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A Prospective Study of an Algorithm Using Cardiac Troponin I and Myoglobin as Adjuncts in the Diagnosis of Acute Myocardial Infarction and Intermediate Coronary Syndromes in a Veteran's Hospital

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Summary

Background: Accurate and cost-effective evaluation of acute chest pain has been problematic for years. The high prevalence of missed myocardial infarctions (MI) has led to conservative triage behavior on the part of physicians, leading to expensive admissions to coronary care units. New algorithms are sorely needed for more rapid and accurate triage of patients with chest pain to appropriate treatment settings.

Hypothesis: We sought to test an algorithm for rapid diagnosis of MI and acute coronary syndromes using cardiac troponin I (cTnI) and myoglobin as adjuncts to creatine kinase (CK)-MB. We hypothesized our algorithm would be both sensitive and specific at early time points, and would allow safe stratification of patients not ruling in by conventional CK-MB criteria.

Methods: This was a 6-month prospective study of 505 consecutive patients who presented with chest pain at a university-affiliated veteran's hospital. The percentage of MIs at various time points was identified using combinations of markers. Safety outcomes were assessed by follow-up of patients discharged home. Cost savings analysis was assessed by surveying the physicians as to whether the use of the algorithm affected their disposition of patients. Forty-nine patients ruled in for MI. Using the combination of cTnI, 2-h doubling of myoglobin, and CK-MB, 37 (76%) ruled in at the time of presentation, 43 (88%) at 2 h, and 100% by 6 h.

Results: Cardiac troponin I plus a 2-h myoglobin was as accurate as the combination of all three markers and performed better than CK-MB in detecting patients presenting late and as a predictor for complications when CK-MB was normal. Of the 456 patients with normal markers after 6 h, only 140 were sent to the coronary care unit (CCU), and 176 were sent home. A 3-month follow-up showed minimal adverse events. One-half of physicians completing a survey stated the use of markers changed their disposition of patients, leading to an estimated 6-month cost savings of a half-million dollars.

Conclusions: We developed an algorithm using troponin I and myoglobin as adjuncts to usual CK-MB levels that allowed for rapid and accurate assessment of patients with acute MI. It also afforded physicians important input into their decision making as to how best to triage patients presenting with chest pain. Their comfort in sending home certain subgroups of patients who otherwise would have been admitted to the CCU was rewarded with a good short-term prognosis and a large cost savings to the hospital.

Key words: myocardial infarction, troponin, myoglobin

Introduction

Accurate and cost-effective evaluation of acute chest pain in the emergency department has been recognized as problematic for well over a decade.[1–6] The high prevalence of missed myocardial infarctions (MIs) and the associated litigation potential has led to increased apprehension on the part of physicians, often causing them to err on the side of conservative admission.[7, 8] In addition, the expense of evaluating patients without MI in the coronary care unit (CCU) has increased to an estimated $10 to $13 billion annually in the United States.[9]

Because newer tests appear to detect MI accurately in its acute stages, accelerated diagnostic protocols for evaluation of chest pain have become feasible.[10–18] We hypothesized that

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strategically sampled levels of creatine kinase (CK)-MB, cardiac troponin I (cTnI), and myoglobin would allow for the rapid and accurate diagnosis of acute MI and would aid the physicians in their clinical decision making with regard to patient triage and stratification.

Methods

Preliminary studies with cTnI were approved by the University of California, San Diego, Committee on Human Subjects.

Algorithm

In the 6-month period (October 1996 to March 1997) we prospectively evaluated 505 consecutive patients for chest pain felt to be consistent with myocardial ischemia or MI. Blood was drawn at times 0, 2, 6, and 12 h. At 0 h (time of presentation to our hospital), patients were considered to have an MI if either cTnI was > 1.5 ng/ml or CK-MB was > 9 ng/ml; these patients were sent to the CCU. If patients presented with < 6 h of chest pain, a second sample for myoglobin was drawn 2 h after the initial presentation. Barring another reason for myoglobin to be increased (skeletal muscle injury, hemolysis, etc.), a doubling of serum myoglobin from baseline was considered indicative of MI, and those patients were also admitted to the CCU. Myoglobin levels > 85 ng/ml were considered elevated, and a doubling had to have reached at least 160 ng/ml to be considered positive. At 6 and 12 h of presentation, patients were considered to have an MI if either cTnI was ≥ 1.5 ng/ml or CK-MB was > 9 ng/ml.

In patients admitted for suspected MI, ultimate diagnosis necessitated elevation of the standard of reference (CK-MB > 9 ng/ml). In the 10 cases of patients presenting with delay in symptoms (> 48 h), where CK-MB could no longer substantiate MI, diagnosis was made by evidence of new wall motion abnormality on echocardiography or an ulcerated or occlusive coronary artery demonstrated at the time of angiography.

The patients with elevated cTnI > 0.6 ng/ml, but with normal or minimally elevated CK-MB, and who had not had chest pain for > 48 h before coming to the hospital were considered to have minor myocardial damage and were admitted to the hospital, mostly to the CCU. These patients were treated at the discretions of their physicians and followed up at 6 months.

In patients in whom enzymes were negative by 12 h, MI was considered to be ruled out. Likewise, if a patient presented with chest pain of more than 6 h duration, an MI was felt to be unlikely if the initial set of markers was negative. At any time physicians could triage patients to appropriate settings based on clinical suspicion and/or electrocardiographic (ECG) changes. Physicians filled out surveys at the time of disposition as to whether the algorithm played a major role in their clinical decision-making. Patients discharged home from the emergency room were followed up within 3 months by phone call, letter, or chart review.

Assays

Blood (about 2–3 ml) was collected in green top tubes containing heparin and was centrifuged before analysis. All three enzymes were assayed using the Opus Plus Analyzer (Behring Diagnostics, Westwood, Mass.). Turnaround time for the three assays combined was approximately 20 min. The cost of each assay was approximately $8.00. All assays were based on the principle of two-site or sandwich immunoassay, using two goat polyclonal antibodies purified to recognize different polypeptide segments unique to the cardiac isoform of cTnI, CK-MB, or myoglobin.

Statistical Analysis

Accuracy of single or combination of myocardial markers at each time period was recorded as the percentage with 95% confidence intervals (CI). Comparisons between the different combinations of markers were made using the McNemar test, with an alpha of 0.05 for statistical significance.

Results

A flow sheet of patient flow in our algorithm is presented in Figure 1. In all, 505 patients (495 men, 10 women) presented with chest pain during the 6-month study period. Of these, 62% had their cardiac markers drawn within the first 6 to 12 h of onset of chest pain. Forty-nine patients subsequently ruled in for MI. Eight patients (four of whom received thrombolytic therapy) had ST elevation at the time of presentation, the other 41 subsequently ruled in with non Q-wave infarctions.

Using our panel of three markers, 37 of 49 infarcts were uncovered at the time of admission (sensitivity 76%; CI 64–88%) (Fig. 2, Table I). The addition of 2-h myoglobin (Fig. 3, Table I) added six more infarctions, so that within 2 h of presentation 43 of 49 infarctions were detected (sensitivity 88%, CI 77–100%). The algorithm required that samples be drawn at least through the 12-h study period. By 6 h of presentation, however (Fig. 3, Table I), the algorithm detected all 49 infarctions (sensitivity 100%). The negative predictive value of our combination of markers was 97% (68–90%) at 0 h and 99% (98–100%) at 2 h.

At the time of presentation, elevations of cTnI were seen in 37 of 49 patients subsequently proved by other criteria to have MIs (sensitivity 76%, CI 64–88%) (Fig. 3, Table I). This compares with only 24 patients whose infarction was detected by an elevated CK-MB (49% sensitivity, CI 36–62%, $p < 0.001$). In the 13 patients ruled in by cTnI but not CK-MB at 0 h, 10 were due to delayed patient presentation. The other three patients ruled in by CK-MB at a later time point.

At 6 h, cTnI was positive in all 49 patients in whom an MI was ultimately substantiated either by CK-MB elevation, or new left ventricular dysfunction (sensitivity 100%) (Fig. 3, Table I). Of the 49 patients, 35 had high CK-MB at 6 h (sensitivity 71%, CI 58–84%) and 39 of 49 were CK-MB+ by 12 h (sensitivity 80%, CI 71–81%). Thus, there were four patients

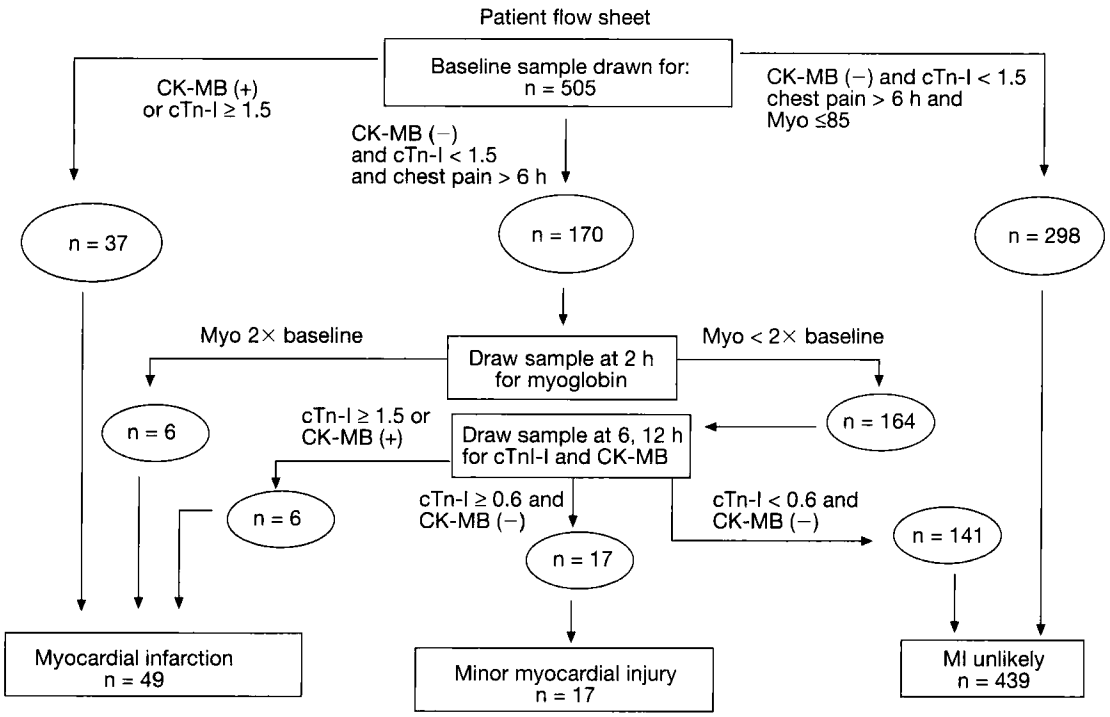

FIG. 1 San Diego Veterans Administration cardiac marker protocol-patient flow sheet. Myo = myoglobin. Other abbreviations as in Table I.

who ruled in by cTnI by 6 h but who did not rule in by CK-MB elevation until the 12-h blood draw. The specificity and negative predictive values for cTnI and CK-MB combined exceeded 90% at 0 and 6 h. The negative predictive value of cTnI at 6 h was 100%.

There were 27 patients who had elevated cTnI levels but normal CK-MB; ten were late presentations of MI. The other 17 patients were classified as "minor myocardial damage," and were characterized by prolonged chest pain, often at rest, persistent ST changes, and high-grade eccentric stenoses at coronary angiography. Six-month follow-up revealed 10 deaths, many of which were directly or indirectly cardiac related, including three coronary artery bypass graft (CABG) procedures and one subsequent MI.

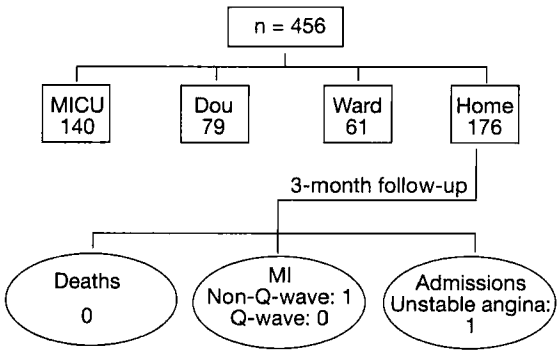

FIG. 2 Disposition of patients who ruled out for myocardial infarction (MI) (normal enzymes at 6 h). Once an MI was ruled out, physicians were then given the choice of disposition of patients to the coronary care unit, telemetry, the ward, or home. Approximately 50% of physicians surveyed felt the new marker protocol played a major role in their decision making. Patients discharged from the emergency room to their home were followed up within 3 months by phone call, letter, or chart review. MICU = medical intensive care unit, DOU = direct observation unit.

Myoglobin

In patients presenting with < 6 h of chest pain, and in whom a 0-h cTnI or CK-MB was negative, myoglobin was drawn again 2 h after the initial presentation. A doubling of myoglobin at 2 h was seen in 6 of the remaining 12 infarcts (sensitivity 50%, CI 22–78%) (Fig. 3, Table I). Most of these false negatives had elevated 2-h myoglobin that had not quite doubled from the original values, which were in themselves often higher than normal. These patients had a slightly longer time until presentation (5–6 h vs. 2–5 h). All patients who subsequently ruled in for MI and who presented within 6 h of chest pain and had a normal baseline myoglobin had subsequent doubling at 2 h. The specificity of the 2-h myoglobin was 100%, with a negative predictive value of 99%.

The present study, using only the combination of cTnI plus a 2-h doubling of myoglobin, detected as many infarctions as the combination of cTnI, myoglobin, and CK-MB (Fig. 3, Table I). At 2 h the combinations of cTnI and myoglobin detected 43 of 49 infarcts (sensitivity 88%, CI 77–100%), compared with only 29 of 49 infarcts using CK-MB plus myoglobin (sensitivity 60%, CI 46–74%, $p < 0.001$).

TABLE I Accuracy of markers at 0, 2 and 6 h

	Treatment	#MIs	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Accuracy of markers at 0 h	Combination	37/49	76 (64–88)	98 (97–99)	79 (68–90)	97 (96–98)
	cTnI only	37/49	76 (64–88)	98 (97–99)	79 (68–90)	97 (96–98)
	CK-MB only	24/49	49 (32–62)	100	100	94 (92–96)
Accuracy of markers at 6 h	Combination	49	100	98 (97–99)	83 (74–92)	99 (98–100)
	cTnI only	49	100	98 (97–99)	83 (74–92)	100
	CK-MB only	35	71 (58–84)	99 (98–100)	99 (96–100)	97 (95–99)
Accuracy of markers at 2 h	Combination	43/49	88 (77–100)	98 (97–99)	81 (71–91)	99 (98–100)
	Myoglobin doubling	6/12	50 (22–78)	100	86 (60–100)	99 (98–100)
	cTnI + myoglobin doubling	43/49	88 (77–100)	98 (97–99)	81 (71–91)	99 (98–100)
	CK-MB + myoglobin doubling	29/49	60 (46–74)	100	100	94 (91–97)

For 0 and 6 h, data recorded for combination of all three markers, cTnI only, and CK-MB only as the percentage with 95% confidence intervals. For 2 h data recorded for combination of all three markers, 2-h myoglobin doubling, cTnI elevation plus myoglobin doubling, and CK-MB elevation plus myoglobin doubling as the percentage with 95% confidence intervals.
Abbreviations: PPV = positive predictive value, NPV = negative predictive value, MI = myocardial infarction, cTnI = cardiac troponin I, CK-MB = creatine kinase-MB.

Disposition of Patients Whose Cardiac Panel Was Normal: Cost Savings Analysis

Figure 2 shows the disposition of patients with normal cardiac enzymes. Patients were triaged whenever their physicians felt they had obtained enough information to make an appropriate disposition. Clinical decision making was also based on history, physical examination, and ECG findings. No patient with > 6 h of chest pain was discharged home unless enzymes were also normal.

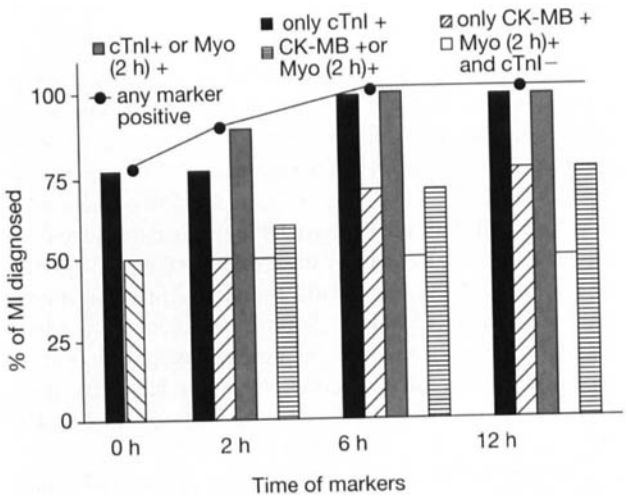

FIG. 3 Comparative accuracy of markers in acute myocardial infarction (MI). Figure depicts the percentage of MIs diagnosed at 0, 2, 6, and 12 h. Time represents number at the point when markers were first drawn. The straight line depicts results using all three markers (any marker positive) and the boxes represent various combinations of markers.

Of the 455 patients who ruled out for MI, only 127 had been sent to one of the intensive care units; 88 had been sent to a telemetry unit, 54 to the ward, and 186 were discharged home. Figure 2 shows that in a 3-month follow-up (> 90% response rate), only one patient suffered a non-Q wave MI.

About one half of the physicians completing the survey stated that they were aided in their clinical decision making by having the algorithm available. In other words, in about one half of the cases, patients who normally would have been admitted to the CCU were admitted elsewhere or sent home. Our cost savings analysis was based on the assumption that half the total number of patients either sent home or admitted to a non-CCU setting might have been admitted to the CCU had the algorithm not been available. Our estimated 6-month cost savings based on a typical 3-day stay for chest pain (one day each in CCU ($2,160.00 per day), telemetry ($1,400.00 per day), and the ward ($650.00 per day) was $496,000.00 for the 6-month period. The cost of the markers on an individual basis was less than that for the previous use of total CK plus CK-MB ($8.00 vs. $15.00). Not included in this analysis is the potential savings incurred by not misdiagnosing an MI.

Discussion

We developed and prospectively tested an algorithm using both troponin I and myoglobin as adjuncts to CK-MB for diagnosing acute MI at a university-affiliated veteran's hospital. This algorithm allowed rapid and accurate assessment, diagnosing all infarcts within 6 h of admission, with 6-h specificity and sensitivities of better than 98%. It also afforded physicians important input into their clinical decision making as to how best to triage patients presenting with chest pain. Their comfort in sending certain subgroups of patients home who

otherwise would have been admitted to the CCU was substantiated by a good short-term prognosis for these patients. In addition, use of this algorithm was extremely cost effective, with an estimated 6-month saving of half a million dollars. This figure does not include the ultimate cost in those patients who, without use of the algorithm, might have been discharged only to suffer an MI at home.

Why Use Cardiac Troponin I?

While just as sensitive as a CK-MB for infarction, cTnI is more specific for the heart, thereby negating the influences of skeletal muscle involvement that might be seen in trauma, renal failure, or postoperatively.[19–29] Cardiac troponin I also remains elevated longer, usually up to 10–14 days.[20] Recently it has also been shown that cTnI is an important prognostic indicator in patients presenting with unstable angina, even when CK-MB is not elevated.[17, 30–34] Our study supports that notion. We had 17 patients with elevated cTnI in whom CK-MB levels were normal. By 6 months 10 had died, many having suffered cardiac complications. We have labeled this group of patients as having "minor myocardial injury." Thrombotic microembolization from ruptured atherosclerotic plaques are thought to be the underlying cause in many of these patients.[35]

Myoglobin as an Adjunct in Diagnosing Myocardial Infarction

Myoglobin is a low-molecular-weight protein present in cardiac and skeletal muscle, and while sensitive for cardiac death within the first 2–4 h, is not specific for myocardial death.[16, 25, 36] In the absence of skeletal muscle injury and renal failure, however, serial myoglobin testing has been helpful in diagnosing acute MI.[16, 25, 36–41] Of 59 patients who presented to a community hospital with chest pain, serum myoglobin elevation at 3 h identified all 21 patients with MI.[41] More important, a lack of doubling of myoglobin over a short time period had a high negative predictive value for MI.

The present study was not designed to evaluate isolated elevations of myoglobin seen in patients over the course of their evaluation; rather, we studied the value of a doubling of myoglobin in patients who presented within the first 2–6 h of chest pain. If initial cTnI or CK-MB was positive, or if a patient presented with chest pain >6 h, a 2-h myoglobin was not measured. We found myoglobin to be extremely beneficial as an adjunct in diagnosing MI. A doubling of myoglobin at 2 h was seen in 6 of the remaining 12 patients who eventually ruled in for MI (sensitivity 50%). There were no cases in which myoglobin doubled after 2 h and in which the patient did not subsequently prove to have an MI by CK-MB and cTnI. Thus, the specificity and positive predictive value of a 2-h doubling of myoglobin in the present study were 100%. While falsely elevated myoglobin levels might be seen in patients with concomitant skeletal muscle injury, trauma, or burns,[16, 25, 29, 40] no patients with those descriptors were seen in the present study. The likely reason for the 50% sensitivity in our study was that most patients had initial elevations of myoglobin so that the 2-h level, while increased, did not meet the doubling criteria. However, when an initial myoglobin was normal in a patient presenting within 4–6 h of chest pain, the lack of a doubling of myoglobin ruled out MI in 100% of those patients. While the narrow window of myoglobin elevation limits its usefulness, it nevertheless has important implications for treatment of patients. On the basis of our study, one could be reasonably sure that if a patient presented to the emergency room with chest pain of ≤4 h, two nonrising myoglobins over a 2-h period would exclude MI.

Conclusion: The San Diego Veterans Administration Algorithm

This study was prospectively designed for the reliable and accurate diagnosis of patients with acute MI and intermediate coronary syndromes. The use of all three markers allowed us a wide window (2 h to more than a week) in which to make the correct diagnosis. Unlike many other studies, we received direct input from the treating physicians as to the utility of having the markers available in each case as an adjunct to their clinical decision making. Their responses suggest this algorithm was of great utility in making appropriate triage decisions. Furthermore, the favorable prognosis in those patients sent home, as well as the large cost savings, suggest that this algorithm was successful in its endeavor. All three markers proved valuable in different ways. They can be run rapidly, easily, and inexpensively. The next generation of point-of-care markers will be multipanel quantitative assays. The newly approved Triage Cardiac Panel, for example (Biosite Diagnostics, San Diego, Calif.), is a portable fluorescence immunoassay which provides myoglobin, CK-MB, and CTnI results in about 15 min.[36]

Finally, this algorithm is a highly accurate and efficient way to triage patients presenting with chest pain. It holds great promise, when used in the setting of the clinical history and ECG, to offer better care to our patients at a fraction of the usual cost.

References

1. Fiebach NH, Cook EF, Lee TH, Brand DA, Rouan GW, Weisberg M, Goldman L: Outcomes in patients with myocardial infarction who are initially admitted to stepdown units: Data from the Multicenter Chest Pain Study. *Am J Med* 1990;89:15–20
2. Fruergaard P, Launbjerg J, Hesse B, Jorgensen F, Petri A, Eiken P, Aggestrup S, Elsborg L, Mellemgaard K: The diagnoses of patients admitted with acute chest pain but without myocardial infarction. *Eur Heart J* 1996;17:1028–1034
3. Goldman L, Cook EF, Johnson PA, Brand DA, Rouan GW, Lee TH: Prediction of the need for intensive care in patients who come to the emergency departments with acute chest pain. *N Engl J Med* 1996;334:1498–1504
4. Herlitz J, Hjalmarson A, Karlson BW, Nyberg G: Long-term morbidity in patients where the initial suspicion of myocardial infarction was not confirmed. *Clin Cardiol* 1988;11:209–214
5. Kannel WB, Abbott RD: Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. *N Engl J Med* 1984;311:1144–1147

6. Lee TH, Rouan GW, Weisberg MC, Brand DA, Acampora D, Stasiulewicz C, Walshon J, Terranova G, Gottlieb L, Goldstein-Wayne B, Copen D, Daley K, Brandt A, Mellors J, Jakubowski R, Cook F, Goldman L: Clinical characteristics and natural history of patients with acute myocardial infarction sent home from the emergency room. *Am J Cardiol* 1987;60:219–224
7. Karlson BW, Herlitz J, Wiklund O, Richter A, Hjalmarson A: Early prediction of acute myocardial infarction from clinical history, examination and electrocardiogram in the emergency room. *Am J Cardiol* 1991;68:171–175
8. Stark ME, Vacek JL: The initial electrocardiogram during admission for myocardial infarction. Use as a predictor of clinical course and facility utilization. *Arch Intern Med* 1987;147:843–846
9. Roberts R, Kleiman NS: Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a "new diagnostic mind-set" (see comments). *Circulation* 1994;89:872–881
10. Lee HS, Cross SJ, Garthwaite P, Dickie A, Ross I, Walton S, Jennings K: Comparison of the value of novel rapid measurement of myoglobin, creatine kinase, and creatine kinase-MB with the electrocardiogram for the diagnosis of acute myocardial infarction. *Br Heart J* 1994;71:311–315
11. Gaspoz JM, Lee TH, Weinstein MC, Cook EF, Goldman P, Komaroff AL, Goldman L: Cost-effectiveness of a new short-stay unit to "rule out" acute myocardial infarction in low risk patients. *J Am Coll Cardiol* 1994;24:1249–1259
12. Grijseels EW, Deckers JW, Hoes AW, Hartman JA, Van der Does E, Van Loenen E, Simoons ML: Pre-hospital triage of patients with suspected myocardial infarction. Evaluation of previously developed algorithms and new proposals. *Eur Heart J* 1995;16:325–332
13. Lee TH, Cook EF, Weisberg M, Sargent RK, Wilson C, Goldman L: Acute chest pain in the emergency room. Identification and examination of low-risk patients. *Arch Intern Med* 1985;145:65–69
14. Lee TH, Goldman L: Serum enzyme assays in the diagnosis of acute myocardial infarction. Recommendations based on a quantitative analysis. *Ann Intern Med* 1986;105:221–233
15. Tierney WM, Roth BJ, Psaty B, McHenry R, Fitzgerald J, Stump DL, Anderson FK, Ryder KW, McDonald CJ, Smith DM: Predictors of myocardial infarction in emergency room patients. *Crit Care Med* 1985;13:526–531
16. de Winter RJ, Koster RW, Sturk A, Sanders GT: Value of myoglobin, troponin T, and CK-MB mass in ruling out an acute myocardial infarction in the emergency room. *Circulation* 1995;92: 3401–3407
17. Hamm CW, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T: Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I (see comments). *N Engl J Med* 1997;337:1648–1653
18. Ravkilde J, Horder M, Gerhardt W, Ljungdahl L, Pettersson T, Tryding N, Moller BH, Hamfelt A, Graven T, Asberg A, Helin M, Penttila I, Thygesen K: Diagnostic performance and prognostic value of serum troponin T in suspected acute myocardial infarction. *Scand J Clin Lab Invest* 1993;53:677–685
19. Adams JED, Bodor GS, Davila-Roman VG, Delmez JA, Apple FS, Ladenson JH, Jaffe AS: Cardiac troponin I. A marker with high specificity for cardiac injury (see comments). *Circulation* 1993;88: 101–106
20. Adams JER, Schechtman KB, Landt Y, Ladenson JH, Jaffe AS: Comparable detection of acute myocardial infarction by creatine kinase MB isoenzyme and cardiac troponin I. *Clin Chem* 1994;40: 1291–1295
21. Anderson PA, Malouf NN, Oakeley AE, Pagani ED, Allen PD: Troponin T isoform expression in humans. A comparison among normal and failing adult heart, fetal heart, and adult and fetal skeletal muscle. *Circ Res* 1991;69:1226–1233
22. Bhavsar PK, Dhoot GK, Cumming DV, Butler-Browne GS, Yacoub MH, Barton PJ: Developmental expression of troponin I isoforms in fetal human heart. *FEBS Lett* 1991;292:5–8
23. Bhayana V, Gougoulias T, Cohoe S, Henderson AR: Discordance between results for serum troponin T and troponin I in renal disease (see comments). *Clin Chem* 1995;41:312–317
24. Bucher EA, Maisonpierre PC, Konieczny SF, Emerson CP Jr: Expression of the troponin complex genes: Transcriptional coactivation during myoblast differentiation and independent control in heart and skeletal muscles. *Mol Cell Biol* 1988;8:4134–4142
25. Cummins P, Young A, Auckland ML, Michie CA, Stone PC, Shepstone BJ: Comparison of serum cardiac specific troponin-I with creatine kinase, creatine kinase-MB isoenzyme, tropomyosin, myoglobin and C-reactive protein release in marathon runners: Cardiac or skeletal muscle trauma? *Eur J Clin Invest* 1987;17: 317–324
26. Li D, Keffer J, Corry K, Vazquez M, Jialal I: Nonspecific elevation of troponin T levels in patients with chronic renal failure. *Clin Biochem* 1995;28:474–477
27. Wilkinson JM, Grand RJ: Comparison of amino acid sequence of troponin I from different striated muscles. Nature 1978;271:31–35
28. Saggin L, Gorza L, Ausoni S, Schiaffino S: Troponin I switching in the developing heart. *J Biol Chem* 1989;264:16299–16302
29. Toyota N, Shimada Y: Differentiation of troponin in cardiac and skeletal muscles in chicken embryos as studied by immunofluorescence microscopy. *J Cell Biol* 1981;91:497–504
30. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E: Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes (see comments). *N Engl J Med* 1996;335:1342–1349
31. Galvani M, Ottani F, Ferrini D, Ladenson JH, Destro A, Baccos D, Rusticali F, Jaffe AS: Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina. *Circulation* 1997; 95:2053–2059
32. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, Goldmann B, Katus HA: The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;327: 146–150
33. Lindahl B, Venge P, Wallentin L: Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group (see comments). *Circulation* 1996;93:1651–1657
34. Stubbs P, Collinson P, Moseley D, Greenwood T, Noble M: Prognostic significance of admission troponin T concentrations in patients with myocardial infarction. *Circulation* 1996;94:1291–1297
35. Vetrovec GW, Cowley MJ, Overton H, Richardson DW: Intracoronary thrombus in syndromes of unstable myocardial ischemia. *Am Heart J* 1981;102:1202–1208
36. Mair J, Artner-Dworzak E, Lechleitner P, Morass B, Smidt J, Wagner I, Dienstl F, Puschendorf B: Early diagnosis of acute myocardial infarction by a newly developed rapid immunoturbidimetric assay for myoglobin. *Br Heart J* 1992;68:462–468
37. Kagen L, Scheidt S, Butt A: Serum myoglobin in myocardial infarction: The "staccato phenomenon." Is acute myocardial infarction in man an intermittent event? *Am J Med* 1977;62:86–92
38. Montague C, Kircher T: Myoglobin in the early evaluation of acute chest pain. *Am J Clin Pathol* 1995;104:472–476
39. Ohman EM, Casey C, Bengtson JR, Pryor D, Tormey W, Horgan JH: Early detection of acute myocardial infarction: Additional diagnostic information from serum concentrations of myoglobin in patients without ST elevation. *Br Heart J* 1990;63:335–338
40. Tucker JF, Collins RA, Anderson AJ, Hess M, Farley IM, Hagemann DA, Harkins HJ, Zwicke D: Value of serial myoglobin levels in the early diagnosis of patients admitted for acute myocardial infarction. *Ann Emerg Med* 1994;24:704–708
41. Gibler WB, Gibler CD, Weinshenker E, Abbottsmith C, Hedges JR, Barsan WG, Sperling M, Chen IW, Embry S, Kereiakes D: Myoglobin as an early indicator of acute myocardial infarction (see comments). *Ann Emerg Med* 1987;16:851–856