



The Future of Cardiac Biomarkers

NEW CONCEPTS AND EMERGING TECHNOLOGIES FOR EMERGENCY PHYSICIANS

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Dear Colleagues,

Cardiac biomarkers such as CK-MB, troponins, and myoglobin provide the basis for the diagnosis of acute myocardial infarction (AMI) through identification of the necrosis of myocardial cells in the heart. For emergency physicians, or any clinician evaluating and treating patients presenting to the hospital with acute coronary syndrome (ACS), ischemic changes on the 12-lead electrocardiogram or elevation of a cardiac biomarker such as troponin identifies patients at high risk for ischemic complications including AMI, recurrent ischemia, and death.

In this EMCREG-International newsletter, Judd E. Hollander, MD, from the Hospital of the University of Pennsylvania, discusses the development and current emergency department use of cardiac necrosis biomarkers (CK-MB, troponin, myoglobin), biomarkers of inflammation (C-reactive protein), and newer cardiac biomarkers of myocardial ischemia (brain natriuretic peptide).

Finally, Dr. Hollander discusses the novel approach of combining the results of multiple cardiac biomarkers of necrosis and ischemia to improve the diagnostic capabilities of all cardiac biomarkers. A mathematical algorithm integrates the results of four cardiac biomarkers into an index number which provides greater diagnostic accuracy than any individual cardiac biomarker result.

Hopefully this EMCREG-International newsletter will be a useful tool for emergency healthcare providers and provide a better understanding of the cardiac biomarkers used in emergency practice for diagnosis of ACS. We hope that this information will help clinicians provide outstanding care for their patients.

Sincerely,



Andra L. Blomkalns, MD
Director of CME,
EMCREG-International



W. Brian Gibler, MD
President,
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Introduction

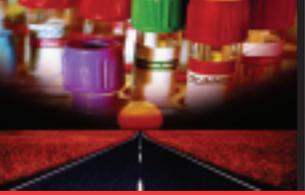
Ischemic heart disease is the leading cause of death among adults in the United States. Over 6 million U.S. citizens have coronary artery disease and there are approximately 5 million emergency department (ED) visits for acute chest pain syndromes annually. Broad based studies that include all ED patients who received an ECG for the evaluation of chest pain syndromes found that 5% of these patients were ultimately diagnosed with acute myocardial infarction (AMI) and an additional 10% had non-AMI acute coronary syndromes (ACS). Thus, 85% of patients have non-ACS causes for their symptoms. From the ED perspective, it is important to expeditiously distinguish between these two groups of patients.

Although the standard 12-lead electrocardiogram (ECG) is the single best test to identify patients with AMI upon ED presentation,¹ it still has relatively low sensitivity for detection of AMI. The sensitivity of ST-segment elevation for the detection of AMI is 35-50%, leaving more than half of all AMI patients unidentified.^{1,2} Because of the relatively poor sensitivity of the standard 12-lead ECG to detect patients with ACS, additional strategies are needed. Cardiac biomarkers are the second most commonly used test to identify patients with potential ACS.

The utility of individual cardiac biomarkers depends upon their ability to detect and risk stratify patients with potential ACS. In the ED, the ideal cardiac biomarker will allow early detection of patients with ACS, and enable optimal treatment pathways to be initiated and assist with rapid patient disposition and treatment. The optimal use of cardiac biomarkers depends on how exactly the physician is trying to use them. Since up to 85% of patients who present to the ED with potential ACS do not ultimately have a cardiac etiology for their symptoms, a cardiac biomarker with a high negative predictive value is useful to allow expeditious evaluation and discharge from the ED. Cardiac biomarkers with high positive predictive values are ideal to tailor aggressive care for patients at high risk of cardiovascular complications. To that end, a panel of cardiac biomarkers may ideally provide for both a rapid "rule out" and for a rapid identification of patients with high risk ACS.



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Creatinine Kinase MB fraction

In the setting of AMI, creatinine kinase MB (CK-MB) levels rise to twice normal within six hours and peak within 12-24 hours. Serial CK-MB mass measurements have nearly a 90% sensitivity three hours after ED presentation (approximately 6 hours after symptom onset) but are only 36-48% sensitive when utilized at or shortly after presentation.^{3,4} Single CK-MB measurements cannot be safely used to assist in the admission/discharge decision since they do not attain adequate negative predictive values for ACS and would result in an unacceptable miss rate for both AMI and cardiovascular complications. Serial CK-MB measurements over 6-9 hours have been widely employed in chest pain observation units and are considered sufficient, if negative, to safely exclude AMI or allow further diagnostic testing or ED release, depending upon the clinical scenario.⁵ An alternative strategy is to examine the change in CK-MB values within 2 hours of ED presentation. Using this strategy, the clinician must compare the two CK-MB values because a positive value is based upon the "delta" or change between values. Thus both values may be "negative" but if there is a change in value, even within the normal range, it may be a "positive" test. A rise in CK-MB > 1.6 ng/ml over the 2 hour period following presentation achieves a sensitivity for detection of AMI of 94%, which is better than using the 2 hour CK-MB value alone (75%).⁶

Patients with skeletal muscle disease, acute muscle exertion, chronic renal failure, and cocaine use can have elevations in levels of CK-MB in the absence of infarction.^{7,9} In order to distinguish "true positive" elevations (secondary to myocardial injury) from the "false positive" elevations (due to skeletal muscle injury), the measurement of CK-MB as a percentage of total CK has been used (relative index). There is no clear consensus on whether absolute CK-MB or the CK-MB relative index is the preferred test for patients with potential ACS. The World Health Organization international diagnostic criteria, and several other consensus conferences recommend use of absolute CK-MB.^{10,11} Many major clinical trials also have used the absolute CK-MB as the diagnostic test for AMI. Individual institutions are quite variable in their preference for either the absolute CK-MB or the relative index. In the only ED based study to examine this issue, the use of relative index, rather than absolute CK-MB at the time



Like troponin I, troponin T remains elevated for 7-10 days after injury.

of ED presentation to detect AMI improves specificity (96 vs. 93%) and positive predictive value (46 vs 36%) but decreases sensitivity (52 vs 47%) without significantly impacting negative predictive value (96 vs. 96%).¹² It is also important to note that a patient with skeletal muscle damage can also sustain a myocardial infarction, and thus, the large amount of total CK may reduce the percentage value of CK-MB by

obscuring a relatively smaller, but significant, CK-MB release from the heart. This may impact the ability to diagnose AMI in a setting where both ACS and rhabdomyolysis may occur, such as in cocaine users.

Cardiac Troponins

The cardiac troponins are more specific than other cardiac biomarkers for myocardial injury. Following AMI, cardiac troponin I (cTnI) becomes elevated at the same rate as CK-MB. It peaks at 12-24 hours, and remains elevated for 7-10 days. Troponin I has a higher specificity for myocardial necrosis than CK-MB in selected subsets of patients with ACS, such as patients with recent surgery, cocaine use, chronic renal failure, and skeletal muscle disease.^{7,9} In ED patients with potential ACS without these confounding conditions, cTnI has similar sensitivity and specificity for detection of AMI as CK-MB.^{8,13,14} In both ED patients with unselected chest pain syndromes and those with definite ACS, elevations in cTnI predict cardiovascular complications independent of CK-MB and the ECG.^{13,14}

Cardiac troponin T (cTnT) is released from the cell within 3 to 6 hours following symptom onset. Like cTnI, it remains elevated for 7-10 days after injury. This extended period of elevation results from disintegration of the contractile apparatus and the continued release of cTnT. Cardiac troponin T is also an independent cardiac biomarker of cardiovascular risk in patients with ACS.^{13,15} Minor elevations in cTnI and cTnT can also identify patients more likely to benefit from treatment with glycoprotein IIb/IIIa inhibitors and an early invasive treatment strategy (catheterization within 48 hours).¹⁶

Combined analysis of four studies assessing the predictive properties of single cTnI values at the time of presentation for AMI found a sensitivity of 39% and specificity of 93% (Table 1).³ A similar analysis of six cTnT studies found the same results.³ Serial sampling increases sensitivities to 90-100% with specificities of 83-96% for cTnI and a sensitivity of 93% for cTnT.³ Elevated values of the cardiac troponins in patients with non ST-segment elevation MI (NSTEMI) increase the short term risk of death 3.1 fold (1.6% vs. 5.2%).¹⁷ Although the cardiac troponins are useful for both diagnosis and risk stratification of patients with chest discomfort,¹⁸ ACS and AMI, cardiac biomarker testing in the ED will not always identify patients that subsequently develop adverse events.^{19,20} Thus, patients with negative cardiac biomarkers may still require further evaluation



A panel of cardiac biomarkers may ideally provide for both a rapid "rule out" and for a rapid identification of patients with high risk ACS.



Table 1: Summary of predictive properties of cardiac biomarkers for diagnosis of AMI. Reprinted from Ann Emerg Med. 2001;37, Lau J, Ioannidis JPA, Balk EM, et al. Diagnosing acute cardiac ischemia in the Emergency Department: A systematic review of the accuracy and clinical effect of current technologies. 453-460.

Marker	No. Studies	No. Subjects	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic Odds Ratio (95% CI)
At time of presentation					
Creatine kinase	12	3,195	37 (31-44)	87 (80-91)	3.9 (2.7-5.7)
CK-MB	19	6,425	42 (36-48)	97 (95-98)	25 (18-36)
Myoglobin	18	4,172	49 (53-55)	91 (87-94)	11 (8-15)
Troponin I	4	1,149	39 (10-78)	93 (88-97)	11 (3.4-34)
Troponin T	6	1,348	39 (26-53)	93 (90-96)	9.5 (5.7-16)
CK-MB and Myoglobin	3	2,283	83 (51-96)	82 (68-90)	17 (7.6-40)
Serial markers					
Creatine kinase	2	786	69-99	68-84	12-220
CK-MB	14	11,625	79 (71-86)	96 (95-97)	140 (65-310)
Myoglobin	10	1,277	89 (80-94)	87 (80-92)	84 (44-160)
Troponin I	2	1,393	90-100	83-96	230-460
Troponin T	3	904	93 (85-97)	85 (76-91)	83 (33-210)
CK-MB and Myoglobin	2	291	100	75-91	4.3-14

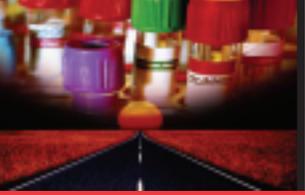
and testing, such as radionuclide imaging, as dictated by their clinical presentation. Elevation in cTnT, and less so cTnI, have been noted in patients with renal failure. Although these have been incorrectly considered to be "false positives", they do predict a worse outcome.²¹

Myoglobin

Myoglobin has a lower molecular weight and is released more rapidly than CK-MB and the cardiac troponins during AMI. Serum myoglobin levels rise faster than CK-MB, reaching twice normal values within two hours and peaking within four hours of AMI symptom onset. Myoglobin achieves its maximal diagnostic sensitivity within 5 hours of symptom onset.²² The sensitivity of myoglobin at the time of ED presentation is 49%, exceeding that of CK-MB or troponins, but the specificity is lower (only 91%).³ Serial quantitative testing over 1 hour, evaluating both absolute values and a change of 40ng/ml, has 91% sensitivity and up to a 99% negative predictive value for AMI within one hour of ED presentation or approximately 3-4 hours after symptom onset.²³ An elevated myoglobin predicted a 3.4 fold risk of adverse cardiovascular events and identified some high risk patients not otherwise identified by clinical characteristics, CK-MB or cTnT.²⁴ The main advantage of myoglobin is early detection of patients with AMI. The disadvantage is that it has poor specificity for AMI in patients with concurrent trauma or renal failure. When used in appropriately selected patients, myoglobin has significant clinical utility.



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SPECIAL ISSUES AND CARDIAC BIOMARKERS

When cardiac biomarkers of myocardial injury disagree

On occasion the clinician is faced with discordant cardiac biomarker results. Most commonly, both CK-MB and troponin are either both elevated or both negative, facilitating the diagnosis of AMI. When the CK-MB is elevated in the absence of a cTnI elevation, it is most often a "false positive" CK-MB. When one of the cardiac troponins is elevated in the absence of a CK-MB elevation, it is usually a delayed presentation reflecting the longer time period of troponin elevations than for CK-MB. Patients presenting very early, less than 2-3 hours after symptom onset, may have elevations in myoglobin in the absence of CK-MB or troponin elevations. Serial testing usually clarifies if this is the case.

Cardiac biomarkers of myocardial ischemia and inflammation

Some cardiac biomarkers do not require myocardial cell death for release and are called myocardial ischemia markers. These include cardiac biomarkers of inflammation and platelet activation. C-reactive protein has been related to long term prognosis in selected groups of patients, but it does not have proven utility in symptomatic patients in the ED. Cardiac biomarkers of platelet activation such as P-selectin and other integrins are theoretically attractive because they can detect platelet activation prior to myocardial injury. When P-selectin was evaluated in the ED setting, it was not able to risk stratify patients with AMI and ACS relative to patients with non-ischemic chest pain syndromes. The initial sensitivity was 46% and specificity was 76% for AMI. The predictive properties and area under the curve (AUC) for AMI, ACS and serious cardiac events were not better than that of the initial CK-MB.²⁵ Similar results have been found with some inflammatory biomarkers. The favorable predictive properties observed with inflammatory biomarkers in longitudinal cohort studies of patients with potential coronary artery disease may not generalize to the ED, where most patients with potential ACS have confounding medical conditions likely to increase the prevalence of inflammatory biomarkers.

B-type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a neurohormone secreted from the cardiac ventricles as a response to pressure or volume overload. B-type natriuretic peptide, an established cardiac biomarker for patients with heart failure, is also elevated in patients with ACS and can identify ACS patients who are at higher risk for adverse cardiovascular events, including heart

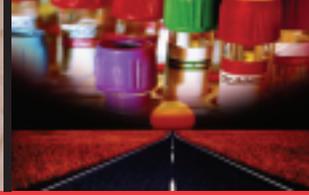
failure or death.²⁶⁻³⁰ The utility of BNP as a diagnostic cardiac biomarker for ACS is based upon the premise that early after the onset of ischemia, impaired diastolic (and often systolic) function occurs with subsequent increases in left ventricular pressure and volume overload, potentially resulting in release of BNP. As the half life of BNP is approximately 20 minutes, dynamic changes in BNP can occur rapidly. B-type natriuretic peptide levels rapidly decrease in unstable angina patients with resolution of ischemia.³¹ This suggests that BNP may provide important diagnostic and prognostic information in patients with potential ACS, particularly in the undifferentiated ED population.

Making the most of cardiac biomarkers

Cardiac biomarkers of myocardial injury, when used individually at the time of ED presentation do not attain sufficient negative predictive value to safely allow immediate ED discharge. However, it makes intuitive sense that combinations of two or more cardiac biomarkers increase the early predictive value of these types of strategies. Although both troponins and CK-MB have approximately the same rate of rise, there is benefit to using more than one of the cardiac biomarkers to predict adverse cardiovascular events. At the time of ED presentation, the use of both cardiac biomarkers rather than either alone, increases diagnostic sensitivity more than 25%.²⁴ Myoglobin and CK-MB, when used in combination has a sensitivity of 85% at the time of presentation and in one study attained 100% sensitivity, specificity and negative predictive value within 4 hours of ED presentation.³² When patients with diagnostic ECG's were excluded, the sensitivity of this combination strategy was 80% with a specificity of 84% at that time of presentation. Both sensitivity and specificity were 100% within 4 hours of ED arrival.³² A combination of myoglobin and cTnI can achieve a diagnostic sensitivity of 97% for AMI with a 99% negative predictive value, within 90 minutes of ED presentation.³³ The addition of CK-MB did not improve diagnostic accuracy within this time frame, but the CK-MB and myoglobin combination did have a 92% sensitivity and 99% negative predictive value within this same period. These studies show that combinations of cardiac biomarkers may prove more useful in the clinical setting.



A combination of myoglobin and cTnI can achieve a diagnostic sensitivity of 97% for AMI with a 99% negative predictive value, within 90 minutes of ED presentation.



The addition of BNP to cardiac biomarkers of myocardial cell death

In an ED-based study of patients with potential ACS, the addition of BNP to cardiac biomarkers of myocardial necrosis (CK-MB, troponin, and myoglobin), increased the detection of patients with adverse cardiovascular outcomes at the time of ED arrival. The sensitivity of the initial cardiac biomarkers for detection of a 30 day adverse outcome was 63% (95% CI, 53-73%), specificity was 65% (95% CI, 61-70%); negative predictive value, 93% (95% CI, 90-96%) and positive predictive value, 20% (95% CI, 14-26%).³⁴

A novel approach to integrating multiple cardiac biomarkers is being developed. This method uses a mathematical algorithm whereby the results of four cardiac biomarkers (CK-MB, cTnI, myoglobin and BNP) are integrated into one index. This multimarker index (MMX) including BNP and cardiac biomarkers of myocardial necrosis has improved performance for detection of AMI on the initial sample relative to the same individual cardiac biomarkers and a composite of the same four cardiac biomarkers using traditional thresholds. **Table 2** shows the AUC for the MMX relative to individual cardiac biomarkers at the time of ED presentation. Compared to a composite of the same four individual cardiac biomarkers, the MMX had significantly better specificity, likelihood ratio positive, and positive predictive value, while being similar on other performance characteristics (**Table 3**).³⁵ Hence, the use of multimarker panels may improve the ability of clinicians to make decisions earlier during the evaluation period.

Table 2: The area under the curve (AUC) for the multimarker index relative to individual markers at the time of ED presentation. Greater areas under the curve represent greater diagnostic accuracy.

Marker	AUC	95%CI
MMX	0.98	.97-.98
CKMB	0.91	.90-.92
cTnI	0.94	.93-.96
Myoglobin	0.78	.76-.81
BNP	0.85	.83-.88

MMX = multimarker index; AUC = area under the curve; CK-MB = creatinine kinase MB; cTnI = cardiac troponin I; BNP = brain natriuretic peptide

Table 3: Predictive properties of a composite of four individual markers (BNP, CK-MB, cardiac troponin I and myoglobin) compared to the multimarker index (MMX) using the same four markers.^{34,35}

	Multimarker index	Composite of 4 markers
Sensitivity	91% (90-93)	94% (93-95)
Specificity	94% (92-97)	70% (66-75)
Negative predictive value	77% (73-81)	77% (73-81)
Positive predictive value	98% (97-99)	91% (89-92)
Likelihood ratio +	16.1 (11-24)	3.2 (2.7-3.7)
Likelihood ratio -	0.1 (.08-.12)	0.08 (.07-.11)

Receiver Operator Curve (ROC) Characteristics

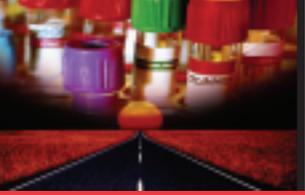
A ROC curve is a graphical representation of the trade off between the true positive and false positive rates for every possible cut off of the test result. In essence, the ROC curve is the tradeoff between sensitivity and specificity.

A large area under the curve (AUC), as shown in the table, means the test being assessed is a better diagnostic test. If the area is 1.0, the test has both 100% sensitivity and 100% specificity and represents an ideal test. If the area is only 0.5, the test has a 50% sensitivity and 50% specificity – the same as getting heads on the flip of a coin. Therefore, the closer the AUC is to 1.0, the better the test is for diagnosis.

Likelihood ratios

The likelihood ratio incorporates both the sensitivity and specificity of a test to estimate how much a test result will change the odds of having a disease. The likelihood ratio for a positive result (LR+) tells you how much the odds of the disease increase when a test is positive. The likelihood ratio for a negative result (LR-) tells you how much the odds of the disease decrease when a test is negative.

In essence, the clinician should combine the likelihood ratio with information about the pretest probability of disease to determine the post-test odds of disease. In general, the best tests should have an LR+ of 5 or more and an LR – of 0.1, substantially altering the likelihood of disease based upon the test result.



The Future of Cardiac Biomarkers

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Disclosures

In accordance with the ACCME Standards for Commercial Support of CME, the authors have disclosed the following relevant relationships with pharmaceutical or device manufacturers: Dr. Hollander has received honoraria and/or research support, either directly or indirectly, from Biosite and Scios

CME Accreditation

The University of Cincinnati College of Medicine designates this educational activity for a maximum of one (1) Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits he/she actually spend in the educational activity. The University of Cincinnati College of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Application has been made to the American College of Emergency Physicians for ACEP Category 1 credit.

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CME Post Test

After you have read the monograph, carefully record your answers by circling the appropriate letter for each question.

(Please circle answers below)

- 1) **Single CK-MB measurements may be used to reliably "rule-out" ACS in an ED population.**
a) True
b) False
- 2) **Myoglobin, CK-MB, and troponin are all markers of myocardial necrosis.**
a) True
b) False
- 3) **BNP may be elevated in ACS due to CHF or ventricular strain related to the ischemic syndrome.**
a) True
b) False
- 4) **When interpreting the receiver operator curve (ROC) and area under the curve (AUC) characteristics, greater areas are associated with greater diagnostic accuracy optimizing sensitivity and specificity.**
a) True
b) False
- 5) **The use of a multi-marker index may improve the predictive properties and diagnostic accuracy of several cardiac biomarkers.**
a) True
b) False

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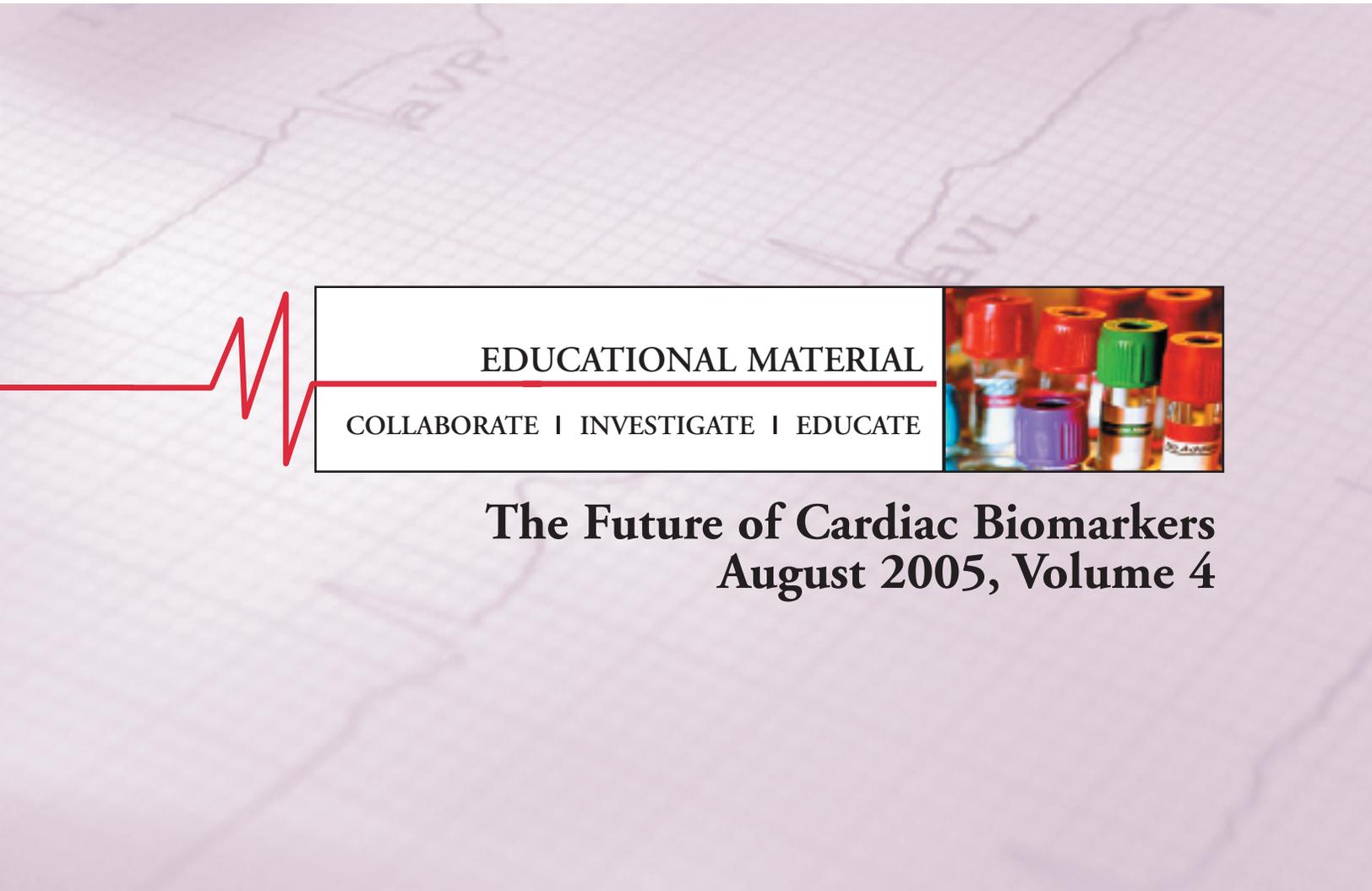


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August 2005, Volume 4

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