Cardiac Biomarkers for Rapid Evaluation of Chest Pain

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Physicians caring for acute chest pain patients constantly maneuver between unnecessary admissions and premature discharges. The ECG is the most readily available tool for identifying patients with ST-segment elevation, who are likely to have myocardial infarctions and who should receive reperfusion treatment. Establishing the correct diagnosis in the patients without ST-segment elevation, however, can be much more challenging. Undetected infarctions remain a serious public health issue and represent the leading cause of malpractice cases in the emergency room setting.1 Prematurely discharged patients often have been seen by physicians with less professional experience. Such patients frequently have more atypical complaints and nondiagnostic ECG findings, are younger, and are at higher risk than admitted patients.1,2

The ECG has limited prognostic relevance because abnormalities are infrequent and are of low sensitivity and specificity. Only ST-segment depression, which is found in about one third of the patients, is associated with short- and long-term adverse outcome.3,4

**Biomarkers in the New Guidelines**

In recent years, novel biochemical markers have emerged that play a pivotal role in diagnosis, risk stratification, and guidance of treatment. Markers of inflammation, such as C-reactive protein, have been found helpful in predicting the long-term prognosis, whereas the improved markers of cell necrosis, mainly cardiac troponins, are valuable tools in the acute phase assessment.5 There is solid evidence from numerous studies that the unstable patient with elevated troponins has an ~9-fold increased risk for myocardial infarction or death in the next 30 days.6 Consequently, the American College of Cardiology/American Heart Association guidelines7 as well as the European Society of Cardiology Task Force Report8 last year incorporated troponin measurements into their diagnostic algorithms for patients with acute coronary syndromes. However, many practical aspects for optimizing the sampling protocols in the emergency unit and for combining troponin measurements with other markers in the clinical routine setting still need to be clarified.

There is general consent that a single test for troponins on the arrival of the patient to the hospital is insufficient because a single test can miss 10% to 15% of at-risk patients. The timing for the second test has not yet been clearly defined. The European Society of Cardiology recommends repeating troponin testing between 6 to 12 hours after arrival in the emergency unit.8 The American version asks for a repeat test 8 to 12 hours after the onset of pain—a minor, but sometimes decisive difference in perception in the work-up of the individual patient. Previous studies before the era of troponins had suggested a 12-hour rule-out strategy.9 Troponins have helped to shorten and to improve the diagnostic workup. A prospective study using troponin T and troponin I bedside tests proposed an interval of 6 hours to identify high-risk patients.10 The study in this issue of Circulation by McCord et al11 goes even further and reduces the time to safely exclude myocardial infarctions to 90 minutes after presentation in the hospital by using a point-of-care test system combining creatine kinase (CK)-MB, troponin I, and myoglobin measurements. Undoubtedly, these results are provoking and will stimulate a new discussion.

**Myocardial Infarction Redefined**

A key point in the discussion will relate to the fact that the gold standard for myocardial damage has changed and myocardial infarction has been redefined.12 The consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee has based the new definition on biochemical grounds (eg, troponins), a choice that was guided by the insight that troponins indicate irreversible cell damage.12,13 Although many physicians currently have conceptual difficulties with the translation of this paradigm change into clinical practice, the increased risk in patients with elevated troponin levels justifies this new perception. Consequently, our procedures for ruling out myocardial infarction need to be based on troponins, which are the more sensitive and specific cardiac markers and which may be elevated when all other markers are still normal.

In the study by McCord et al,11 the traditional CK-MB standard is still used to determine that a patient has had a myocardial infarction. Accordingly, diagnostic sensitivity and negative predictive values, as presented by McCord et al,11 must be interpreted against the new background. Today’s emergency room triage does not end by ruling out CK-MB–elevation myocardial infarctions but rather must be extended to the patient with elevated troponins. The purpose is not only to comply with the new myocardial infarction definition, but

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more importantly, to identify the patient who is at risk for a serious coronary event in the near future. Therefore, safe discharge of the chest pain patient is not advised before the troponin measurements according to the currently valid sampling guidelines are available.7,8

How Many Markers?

Another unresolved issue addressed in the study by McCord et al11 relates to the question of what we gain in diagnostic accuracy when multiple markers are used. The National Academy of Clinical Biochemistry recommends the use of an early (within 6 hours’ rise) and definite marker for establishing the diagnosis of myocardial infarction.14 Troponins are today the gold standard for detecting myocardial cell necrosis and therefore must be measured.13 Qualitative (positive/negative) and quantitative point-of-care test devices for troponin I as well troponin T have been shown to deliver reliable results.10,11,15 Myoglobin is released earlier in acute myocardial infarction but lacks cardiac specificity. The combination of both markers therefore is appealing, and the data of McCord et al11 demonstrate that this test system is producing reliable results. However, the optimistic results of McCord et al11 regarding myoglobin are not shared by another recent study involving 6352 patients with relatively early presentation to the hospital (median, <3 hours).16 The difference in results may be related to different analytical techniques and cut-offs, but it could also be caused by the patients’ relatively late arrival to the hospital (median, 4.3 hours) in the study by McCord et al.11 It appears that the value of adding myoglobin to diagnostic work-up programs is greatest in the time window of 4 to 6 hours after the onset of pain.17

Elevated myoglobin levels may be helpful for early triage of the level of care but, in contrast to troponins, have so far no proven implications for treatment. There is no clear indication for fibrinolytics without ST elevation or new left bundle-branch block.18 A patient with elevated myoglobin levels may be a candidate for immediate coronary angiography to clarify the condition; however, invasive facilities are neither available everywhere nor available around the clock, and apparently are not often used in this scenario.19 Therefore, patients generally will have to wait ≥6 hours for the troponin results that complete the risk stratification protocol.

Myoglobin can be helpful for detecting reinfarction in patients with post-infarction angina when troponins are still elevated. Measurement of CK-MB may be performed because it is an inexpensive procedure and still provides a kind of familiar back-up safety. For risk stratification, however, CK-MB and myoglobin play no role. Therefore, it may be suggested for the future that resources be saved for an additional marker of inflammation, such as C-reactive protein, that allows for the estimation of long-term risk. For example, a patient with normal markers of myocardial cell necrosis but elevated C-reactive protein may be treated more aggressively with statins.19 More evidence will emerge in the coming years to elucidate this new field.

Point-of-Care Testing

There is no question that point-of-care testing for biochemical markers is of great advantage when valuable time can be saved. Prerequisite is that the off-site measurement must be as accurate as it would be if it were performed by automated analyzers in a central laboratory. In the study by McCord et al,11 the time gained by point-of-care testing was 47 minutes. However, the central laboratory required 71 minutes to provide results, which is far from the 30 to 60 minutes recommended by the ACC/AHA guidelines.7 The National Academy of Clinical Biochemistry advises the implementation of point-of-care test systems if the hospital logistics cannot consistently deliver cardiac marker results within 1 hour.14 Provided the patient stabilizes clinically, minor time delays may not be as critical as in ST-elevation myocardial infarction. Recent study data indicate that in the case of elevated troponins, glycoprotein IIb/IIIa antagonists are most effective in preventing early complications.20–22 Coronary angiography and invasive strategies should be scheduled for patients with elevated troponins within a time window of 48 hours to improve long-term outcome.23

Perspectives

Diagnostic strategies in patients with acute chest pain have to be reliable and simple. The objective is to reduce mortality and morbidity by initiating the best therapy. The ECG allows the exclusion of acute myocardial infarctions requiring immediate therapeutic response. Troponins can identify high-risk coronary patients that should be treated with glycoprotein IIb/IIIa antagonists and referred for invasive evaluation at earliest convenience. Common diagnostic sense is necessary to detect other noncoronary but critical conditions such as dissecting aortic aneurysms. Other biochemical markers are nice to have but will not reduce the time for observation. Even under the best circumstances it will still take 6 to 12 hours to reliably exclude high-risk conditions. The achievements in recent years with regard to risk stratification have been enormous, and the search for new markers will continue. A rise in myoglobin levels means that substantial amounts of myocardium are going into necrosis. Elevated troponins also indicate irreversible cell injury, and even if only a few cells are affected, we should not rest before we find ways to detect this beforehand.

References


**KEY WORDS:** Editorials ■ myoglobin ■ diagnosis ■ myocardial infarction ■ troponin
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Circulation. 2001;104:1454-1456
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
http://circ.ahajournals.org/content/104/13/1454

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