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Cardiac Markers: Centralized or Decentralized Testing?

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Testing for the diagnosis of acute myocardial infarction and other diseases included in the spectrum of the "acute coronary syndrome" is rapidly changing from the traditional enzymatic assays to mass measurement of more specific and sensitive markers (cardiac troponins, CK-MB and myoglobin). Several questions have arisen since the introduction of these new markers into the clinical setting: the choice of strategies for optimizing the utilization of biochemical assays combining different (early and specific) markers, a rationale for sampling specimens and the identification of clinically useful turnaround times. In particular, for achieving the last goal, attention has been directed toward near-patient testing for cardiac markers in addition to, or as a replacement for, traditional diagnostic methodologies. While qualitative methods for measuring cardiac markers at the bedside have some limitations which compromise their clinical usefulness, new quantitative devices offer a real alternative to decentralized testing. Regulatory and quality management issues related to near-patient testing, as well as the performance of recently introduced devices for a decentralized measurement of cardiac markers are reviewed.

Key words: Acute myocardial infarction; Acute coronary syndromes; Near-patient testing; Cardiac troponins; Myoglobin; CK-MB.

Coronary Heart Disease: Epidemiology and Diagnostic Strategies

Investigators from the Atherosclerotic Risk in Communities (ARIC) study on trends in mortality due to coronary heart disease (CHD) observed significant annual decreases in mortality without a reduction in the incidence of hospitalization for acute myocardial infarction (AMI) from 1987 to 1994 (1). The decline in mortality from CHD is probably attributable to advances in both primary and secondary prevention: in addition to the enormous advances in the management of acute myocardial infarction – revascularization procedures, increased use of aspirin, thrombolytic therapy, beta-blockers, angiotensin-converting-enzyme inhibitors and lipid-lowering therapy – a reduction in the severity of AMI in response to efforts at prevention could also lower the mortality rate. The slight increase in the incidence of CHD should derive from the improved education of physicians and increased availability of diagnostic tests.

Of the four million chest pain patients admitted each year for ruling out AMI (2), 50% may present to the emergency department (ED) with normal or non-diagnostic electrocardiograms (ECG), making the 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 malpractice dollar losses and leads to an increased morbidity and mortality (4, 5). In a recent review of missed AMI malpractice claims, about 25% of overlooked AMI cases were because of ECG misinterpretation, in 25% of cases the ECG was correctly interpreted but the clinical significance of the ECG findings were not appreciated, and the remaining 50% had non-diagnostic ECG and atypical symptom complexes (6).

Serial measurement of biochemical markers is now universally accepted as an important determinant in ruling in or ruling out AMI; moreover, new biochemical markers have demonstrated significant benefit in the risk stratification of patients presenting with unstable angina, as well as in outcome prediction and therapy selection.

Biochemical Cardiac Markers

The state of the art of cardiac markers derived from an evidence-based approach consists of early and specific markers. Early markers, such as myoglobin, demonstrate an excellent early negative predictive value, approaching 100% within two hours of admission for ruling out AMI (7). The model described by the Heart Emergency Room (ER) program (8) showed that serial testing for the creatine kinase MB isoenzyme (CK-MB) mass on presentation and 3, 6, and 9 hours later in patients with symptoms suggestive of acute ischemic coronary syndrome presenting with a non-diagnostic or equivocal electrocardiogram was more effective than continuous serial electrocardiograms, echocardiography, and graded exercise testing. More recently, researchers have demonstrated that cardiac-specific troponin I (cTnI) and troponin T (cTnT) have comparable utility for the detection of AMI compared with CK-MB, suggesting that their serial testing could replace CK-MB for the detection of AMI (9). Moreover, and more consistently from a clinical viewpoint, cardiac troponins can help clinicians deal with patients with an equivocal electrocardiogram and they are powerful in the risk stratification of patients with unstable angina as well as in predicting clinical outcomes (10).

The wide array of improved analytical procedures for measuring old and new cardiac markers offers new

clinical perspectives, but may confuse clinicians. Clinical laboratories, emergency departments and divisions of cardiology should therefore work together to develop a rational strategy for the optimal use of old and new biochemical markers. The Holy Grail of the interface between cardiology and biochemistry is still elusive but promising efforts are being made to improve cooperation. Both on national and international levels, multidisciplinary groups are now striving to achieve consensus on the most efficient biochemical tests and implementing their appropriate use in the clinical setting.

In particular, a Committee of the National Academy of Clinical Biochemistry (NACB) has circulated a proposal for guidelines, which focus on some critical issues: test combination, recommended cut-off limits, suggested turnaround times, specimens of choice and point-of-care testing (11). Here, two biochemical markers are recommended for routine AMI diagnosis: an early marker (reliably increased in blood within 6 hours after onset of symptoms), and a definitive marker with high specificity and sensitivity for myocardial injury, cTnI or cTnT. We have recently demonstrated that the combined serial measurement of myoglobin and troponin I allows the high sensitivity of the early marker to be maintained and the specificity of the cardio-specific marker (troponins) to be improved. The high negative predictive value of myoglobin associated with the high positive value of cTnI increased the diagnostic accuracy of combined serial measurement, that was, for different prevalences of the disease, higher than that achieved by combined myoglobin and CK-MB testing (12).

Near-Patient Testing

Near-patient testing (NPT) is defined as "laboratory tests performed at or near the patient and usually by non-laboratory personnel" (13). In recent years, progressive improvement has occurred in technology for performing NPT. Unfortunately, some of these technologies have been introduced into the hospital without the knowledge of the clinical laboratory and without any organizational plan to ensure quality testing. Hospitals were largerly unprepared to manage these new technologies, resulting in major issues concerning the costs and quality of NPT systems. In fact, the open question is whether technology has been developed in response to clinical need or whether marketing strategies have led to a false perception of a need for the technology. So far, few institutions have been able to document significant economic or clinical benefits from universal NPT implementation. This is partly due to the difficulty in managing testing outside the sphere of the laboratory itself. In particular, as regards biochemical cardiac markers, before implementing NPT within an institution, it should be necessary to decide the diagnostic strategies to optimize their utilization and for identifying their effective turnaround times in relation to medical goals.

Near-Patient Testing and Cardiac Markers

Cardiac markers measurement appears to be an effective noninvasive means to determine the presence and the degree of injury of cardiomyocytes, but few data are available to demonstrate their contribution to improving patients' outcomes. In the study conducted by Anderson *et al.* (14), the change in CK-MB policy, from batch analysis twice per day using electrophoresis to stat testing 24 hours per day using a CK-MB mass assay, led to a reduction in the length of stay and laboratory costs. In another study, length of stay (LOS) and laboratory costs were compared against CK-MB testing policies of different hospitals (15). Patients with complications had longer LOS and higher laboratory costs when seen in hospitals whose laboratory had a batch CK-MB testing policy than those tested under random access. So far, therefore there is evidence of the link between a frequent testing policy of cardiac markers and medical outcomes, not between results available on a stat basis and clinical outcomes.

However, as for other constituents, rapid assays are now available for measuring cardiac markers at the bedside and this opportunity allows us to discuss the feasibility and the cost/effectiveness of a decentralized testing policy. Assays for cardiac markers can be subdivided into qualitative and quantitative, although, as shown in Table 1, qualitative methods have severe limitations, which compromise their clinical usefulness. Important criteria for assuring total quality with quantitative methods are shown in Table 2. Very recently, some diagnostic systems were made available for the quantitative measurement of cardiac markers, specifi-

Tab. 1 Limitations of qualitative methods for measuring cardiac markers.

Reading errors with substantial interobserver variability
Uncertainty around the cut-off limit (the so-called "*grey zone*")
Lack of information on the degree of positivity, which makes unhelpful the recommended adoption of two cut-off limits
Impossibility of using cardiac troponin levels for main clinical objectives, which are risk stratification and outcome prediction
The baseline value cannot be used for comparing subsequent quantitative results
No baseline information for further monitoring disease evolution and evaluating the efficacy of therapy (reperfusion, angioplasty, etc.)

Tab. 2 Requirements for quantitative methods.

Whole blood or heparinized plasma specimens
Effective "therapeutic" turnaround time (less than 30 min)
Automated testing of different analytes (myoglobin, troponin I or T, mass CK-MB) with possibility of patient- and time-oriented choice
Sensitivity, specificity, and analytical standardization
Satisfactory cost/effectiveness ratio

cally designed for NPT. They are the Triage Cardiac Panel, the Stratus CS and the Cardiac Reader.

Biosite Triage Cardiac Panel

This is a self-calibrating fluorescence immunoassay system for the quantitative determination of myoglobin, CK-MB and cTnI and is optimized for heparinized whole blood and plasma specimens. Briefly as taken from the manufacturer's (Biosite, San Diego, CA, USA) package insert, after addition of the sample (six drops) to the sample port, the cells are separated from the plasma via a filter contained in the device. A predetermined quantity of plasma is allowed to react with fluorescent antibody conjugates within the reaction chamber. After incubation, the reaction mixture flows down the device detection lane. Complexes of the analytes and fluorescent antibodies conjugates are captured on discrete zones, producing binding assays that are specific for each analyte. The concentration of each analyte, directly proportional to the fluorescence detected, is measured by the Triage meter. All results are available within 15 minutes.

Apple *et al.* (16) evaluated the analytical and clinical efficiency of this system and its practicability for the detection of myocardial infarction. Optimum cut-offs for the discrimination of AMI as determined by receiver operating curve (ROC) analyses were as follows: 0.4 µg/l for cTnI; 4.3 µg/l for CK-MB; and 107 µg/l for myoglobin. The Triage Cardiac Panel showed the following concordances for detection or ruling out AMI compared to established devices (Dade Stratus): cTnI >89%; CK-MB >81%; myoglobin >69% for the diagnosis of AMI. Efficacy, sensitivity and specificity were comparable to those obtained with Dade, Beckman, and Behring CK-MB, cTnI, and myoglobin assays. The areas under the ROC curves for the Biosite myoglobin, CK-MB, and cTnI were 0.818, 0.905, and 0.970, respectively. The authors conclude that the Triage Cardiac Panel offers clinicians a whole blood, point-of-care analysis of multiple cardiac markers providing excellent clinical sensitivity and specificity for the detection of AMI.

Dade Stratus CS

The Stratus CS STAT (SCS) fluorometric analyzer (Dade-Behring, USA), a microprocessor-controlled instrument designed for the rapid turnaround of diagnostic tests, employs ready-to-use reagents, calibrators, and diluents for measuring myoglobin, CK-MB and cTnI. The analyzer provides on-board centrifugation of whole blood samples collected in lithium heparin and up to four results in each sample which can be automatically identified by a bar code reader. The first result is available within 14 minutes, further results being available after 4 minutes. The traceability of procedures and operators is assured; the instrument stores results for the last 20 samples processed. A system check lockout controls all the testing phases with a frequency ranging from 1 to 30 hours according to the operator's request. A quality control lockout for each level and for each method is available at a variable frequency. The calibration can be used up to 10 weeks. We recently evaluated the analytical efficiency and practicability of the system. The analytical performance of the system for the three analytes is described in Table 3.

Tab. 3 Analytical performance of Stratus CS.

Inter-assay reproducibility	µg/l	CV (%)
Myoglobin	48.68	3.73
TnI	0.60	5.01
CK-MB	3.46	4.17
Accuracy		
SCS myoglobin = 1.042 Stratus II + 2.002;		r = 0.99
SCS TnI = 0.805 RxL + 0.352;		r = 0.960
SCS CK-MB = 0.954 RxL – 0.119;		r = 0.996

SCS: Stratus CS STAT; RxL: Dimension RxL (Dade-Behring)

In particular, the functional sensitivity (minimum value at which the coefficient of variation is <20%) of Stratus CS cTnI assay is significantly improved (0.03 µg/l), allowing a more satisfactory detection of minor increases of the marker (17). Moreover, the relative increase of cTnI and its diagnostic sensitivity for the detection of AMI and minor myocardial injury have been found higher than those obtained with previous assay (18).

As concerns practicability, the system is really easy-to-use and it provides all the features necessary for documenting all the critical elements required in modern accreditation/certification programs.

Cardiac Reader

The Cardiac Reader system (Roche Diagnostics, Germany) is a desktop analyzer for the quantitative measurement of myoglobin and cardiac Troponin T in whole bood specimens collected in lithium heparin. No sample preparation is required and an automatic identification of the sample by a bar code reader is available. The reaction time is 10 minutes for myoglobin and 14 minutes for cTnT. The system enables us to record the last 16 patients results, and controls values. A standard serial interface allows the analyzer to be connected to the host computer.

A multicentric evaluation of the system was recently carried out (19).

Quality Issues

A common theme in considering the quality aspects of NPT is that standards for testing are site-neutral; that is, the same quality assurance, quality control and quality documentation procedures must be in place regardless of whether testing is performed in a central laboratory, a satellite laboratory, or by the patient's bedside. The concept of "testing site neutrality" was introduced in the preamble of the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) (13), representing a milestone in regulations for U.S. laboratories. The

Tab. 4 Quality assurance in near-patient testing: a four-level strategy.

1. Internal quality control
2. Correlation samples (to demonstrate accuracy and comparability of methodologies within the institution)
3. External quality assessment (EQA)
4. Review of medical records

same concept is now present in some programs for accreditation of medical laboratories, such as in the additional criteria for quality systems of medical laboratories formulated by the EC4 Working Group (20). A critical point is that, in addition to requirements for assuring the analytical quality (quality control, external quality assurance, written procedures for all assays), special emphasis should be placed on assuring the education, training and development of personnel carrying out NPT analyses, in documenting all results and in undertaking periodic reviews of the clinical efficacy of the NPT services. Moreover, pre- and post-analytical aspects should be taken into consideration for assuring quality. According to these principles, a four level quality assurance scheme should be implemented in NPT facilities following the scheme shown in Table 4.

A survey on clinicians' attitudes towards NPT well documented the need of implementing a quality system also for decentralized testing. In fact, while 85% of clinicians trusted laboratory results from the central hospital laboratory, only 34% trusted laboratory results from NPT. This led to overutilization and increased costs from duplication of testing (21).

Thus, the existence and the documentation available to clinicians on a quality assurance system in NPT seems to be a prerequisite for assuring the rational utilization of NPT results.

Thus the early detection of myocardial damage is one of the major challenges in contemporary cardiology. New biochemical markers have now emerged which appear to be highly sensitive and specific for the assessment not only of patients with AMI but also of those with unstable angina and prolonged chest pain. NPT is becoming increasingly popular: it may provide useful information to the clinician but careful evaluation of quality issues as well as of the cost/efficacy ratio should be done before implementing a NPT policy.

Particularly, biochemical cardiac markers allow clinicians to improve the strategy for ruling in/ruling out patients with suspected AMI; their measurement may also help in predicting which patients are likely to experience complications and, therefore, need special therapeutic regimens. However, despite some evidence of a link between a frequent test policy and medical outcomes, no data are available on the impact of STAT results in making more effective decisions on patient management. A recent paper (18) provides some information on this topic, but another study, recently published by Hudson *et al.* (22), demonstrates the limitations of existing studies on NPT for cardiac markers. Certainly, the impact of NPT devices will depend on venue: in settings where quantitative values are already available in real time from a central laboratory, the impact of NPT would be expected to be less than in settings where biochemical marker testing is batched and available only at preset times. NPT options should be compared in each institution with these available from the central laboratory, which can now use rapid pneumatic tube sample delivery systems, rapid random-access immunoassay analyzers, and rapid reporting of results from on-line instruments. The choice of the solution should be based on existing facilities and logistic-organizational issues as well as the financial impact and the cost-effectiveness in each venue, preserving quality aspects.

Future studies evaluating cardiac NPT should focus on their impact on real-time decision making and include a careful comparison of financial and medical outcomes with traditional testing strategies available from laboratories.

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