73	2.02	14.7	$2019	$189
Test**	81	1.62	12.3	$1635	$158
		AMI positive patients			
Control	19	5.69	36.0	$7425	$462
Test	15	4.56	23.6	$5614	$303

*"Control" indicates use of the traditional enzymatic (CK & CK-MB) approach.
**"Test" indicates use of the two-marker (myoglobin & cardiac troponin I) approach.

physician wishes to act or may act on the myoglobin data. If the assay data will not result in initiation of treatment or discharge, then it is of no value. In this case, only measurement of cardiac troponin is suggested with a sampling frequency of admission, 6 and 12 h (11).

DECISION LIMITS FOR CARDIAC TROPONINS

One of the most important problems in the practical use of the cardiospecific troponins is the right definition of decision limits (21). According to Robert Jesse (22), the basic question is: "How much necrosis is needed to make the diagnosis of AMI ?". In the purest physiologic sense, the answer is that any detectable necrosis is an infarction. Consequently, even small elevations of specific markers of myocardial damage, such as troponins, should be acknowledged as indicative of significant injury. Pragmatically, the use of this approach as a diagnostic criterion for AMI would effectively increase the numbers of infarct patients in the acute coronary syndrome population from 15 to 30% (23). However, we must consider the clinical and societal implications of this improved diagnostic capability. From a practical point of view, it may be important not to classify these patients as classic AMI patients, because of social, psychological, and economic problems. There is some justified reluctance on the part of the medical community to assign the diagnosis of AMI to these patients (24).

For these reasons, two cutoff limits are probably needed at present for a convenient use of troponins, one to establish the presence of "minor" myocardial damage and one to diagnose AMI (Figure 1). It should be noted that this concept is of course effective only when the appropriate diagnostic window for the marker is considered as in the protocol previously recommended. An important point is the correct definition of these limits. The first lower limit should be simply determined as the 97.5 percentile of results from an apparently healthy population. Receiver operating characteristic (ROC) curves should be used to establish decision limit for AMI diagnosis. This second limit is determined by comparing troponin concentrations in samples collected within the established diagnostic

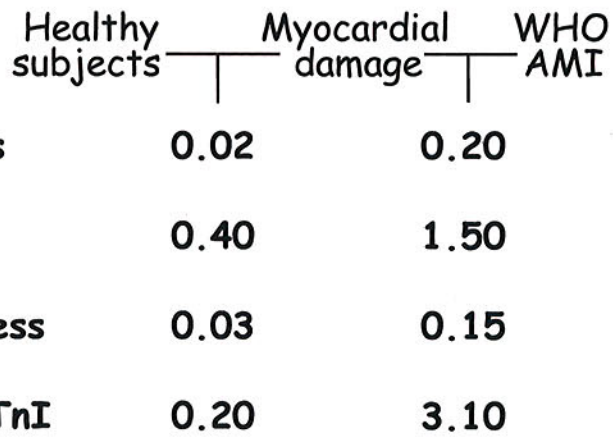

Figure I
Suggested decision limits for cardiac troponin assays. WHO, World Health Organization; AMI, acute myocardial infarction; cTnT, cardiac troponin T; cTnI, cardiac troponin I

Table 3
Total imprecision around the diagnostic cutoffs of commercial assays for cardiac troponin determination

Company/Platform	Troponin concentration, µg/L	CV_{TOT},%	Reference
Abbott AxSYM	2.90	10.0	Apple et al. (27)
Bayer ACS:180	1.33	4.1	Panteghini et al. (28)
Bayer Immuno 1	1.00	4.9	Wu (29)
Beckman Access	0.08	12.9	Panteghini et al. (30)
Biosite Triage	0.34	19.5	Wu (29)
Dade Behring Opus	3.70	13.0	Panteghini et al. (31)
Dade Behring Stratus II	0.66	13.6	Kuhr et al. (32)
Dade Behring Stratus CS	0.10	4.5	Heeschen et al. (33)
DPC Immulite	1.00	9.2	Wu (29)
Roche Cardiac Reader	0.33	18.0	Muller-Bardorff et al. (34)
Roche Elecsys	0.11	3.6	Bonetti et al. (35)

CV_{TOT}, total coefficient of variation

window for that marker, on patients with confirmed AMI, using WHO criteria, compared with concentrations found in patients with acute coronary syndrome but without WHO-defined infarction (25). According to the suggestions of the IFCC Committee on Standardization of Markers of Cardiac Damage, the diagnostic manufacturers should clearly specify on the package insert sheet of kits the two decision limits (11). This information should be available along with the level of analytical imprecision of the assay at these concentration limits. In fact, for troponin determination, not all the assays on automated platforms perform equally well in routine clinical settings (Table III) (26). Irrespective of how the testing is performed (i.e. laboratory-based or bedside), we need good precision performance at the low end of the assay range if we are going to use a troponin assay for risk stratification in patients with acute coronary syndrome. Clinical biochemists should consider more carefully the effect of imprecision on clinical decision-making when they evaluate new reagent kit sets or methods for troponin determination (36).

In the next future, when the biochemical WHO-criterion for AMI diagnosis will be definitively changed using increased troponin values in the setting of acute ischemia instead of the classic CK-MB findings, there would be only a single cutoff limit for troponin corresponding to the upper limit of the reference distribution, reflecting the incremental risk associated with increasing concentrations of the marker, consistent with the continuous injury concept of acute coronary syndrome.

BIOCHEMICAL MARKERS IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

As previously stated, since the sensitivity of the initial ECG is only 50% for detecting infarction, the use of the biochemical markers may significantly contribute to the early diagnosis and become relevant just when ECG is not diagnostic. Conversely, there is no need for the use of any biochemical marker when the clinical diagnosis of AMI is unequivocal. In these patients, biochemical marker testing is indeed unnecessary for diagnostic purposes, being the electrocardiographic changes, namely ST-segment elevation greater than 1 mm in two or more contiguous leads, not much sensitive but highly specific (37). The ST-segment elevation reflects a transmural myocardial ischemia caused by an occlusive thrombosis in the coronary vessel supplying the corresponding myocardium. The goal of the treatment is to re-open the occluded coronary artery as soon as possible by thrombolysis or acute angioplasty and the results of measurements of marker proteins must not be awaited before recanalization therapy is initiated. In this group of patients, biochemical marker testing may be valuable only for confirmation of diagnosis and may be useful to: 1. qualitatively estimate the size of the infarction, 2. for early stratification of the subsequent risk, 3. to detect the presence of complications such as a reinfarction, and 4. to monitor thrombolytic therapy. These applications are however optional and not definitively supported by scientific evidence.

Cardiac enzymes can be used to estimate infarct size by measurement of their cumulative release. However, this estimate may be affected by thrombolytic therapy through the so-called "wash-out" phenomenon. The peak serum concentration of enzymes may therefore provide only a crude estimate of infarct size (38).

More recent studies have shown that the admission concentration of troponin may contain prognostic information. In the GUSTO IIa study, 30-day mortality was only 5% in infarction patients with a normal troponin at admission, while the mortality was 13% in patients who presented with an elevated troponin value (39). Similar results were observed in the study by Stubbs et al. (40). In this trial, infarct with ST-segment elevation and a positive troponin T (cTnT) on admission was associated with a threefold higher cardiac event rate than infarct with a negative cTnT admission value and the observed hazard persisted for up to 3 years of follow-up (40). These data were recently confirmed in the GUSTO III study, where the 30-day mortality rate was 6.2% in patients who were cTnT negative on admission versus 15.7% in cTnT positive patients (41). The mechanisms behind this difference are not fully elucidated. One possible explanation might be a less successful reperfusion, deriving from a lower efficiency of thrombolytic therapy, in patients with elevated troponin on admission. Whether direct angioplasty can improve the current morbidity in this patient group awaits randomized studies, so that the

therapeutic implications of this finding remain speculative (42).

It may also be appropriate to monitor the continuing decline of cardiac markers daily to show an extension of the infarct. However, in an experience only 3.1% of infarct patients experienced a reinfarction during the stay in Coronary Care Unit (43). Consequently, the standard monitoring of markers to obtain this information may not be cost-effective.

A variety of efforts over many years have also attempted to diagnose reperfusion predicated on changes in marker proteins. A recent review of these efforts showed 11 studies involving 460 patients that monitored various cardiac markers following thrombolytic therapy using different evaluation approaches: slopes, ratios, absolute differences, etc. (44). Unfortunately, even the best data heretofore has been unable to separate TIMI II from TIMI III flow in the revascularized coronary artery[1]. Thus, until and unless marker protein analysis can achieve the ability to detect TIMI III flow from TIMI II which may still require intervention, it is unlikely to become a routine part of the cardiologist armamentarium (45).

Cardiac markers can also be used to detect presence of perioperative AMI in patients undergoing surgical procedures. Use of nonspecific markers such as myoglobin, total CK, CK-MB, and lactate dehydrogenase have limited usefulness as they are released from noncardiac tissues as a result of the surgical procedure itself. Consequently, cardiac troponins should be used for detection of perioperative AMI in patients undergoing noncardiac surgical procedures. On the contrary, there are not so far formal data to recommend the use of cardiac markers for the assessment of perioperative AMI in cardiac surgery. For these patients, no marker is capable of distinguishing injury due to perioperative infarction from the injury associated with the procedure itself. The identification of cutoff values is therefore difficult mainly since postoperative myocardial damage is a continuum.

THE TURNAROUND TIME

The target for the turnaround time, defined as the time by which blood is collected to the reporting of results, has been suggested as 1 h, with plasma as the preferred sample (11). However, this target is definitively dependent on the use to which the information will be put. When very rapid service is required for early discharge from the emergency department, speed of response and receiving the results is of highest importance. Rapid testing and reporting of cardiac marker results may actually produce significant decrease in length of stay and overall hospital costs (46,47).

Recent data have also shown that cardiac troponin measurement can be used to select those patients who will respond to more aggressive therapies (42). This will also require a more rapid turnaround time, since the decision to start or stop expensive therapeutic interventions have to be made on the basis of biochemical testing (23).

The one-hour suggestion is however still arbitrary and not evidence-based. In fact, there are no outcome studies to validate the specific need for one hour turnaround time and also the timing of intervention relative to clinical outcome needs further investigation. Before the critical care practitioner can know the full advantages of early diagnosis and how best to use this information, the link between risk assessment and treatment strategy needs to be better defined.

To conclude, new cardiac markers are a hot topic, with active debate on their use. Heart disease is a major health problem in our countries and much effort is being expended to reduce cardiac morbidity and mortality. The new biochemical markers have a major role to play for cost effective patient management of individuals with chest pain and the laboratory is now poised to assume a vital new role in assessing damage and dermining therapy. In an era of evidence-based medicine, we can no longer overlook the diagnostic, prognostic, and therapeutic benefits provided by more intensive blood sampling regimens and measurement of cardiac proteins.

[1]The accepted standard measurement of reperfusion status is coronary angiography. Blood flow is assessed according to a scale determined by the Thrombolysis in Myocardial Infarction (TIMI) investigators. TIMI grades 0-II indicate various stages of occluded flow, whereas TIMI grade III indicates reperfusion

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