영남의대학술지 제20권 제2호
Yeungnam Univ. J. of Med.
Vol.20 No.2. 197-206. Dec., 2003.

□ 원저 □

Multimarker Approach by Troponin T, C-Reactive Protein, and CK-MB to Assessment in AMI in the Emergency Department

Sam Beom Lee, Jung Ho Kim, Byung Soo Do

Department of Emergency Medicine
College of Medicine, Yeungnam University, Daegu, Korea

Introduction

Investigation of several biochemical markers for risk stratification of patients who present with acute coronary syndromes (ACS) has been an active area of research (1). Increased concentration of one of the acute-phase proteins, C-reactive protein (CRP) appear to be predictive of higher risk for long-term cardiovascular morbidity or mortality in patients with ACS, as well as in asymptomatic patients at risk for coronary artery disease (CAD) (2). This potential predictive capacity of CRP warrants further evaluation alone and in conjunction with other established serum biochemical cardiac markers like cardiac specific troponin T (cTnT), creatine kinase-MB (CK-MB) and B-type natriuretic peptide (BNP) (3).

cTnT is a subunit of the regulatory troponin complex in cardiac myocytes and now well recognized as a sensitive and specific marker of myocardial necrosis. Elevation of serum cTnT has been shown to identify patients with ACS at increased risk for adverse clinical outcomes (2,4).

Creatine phosphokinase is well known cardiac biomarker, already has been used in patients with acute ischemic chest pain, which especially elevated its fraction of MB isoenzyme. Recently, CK-MB became to be calculated quantitatively in the clinical laboratory (4,5).

So, several new cardiac markers have emerged as strong indicators or predictors among patients with ACS and are now routinely used in the emergency department (ED). We hypothesized that simultaneous assessment of all 3 biomarkers could provide complementary information and enable emergency physicians to assess the patient more effectively among the patients with acute myocardial infarction (AMI).

책임저자 : 이삼범, 대구시 남구 대명동 317-1, 영남대학교 의과대학 응급의학교실 TEL. (053) 620-3193 FAX. (053) 628-7106
E-mail: sblee@med.yu.ac.kr

Materials and Methods

All consecutive patients with acute ischemic chest pain, whom were admitted in the ED at Yeungnam University Hospital between January 2002 and December 2002, were included in this study. All patients had ischemic chest pain, prolonged for at least 30 minutes and/or electrocardiographic (ECG) changes compatible to AMI like ST segment elevation/depression of more than 1 mV in two or more consecutive leads, abnormal Q wave, and T wave inversion and/or elevated cardiac enzymes. And also AMI was diagnosed by these results in the emergency department and lately confirmed by coronary angiogram in admission.

We measured the 3 biomarkers, i.e. troponin T, CRP, and CK-MB, initially at the same time in AMI in the emergency department and also analyzed the baseline characteristics, ECG findings, complications, locations and number of involved vessels, treatments, and outcome results, retrospectively. ECG findings compatible to AMI include ST segment elevation or depression, T inversion, and abnormal Q wave. Coronary angiogram was performed for the confirmatory diagnosis in AMI and then it defines that AMI has the infarct-related coronary artery including above 50% stenotic lesions.

Outcome results were reviewed after at least six months and included anyone of major adverse events like re-admission, re-vascularization, nonfatal myocardial infarction and cardiac death, and follow up cardiac events like anginal pain, heart failure, shock, atrioventricular block and ventricular tachycardia or fibrillation.

After then, total enrolled patients were classified by 2 study groups, i.e., group I was the patients elevated below any 1 enzyme, group II was the patients elevated 2 or 3 of all 3 enzymes and the patients whom had the left main coronary artery involved. Elevation of each 3 enzymes was designated as troponin T > 0.2 ng/mL, CRP > 0.06 mg/dL, and CK-MB > 4 ng/mL.

For the statistical analysis, the student's t-test, Chi-square test were performed to compare between the two groups using the programs of Microsoft Excel 2000 and SPSS 10.0 for Windows, and the results were designated as mean value and numbers included and percentage of each groups. A value of p less than 0.05 was considered as statistically significant in this study.

Results

1. Baseline clinical characteristics(Table 1)

Total 130 patients were enrolled in this periods and divided into 2 groups; group I, the patients elevated below any one enzyme of all 3 enzymes, was fourty (mean age 60.4), group II, the patients elevated two or three enzymes of all 3 enzymes, was ninety (mean age 62.7). The ratio of male sex was

Table 1. Baseline clinical characteristics (N=130)

Characteristics	Group I	Group II	p value
No. of patients*	40	90	0.000
Age (year)†	60.4	62.7	0.590
Male sex (%)	32 (80.0)	65 (72.2)	0.237
Risk factors (%)			
Hypertension	8 (20.0)	27 (30.0)	0.166
Diabetes mellitus	6 (15.0)	22 (24.4)	0.164
Smoking	21 (52.5)	35 (38.9)	0.105
Hypercholesterolemia	15 (37.5)	35 (38.9)	0.520
Past medical history (%)			
Angina pectoris	4 (10.0)	4 (4.4)	0.202
Myocardial infarction	8 (20.0)	9 (10.0)	0.103
PTCA*‡	8 (20.0)	2 (2.2)	0.001
CABG‡	0 (-)	1 (1.1)	0.692
Previous medication			
Aspirin	8 (20.0)	8 (8.9)	0.071
Nitrate*	10 (25.0)	8 (8.9)	0.017
Beta-blocker	9 (22.5)	11 (12.2)	0.110
Heparin	7 (17.5)	7 (7.8)	0.092
Previous admission	9 (22.5)	10 (11.1)	0.079
Treatment (%)			
Thrombolytics*	23 (57.5)	32 (35.6)	0.016
PCI‡ (balloon or stent)	21 (52.5)	48 (53.3)	0.540
Shock and/or pulmonary edema on admission (%)	4 (10.0)	16 (17.8)	0.374

* $p<0.05$: statistically significant, † mean age (year), ‡ PTCA: percutaneous transluminal coronary angioplasty, CABG: coronary artery bypass graft, PCI: percutaneous intervention.

not different as much as 80.0% in group I and 72.2% in group II.

Risk factors including hypertension, diabetes mellitus, smoking, and hypercholesterolemia were not different in each groups.

The history of previous percutaneous transluminal coronary angioplasty (PTCA) was higher in group I ($p<0.05$), and previous nitrate administration was also higher in group I ($p<0.05$), however other past histories were not different in each groups.

Thrombolytics was more administered in group I than group II ($p<0.05$).

The occurrence of complications like shock or pulmonary edema was higher in group II, but not statistically significant ($p>0.05$).

2. Electrocardiographic and coronary angiographic findings (Table 2, Table 3)

Electrocardiographic findings compatible to

Table 2. Electrocardiographic findings in the ED

	Group I (n=40)	Group II (n=90)
ST elevation (%)	35 (87.5)	75 (83.3)
ST depression/T inversion (%)	2 (5.0)	10 (11.1)
Non-diagnostic (%)	3 (7.5)	5 (5.6)
Rhythm disturbances (%)	10 (25.0)	14 (15.6)
Anterior wall involved (%)	22 (55.0)	59 (65.6)

* P>0.05 between 2 groups.

Table 3. Coronary angiographic findings

	Group I (n=40)	Group II (n=90)	p value
No. of involved vessels* (%)			0.163
3†	13 (32.5)	17 (18.9)	
2	9 (22.5)	35 (38.9)	
1	15 (37.0)	28 (31.1)	
Not performed CAG‡ (%)	4 (10.0)	10 (11.1)	

* P>0.05, † vessels include the left main coronary artery involved,
‡ CAG: coronary angiography.

AMI include ST segment elevation or depression, T inversion, and abnormal Q wave, but there are many non-diagnostic or nonspecific ECGs. As a our results, most of patients showed ST elevation, but not different in each groups (p>0.05). Rhythm disturbances on ECG were showed in some cases, but not different in each groups (p>0.05).

Coronary angiogram was confirmatory diagnostic tool of AMI in this study. It defines that AMI has the infarct-related coronary artery including above 50% stenotic lesions. The number of involved vessels did not depend on the number of elevated cardiac enzymes and not statistically significant between two groups (p>0.05).

3. Outcome results after six months follow-up periods (Table 4)

Major adverse events included the cases of re-admission, re-vascularization, nonfatal myocardial infarction, cardiac death and anyone of this events, and also follow-up cardiac events included the cases of anginal pain, heart failure, shock, AV block and malignant ventricular tachydysrhythmias like ventricular tachycardia or fibrillation.

During six month follow-up periods, we became to know that contrary to our expectations, major adverse events and follow-up cardiac events except death rate were rather higher in group I than group II in this study, but did not find statistical significances (p>0.05).

Table 4. Outcome results after six months follow-up periods

	Group I (n=40)	Group II (n=90)	p value
Major adverse events (%)			0.527
Re-admission	11 (27.5)	20 (22.2)	0.330
Re-vascularization	6 (15.0)	6 (6.7)	0.119
Nonfatal infarction	4 (10.0)	2 (2.2)	0.072
Death	1 (2.5)	5 (5.6)	0.399
Anyone	12 (30.0)	25 (27.8)	0.436
Follow-up cardiac events* (%)	21 (52.5)	35 (38.9)	0.775
No events (%)	11 (27.5)	12 (13.3)	0.421

* Follow-up cardiac events include anginal pain, heart failure, shock, atrioventricular block and malignant ventricular tachydysrhythmias like ventricular tachycardia or fibrillation.

Discussion

Several cardiac biomarkers are already well-known to clinicians for diagnostic tool of ACS and AMI in the past, which including myoglobin, CK-MB, lactate dehydrogenase (LDH), aspartate aminotransferase (AST). These enzymes are released in the setting of myocardial necrosis and were especially used as diagnostic tools for myocardial infarction (3).

However, several new cardiac biomarkers were developed like troponin T and I, and CRP, BNP (3,6). The most recently described and preferred biomarkers for myocardial damage is cardiac troponin T or I, which has nearly absolute myocardial tissue specificity, as well as high sensitivity, thereby reflecting even microscopic zones of myocardial necrosis. Because cardiac troponin values may remain elevated for 7 to 10 days or longer after myocardial necrosis, care should be exercised in attribution of elevated cardiac troponin levels to very recent clinical events. Troponin T and I are cardiac specific and more sensitive and specific than above mentioned enzymes and provide more informations about pathobiology and prognosis of ACS (3,4,6).

If cardiac troponin assays are not available, the best alternative is CK-MB, which measured by mass assay. This is less tissue-specific than cardiac troponin, but the data documenting its clinical specificity for irreversible injury are more robust. As with cardiac troponin, an increased CK-MB value (i.e., above the decision limit for MI) is defined as one that exceeds the 99th percentile of CK-MB values in a reference control group (4).

Measurement of total CK is not recommended for the routine diagnosis of acute MI, because of the wide tissue distribution of this enzyme. Nevertheless,

total CK has a long history, and some physicians may opt to continue to employ it for epidemiologic or scientific purposes. In such a setting, total CK should be combined with a more sensitive biomarker, such as cardiac troponin or CK-MB, for more accurate clinical diagnosis of acute MI. The cut-off limits for total CK should be relatively higher than those for cardiac troponin or CK-MB (at least twice the upper reference limit for CK). AST, LDH and LD isoenzymes should not be used to diagnose cardiac damage. Along with other clinical factors (e.g., residual left ventricular function), the degree of biomarker elevation is related to clinical risk. A classification for the extent of myocardial damage (microscopic, small, medium or large) should be employed, although no generally accepted grading system of infarct size exists (4).

Joint European Society of Cardiology and American College of Cardiology Committee redefines of myocardial infarction as shown table 5. This new definition also explain the importance of new biomarkers like troponin and CK-MB, however, in contrast, the original World Health Organization definition of AMI requires a combination of two of three characteristics: typical symptoms of cardiovascular disease, a characteristic rise

Table 5. Re-definition of myocardial infarction by Joint European Society of Cardiology and American College of Cardiology Committee in 2002 (4)

I. Definition of MI

A. Criteria for acute, evolving or recent MI

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI;

(1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
  (a) ischemic symptoms
  (b) development of pathologic Q waves on the ECG
  (c) ECG changes indicative of ischemia (ST segment elevation or depression) or
  (d) coronary artery intervention (e.g., coronary angioplasty)

(2) Pathologic findings of an acute MI

B. Criteria for established MI

Any one of the following criteria satisfies the diagnosis for established MI;

(1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.

(2) Pathologic findings of a healed or healing MI

and fall in cardiac enzyme levels, and a typical electrocardiographic pattern involving the development of injury current and/or Q waves (4,5,7).

CRP has been used primarily as a marker of systemic inflammation, and now that inflammation also plays a central role in atherosclerosis and its complications. Thus CRP may not only reflect the degree of underlying inflammation predisposing to atherosclerosis, but may also play a direct role in promoting plaque rupture and thrombosis (3,8-10).

And then, someone had proposed the multiaxis framework in order to more completely appreciate the etiology of unstable angina several years ago (11). Simultaneous assessment of all biomarkers is important, but not surprising to diagnose and to stratify prognostic implications and also to provide complementary clinical informations in AMI. Some authors showed the multimarker approach enabled clinicians to rapidly stratify patients across a 5-fold range of risk for adverse cardiac outcomes, so the prognostic value of multimarker approach remained highly significant (3).

We measured the 3 biomarkers, i.e. troponin T, CRP, and CK-MB, initially at the same time in AMI in the emergency department and also analyzed the baseline characteristics, clinical progressing, and outcome results, retrospectively. Outcome results were reviewed after at least six months and included anyone of major events like re-admission, re-vascularization, nonfatal MI and cardiac death, and follow up cardiac events like angina, heart failure, shock, significant dysrhythmias in our study.

During six month follow-up periods, we became to know that contrary to our expectations, major adverse events and follow-up cardiac events except death rate were rather higher in group I than group II in this study, but did not find statistical significances. We did not suggest the meaningful results of the prognostic and adverse outcome informations except some clinical informations, because of our potential limitations, which is mainly the lack of datas, loss of follow-up informations, and less adverse cardiac events during short periods in this study. So we have to collect enough datas and categorize groups more effectively, and use other cardiac biomarkers in the future and then be able to provide unique prognostic information based on further investigations.

Conclusion

We simultaneously measured the 3 biomarkers such as troponin T, C-reactive protein, and CK-MB in AMI in the emergency department and also analyzed the differences of baseline clinical characteristics, complications, and outcome results between two groups which divided according to the

numbers of elevated cardiac enzymes. In conclusion, multimarker assessment by the numbers of elevated cardiac enzymes in AMI could basically provide the some informations of patients' baseline characteristics and the thrombolytic indications, however did not yet play a role as predictors of complication, the patient's state, and outcome results including major adverse cardiac events and follow-up cardiac events in this limited study. So we have to be able to provide unique prognostic information based on further investigations.

－요 약－

서론: 급성 관동맥 증후군과 심근경색증의 진단과 예후 예측에 도움을 주는 새로운 심효소 인자가 여러 가지 발견이 되어 현재 응급의료센터에서도 기본적으로 허혈성 흉통이 있는 환자에게 많이 사용하고 있다. 특히 최근에는 troponin과 CK-MB의 유용성에 대해서 많이 언급을 하고 있다. CRP도 역시 급성 관상동맥 증후군에서 중요성이 인식되고 있다. 저자들은 세 가지 인자를 동시에 평가하여 상승되는 인자 수에 따라 그 중요성이 다를 수 있다는 가정 하에 총체적인 환자에 대한 정보를 제공할 수 있고, 응급실 근무 의사에게 급성 심근 경색증 환자를 좀 더 효율적으로 평가 할 수 있도록 하기 위하여 다표지 인자에 관한 연구를 시작하였다.

방법: 저자들은 응급의료센터에 내원한 급성 허혈성 흉통이 있는 환자 중 심효소 검사와 심전도에서 급성 심근 경색증에 합당한 소견을 보이고 이후 검사한 심혈관 조영술에서 심근경색증으로 확진된 환자를 대상으로 하였다. 내원 초기에 troponin T와 CK-MB, CRP를 동시에 측정하였고 또한 후향적으로 환자에 대한 기본적인 특징과 정보, 심전도 소견, 합병증 발생, 심혈관 조영술 소견과 경색관련 혈관 수, 치료 및 치료결과 등에 대한 자료를 정리하여 분석하여 보았다. 이때 환자는 두 군으로 나누어 분석하였는데, 1군은 증가된 효소수가 1개 이하인 경우이고, 2군은 2개 또는 3개 및 좌주관상동맥을 포함한 경우로 하였다.

결과: 전체 130명의 환자가 대상이 되었고, 1군 40례, 2군 90례로 2군이 훨씬 많았다. 과거력에서 이전에 관동맥 성형술을 시술받은 경우가 2군에서 유의 있게 많았다($p<0.05$). 이전의 약물 복용은 전체적으로 1군에서 많았으나 질산제 복용($p<0.05$)을 제외하고는 의의가 없었다. 치료는 혈전용해제 사용이 오히려 1군에서 의의있게 많았으나($p<0.05$), 합병증으로 쇽이나 폐부종을 동반한 경우가 2군에서 많았다. 하지만 본 연구에서는 6개월 추적 기간중의 사건 발생이나 합병증, 예후 결과에 대한 양군간의 차이를 발견하지 못했다.

결론: 급성 심근경색증 환자에게 다표지 인자를 이용한 접근법을 적용한 결과, 기본적으로 환자에 대한 몇 가지 정보, 즉 과거에 약물 투여 여부와 혈전용해제 사용, 혈관성형술을 시술 받은 경력과 같은 기초자료에 대한 제한적인 차이를 발견할 수 있었으나, 본 연구에서는 다표지 인자를 이용하여 추적기간중 환자의 상태와 예후를 평가하고 합병증을 조기에 예측한다든지 하는 중요한 역할을 발견하지 못하였다. 그래서 향후 이에 대한 제한점을 해결한 더 보완된 연구가 필요할 것으로 사료된다.

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