Cardiac marker point-of-care testing in the Emergency Department and Cardiac Care Unit

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There has been much interest in improving the accuracy and speed with which chest pain patients presenting to the emergency department are diagnosed and treated. Recently, attention has been directed toward alternative site or point-of-care testing for biochemical markers of myocardial cell necrosis in addition to traditional diagnostic methodologies. The various point-of-care cardiac marker devices available and their potential applications are discussed. Regulatory and quality management issues related to point-of-care testing are reviewed.

Four million chest pain patients are admitted each year for ruling out acute myocardial infarction (AMI). Up to 70% of patients are admitted to the Cardiac Care Unit (CCU) for suspected AMI rule out (1), with estimates suggesting that two to three billion dollars per year could be saved caring for this population in a less intensive setting (2).

However, AMI patients may present to the Emergency Department (ED) with normal or nondiagnostic electrocardiograms (ECGs) 50% of the time, making early diagnosis of AMI difficult (3). Up to 8% of AMI patients may be inadvertently discharged from the ED, and this subset of patients accounts for 20% of emergency medical malpractice dollar losses and leads to increased morbidity and mortality. (4, 5). Frequent misdiagnoses given to AMI patients inadvertently discharged from the ED include esophagitis, muscle strain, and exacerbation of chronic obstructive pulmonary disease. In a recent review of missed AMI closed malpractice claims, ~25% of missed AMI cases were because of ECG misinterpretation, in 25% of cases the ECG was correctly interpreted but the clinical importance of the ECG findings were not appreciated, and the remaining 50% had nondiagnostic ECGs and atypical symptom complexes (6).

A typical workup of the suspected AMI/coronary ischemia patient in the ED includes a history and physical, ECG, and, in some EDs, may include laboratory or other ancillary studies. The most widely accepted criteria for making the diagnosis of AMI are the WHO criteria, which require two of three elements to make the diagnosis of AMI: (a) symptoms of chest discomfort, (b) ECG evidence, or (c) biochemical evidence. It is possible to make the diagnosis with either ECG evidence or biochemical evidence if certain criteria are met [i.e., a twofold rise and fall of the creatine kinase MB isoenzyme (CK-MB)] (7).

Here, we review the utility of point-of-care testing for markers of myocardial cell necrosis in the evaluation, treatment, and disposition of the chest pain patient. Financial and regulatory issues will also be discussed.

Point-of-care Testing

Because of the limited utility of the history, physical exam, and traditional ECG testing, there has been intense interest in utilization of cardiac markers in assisting the clinician to both recognize AMI earlier and to better utilize resources within the hospital. Point-of-care testing in particular has received much interest as a means of assisting the clinician in making real-time clinical decisions that can effect both patient treatment and disposition. Myoglobin, CK-MB, troponin I, and troponin T are markers that have received the greatest recent attention with respect to their utility in point-of-care testing strategies.

MYOglobin AND CK-MB

Myoglobin, with a molecular mass of 17 800 Da, reaches twice unaffected serum concentrations within 2 or 3 h after myocardial infarction and peaks within 4–6 h. CK-MB (molecular mass, 86 000 Da) reaches twice the unaffected concentrations 4–6 h after a myocardial infarction and peaks in 12–24 h. Recent studies have shown myoglobin to be highly sensitive (91%) within 1 h of ED presentation with a high negative predictive value (99%) and, when patients with trauma and renal failure are
excluded, high specificity (96%) (8). CK-MB has also been demonstrated to have a sensitivity of >90% within 3 h of ED presentation and is highly specific (9–12).

The Cardiac STATus CK-MB/myoglobin device (Spectral Diagnostics, Inc.) is a solid-phase chromatographic assay that allows for qualitative detection of CK-MB and myoglobin, utilizing whole blood, serum, or plasma. The device has an 18-min assay time. A recent study evaluated this device for rapidly ruling out AMI in the ED (13). The study protocol included bedside blood sampling at 0, 1, and 3 h after presentation. At the time of actual ED evaluation and disposition of these patients, no biochemical marker data were available to the treating physician. The final diagnosis of AMI was based on standard WHO criteria, utilizing CK-MB testing at 0, 8, and 16 h. Two hundred and seventy-seven patients were enrolled, of whom 52 (19%) had AMI. The mean time from symptom onset to presentation was 187 min (3.1 h). When testing was performed at 0, 1, and 3 h, and a positive result for either CK-MB or myoglobin at any of the three sampling times was considered as a positive test, the sensitivity and specificity of the cardiac status device were as demonstrated in Tables 1 and 2. Within 3 h of patient presentation, the Cardiac STATus device demonstrated a sensitivity of 96% for AMI and a negative predictive value of 99%. The interdevice reliability was 100% (based on 100 serum specimens run in duplicate by the same observer), and the interobserver variability was 2% (based on 50 devices read by two observers blinded to each other’s reading). The device was also retrospectively evaluated for its potential utility in reducing non-AMI admissions to the CCU. Thirty-two of the 277 patients were admitted to the CCU, representing 12% of the study population. (All other patients, including the other AMI patients, were admitted to telemetry/step down unit beds.) Of the 15 AMI patients admitted to the CCU, 2 had a negative Cardiac STATus device result during the 3-h testing interval; neither patient experienced complications. Of the 17 non-AMI patients, 11 had a negative Cardiac STATus device result. None of these 11 experienced complications. Three of them presented with an ST elevation, two had evidence of acute ischemia, and six had non-ischemic/nondiagnostic ECGs. The authors suggest that these six could be considered for retriage on the basis of the Cardiac STATus device testing. Utilizing the device to retriage non-AMI CCU patients, a net savings for the study population of $4,600.00 per 32 CCU admissions could be achieved. Extrapolating this savings ratio for the 2 million CCU admissions nationally per year, the authors suggested a potential national savings of $287 million per year.

### Table 1. Sensitivity and specificity of the Cardiac STATus with serial testing.

<table>
<thead>
<tr>
<th>Time, h</th>
<th>Sensitivity, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Specificity, %&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>71 (53–85)</td>
<td>77 (70–82)</td>
</tr>
<tr>
<td>0 + 1</td>
<td>90 (76–97)</td>
<td>73 (67–79)</td>
</tr>
<tr>
<td>0 + 1+ 3</td>
<td>95 (84–99)</td>
<td>71 (65–77)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Testing was done on 277 patients, of whom 52 (19%) had AMI.
<sup>b</sup> Values in parentheses are 95% confidence intervals.

### Table 2. Positive and negative predictive values of the Cardiac STATus with serial testing.

<table>
<thead>
<tr>
<th>Time, h</th>
<th>PPV&lt;sup&gt;a&lt;/sup&gt;</th>
<th>NPV&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>33 (22–45)</td>
<td>94 (89–97)</td>
</tr>
<tr>
<td>0 + 1</td>
<td>38 (29–49)</td>
<td>98 (94–99)</td>
</tr>
<tr>
<td>0 + 1+ 3</td>
<td>39 (30–50)</td>
<td>99 (96–100)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values in parentheses are 95% confidence intervals.
strated the prognostic utility of point-of-care testing. It should also be noted that, in this particular population, the troponin T-positive patients had a higher frequency of co-morbid conditions and clinical findings.

**TROTONIN I**

A recent study of 29 patients with suspected AMI evaluated the qualitative troponin I Cardiac STATus device (Spectral Diagnostics, Inc.) in conjunction with a quantitative assay for troponin I (18). When the quantitative serum value was <0.20 μg/L, all qualitative assays were negative. If the quantitative assay was >0.23 μg/L, all qualitative assays were positive. It was also noted that the reaction time of the qualitative device decreased as the troponin I concentration increased.

**COMPARATIVE STUDIES**

In a study comparing the Cardiac STATus CK-MB/myoglobin device and the troponin T qualitative device, 101 consecutive patients, 75 of whom had a final diagnosis of AMI, were evaluated (19). Patients were included if they were admitted to the CCU within 12 h from symptom onset (mean, 3.0 h). The Cardiac STATus device was evaluated using two alternative strategies: (1) if either CK-MB or myoglobin was positive, the device was defined as a “positive test”, or (2) both CK-MB and myoglobin must be positive for the device to be a “positive test”. The sensitivity of the Cardiac STATus device using method 1 was 100% when patients were tested >4 h from symptom onset vs a sensitivity of ~40% at 4–6 h and 73% at >6 h for troponin T (see Table 3). The specificity of all devices was 100% in patients tested at the 2- to 4-h and >6-h from symptom onset intervals (Table 4). In patients tested >4 h but <6 h from symptom onset, the specificity of the Cardiac STATus in method 1 was 60%, in method 2 it was 100%, and troponin T was 100%.

Another comparative study of qualitative troponin T (Boehringer Mannheim Corp.) and the Cardiac STATus troponin I (Spectral Diagnostics, Inc.), enrolled 330 patients presenting with chest pain, of which 50 had a final diagnosis of AMI (20). Serum was sampled at 0, 2, 4, and 6 h after admission, with an average time from symptom onset to presentation of 6.4 h. The Cardiac STATus and the troponin T devices had excellent correlation between quantitative and qualitative devices (0.93 and 0.91, respectively). Both the Cardiac STATus troponin I device and the troponin T device were positive in 46 of 50 AMI patients by 6 h.

In a series of 773 consecutive chest pain patients with symptom onset <12 h before presentation and no ST elevation on ECG, qualitative troponin I and troponin T testing was performed on arrival and again at least 6 h after symptom onset (21). Patients with a (−) troponin I or T test had a very low likelihood of death or AMI in hospital or in the 30 days after admission. In fact, no patient with a normal or nondiagnostic ECG and a (−) troponin I test had a cardiac event (Table 5). Patients with either a positive troponin I or T test were less likely to be event-free at 30 days. The odds ratio for predicting cardiac events at 30 days was 2.9 for ST depression, 0.4 for T-wave inversion, 25.8 for positive troponin T, and 61.4 for a positive troponin I.

Semiquantitative as well as bedside quantitative devices are also in evaluation stages for their utility in the point-of-care venue.

**Financial Considerations**

Laboratory costs can be divided into fixed and variable costs. Fixed costs include equipment, depreciation, rent, most labor, and utilities. These costs tend not to vary over short periods of time and tend to run higher for central laboratories than for alternate-site testing venues. Variable costs, which change with each incremental unit, are lower for most central or core laboratories in comparison with alternate-site testing venues. Examples of variable costs include supplies, incremental labor, and reagents.

The core laboratory and alternate-site testing venues differ in cost components and how those costs change with changes in volume of services. With alternate-site testing, the variable component for the clinicians perform-

**Table 3. Sensitivity of Cardiac STATus methods 1 and 2 and TROPT® for AMI, stratified by time from onset of symptoms to serum sampling.**

<table>
<thead>
<tr>
<th>Time from onset of symptoms</th>
<th>0–2 h</th>
<th>&gt;2–4 h</th>
<th>&gt;4–6 h</th>
<th>&gt;6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac STATus 1</td>
<td>0.50</td>
<td>0.92</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiac STATus 2</td>
<td>0.27</td>
<td>0.63</td>
<td>0.80</td>
<td>0.91</td>
</tr>
<tr>
<td>TROPT</td>
<td>0.07</td>
<td>0.13</td>
<td>0.40</td>
<td>0.73</td>
</tr>
</tbody>
</table>

**Table 4. Specificity of Cardiac STATus methods 1 and 2 and TROPT® for AMI, stratified by time from onset of symptoms to serum sampling.**

<table>
<thead>
<tr>
<th>Time from onset of symptoms</th>
<th>0–2 h</th>
<th>&gt;2–4 h</th>
<th>&gt;4–6 h</th>
<th>&gt;6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac STATus 1</td>
<td>0.64</td>
<td>1.00</td>
<td>0.60</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiac STATus 2</td>
<td>0.73</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>TROPT</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Table 5. Number of cardiac events in patients with normal or nondiagnostic ECGs by troponin status.**

<table>
<thead>
<tr>
<th>ECG finding</th>
<th>Number of patients</th>
<th>Number of cardiac events</th>
<th>Troponin T (+)</th>
<th>Troponin T (−)</th>
<th>Troponin I (+)</th>
<th>Troponin I (−)</th>
</tr>
</thead>
</table>
ing the test (labor) and reagent make up the larger portion of the costs. When volume increases in the alternate-site venue, costs may rise substantially because of this increase in variable costs. The fixed expenses for quality control, maintenance, and record keeping are a smaller component of overall costs in the alternate-site venue. However, if the staff performing the testing at alternate-site testing venues is already hired and in place, some argue that these costs should not be included in the alternate-site testing cost analysis.

There are a number of cost analyses of core vs alternate-site testing strategies in the literature (22–24). These studies demonstrate the difficulty in describing actual costs for the different components of core laboratory and alternate-site testing venues.

It is difficult to quantify the exact costs/savings of alternate-site testing in the hospital environment. For example, how would one compare the possible increased costs per test at an alternate-site venue with the potential increase in patient satisfaction that might occur because of rapid turnaround time and treatment/disposition decisions. If patients are discharged earlier because of alternate-site testing, hospital costs may decrease. However, as pointed out by Auerbach (25), only 17.5% of patients might have been discharged earlier from the ED because of quicker availability of test results. Specifically, there are other factors that may impact patients’ length of stay, such as waiting time for radiologic services or consultations. The difficulties in cost analyses are detailed by DeCresce et al. in their review of costs for bedside glucose testing (24). DeCresce et al. illustrated the various methodologies by which authors calculated the costs for glucose testing in clinical laboratory vs alternate-site venues. In one evaluation of clinical laboratory and bedside glucose testing, Greendyke (23) found direct and total costs of glucose analysis to be $1.75 and $1.39, respectively, per test when performed in the core laboratory. The direct and total costs for the alternate-site testing were $10.06 and $11.05, respectively. This differs substantially from a later analysis published by Lee-Lewandrowski et al. (22). Some of the differences might relate to the volume of tests performed as well as the difference in costs attributed to quality assurance per test (the difference being 0.19 cents per test in the study by Lee-Lewandrowski et al. vs $4.02 per test in the study by Greendyke). This illustrates the difficulty in attributing specific costs to testing in the various venues. In general, one must consider both the direct and indirect costs in each venue. Cost will also differ if one is evaluating waived vs nonwaived tests, with nonwaived tests requiring more involved quality procedures. DeCresce et al. (24) point out that the key to improving service and lowering laboratory costs is restructuring and eliminating fixed costs of the central laboratory. That group suggests that only time saving for caregivers and patients should be used currently to justify the higher marginal costs of alternate-site testing compared with clinical laboratory testing.

**Regulatory Issues**

Standards for laboratory testing are set by many governmental and accrediting agencies. These include the Health Care Financing Administration, the Joint Commission on Accreditation of Healthcare Organizations, the College of American Pathologists, and many state departments of health. The Health Care Financing Administration imposes requirements that apply to all patient testing performed in the United States, irrespective of the site of testing. The other agencies may impose additional requirements. A common theme is that standards for testing are site-neutral; that is, the same quality-assurance procedures must be in place regardless of whether testing is performed in a central laboratory, a satellite laboratory, or by the patient bedside. The Health Care Financing Administration does, however, have a list of “waived tests”, which are simple procedures exempt from specific requirements. The College of American Pathologists and other agencies do not recognize any tests as exempt from requirements. Although some of the point-of-care devices for qualitative cardiac marker testing have a simplicity close to that required for waived status, none are on the waived test list at present. Hence point-of-care cardiac marker testing generally has substantial requirements for quality assurance, including proficiency testing, running control specimens, procedure manuals, proper logging, and review of results. Clinical care areas such as the ED may be less accustomed to carrying out all of these procedures than the central laboratory.

**Conclusion**

Point-of-care cardiac marker testing provides useful information to the clinician. It allows the clinician to make the earlier diagnosis of AMI and helps in predicting which patients are likely to experience complications, allowing for better utilization of resources. In addition, the high sensitivity of certain point-of-care devices will be useful in preventing the inadvertent discharge of AMI patients from the ED. The impact of point-of-care devices will depend on venue. In settings where quantitative values are available on a “STAT” basis, the impact of point-of-care devices would be expected to be less than in settings where biochemical marker testing is batched and available only at preset times. In addition, the financial impact and cost-effectiveness will vary depending on the volume of testing performed.

Future studies evaluating cardiac point-of-care testing strategies should focus on their impact on real-time decision making and include careful financial comparisons with traditional testing strategies. In particular, point-of-care options should be compared with new options available from the central laboratory, which now can or will use rapid pneumatic tube sample delivery systems, rapid random-access immunoassay analyzers (some of which use whole blood), and rapid reporting of results from on-line instruments.
References