Cardiac biomarkers and their association in diagnosis and prognosis of Acute Coronary Syndrome

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ABSTRACT

Introduction

Coronary artery disease (CAD) is a modern epidemic, closely following infectious disease in the Indian subcontinent. Indians are likely to account for at least 33.5% of total coronary heart disease (CHD) related deaths by 2015 AD and 60% of all CHD related deaths in the world by 2020 AD. The most disturbing fact is its rising incidence among young people ≤35 years of age.

Materials and Methods:

In our study, a total of 91 patients of either sex aged 20 to 60 years are recruited for this study for a period of one year,of which 30 are ST elevation myocardial infarction (STEMI), 31 are non-ST elevation myocardial infarction (NSTEMI) / unstable angina and 30 are age and sex matched healthy controls. Of the total 91 subjects 30 were of STEMI (Group 1), 15 were of NSTEMI (Group 2), 16 were of unstable angina (Group 3) and 30 were controls (Group 4).

Results:

In this study , out of total 30 cases of STEMI 11 had inferior wall Myocardial Infarction (MI), 5 had Anteroseptal wall MI, 11 had Anterior wall MI, 2 had Anterolateral wall MI and 1 had Apical wall MI. Of the total 59 patients of CAD (STEMI, NSTEMI, and UA) various biomarkers determination was done.

Conclusion:

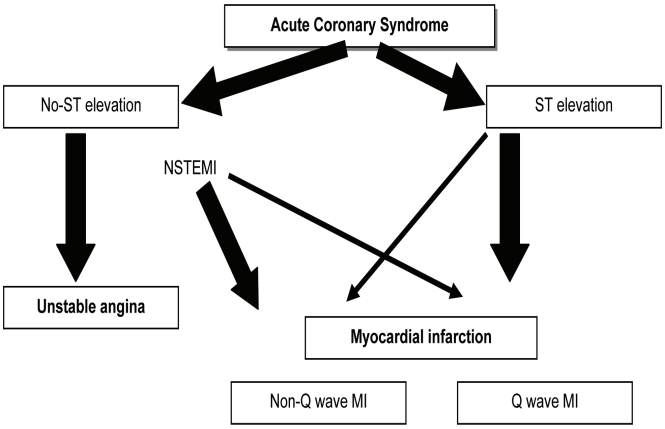
In this present study of 91 subjects we concluded that in patients of Acute Coronary Syndrome (ACS), there was no significant association between Myeloperoxidase (MPO), High sensitive C-Reactive Protein (hs CRP) & CK-MB when taken together to predict complications. Individually MPO is an early marker of plaque, destabilization in the overall spectrum of atherogenesis, it was postulated that it will be extremely useful in risk stratification of patients with chest pain, thereby preventing complications with help of timely intervention.

Keywords: Acute Coronary Syndrome (ACS), High sensitive C-Reactive Protein (hs-CRP), Myeloperoxidase (MPO),Atherogenesis, Myocardial Infarction.

INTRODUCTION

Coronary artery disease (CAD) is a modern epidemic, closely following infectious disease in the Indian subcontinent. Indians are likely to account for at least 33.5% of total coronary heart disease (CHD) related deaths by 2015 AD[1] and 60% of all CHD related deaths in the world by 2020 AD[2]. The most disturbing fact is its rising incidence among young people ≤35 years of age, varying between 4-10%[3]. CHD among Indians has been found to be more severe, manifesting at a younger age and following a malignant course[4,5].

Acute coronary syndrome (ACS) represent a spectrum of clinical presentation of acute myocardial ischemia, referred to as unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI)[6]. The most common cause of acute coronary syndrome is erosion of an atherosclerotic plaque, resulting in platelet aggregation and thrombus formation. However, any sudden imbalance between myocardial oxygen supply and demand can result in acute ischemia. In unstable angina and non-STEMI, the thrombus is rich in platelets and is usually non-occlusive. In STEMI the thrombus is composed of platelets, fibrin, RBC and occlusion is total or near total. In patients with ACS the traditional markers being used are CPK and Trop-T & I. Its level in blood as low as 0.08 ng/ml can be easily detected by conventional quantative assay. Elevated level of Trop T, I, CK-MB, CRP each is associated with higher rates of death and recurrent ischemic events. Several new cardiac biomarkers have emerged as strong predictors of risk among patients presenting with ACS and work is going on to make it routinely available to clinician.



The present study was done to know the various biomarkers of ACS and their correlation, if any between serum myeloperoxidase, hs-CRP and CPK-MB in diagnosis and prognosis of acute coronary syndrome (STEMI and NSTEMI/ unstable angina).

MATERIALS AND METHODS

A prospective study was done for a period of one year duration on 91 patients of either sex aged 20 to 60 years are recruited , of which 30 are STEMI, 31 are NSTEMI / unstable angina and 30 are age and sex matched healthy controls. Patients with following complaints of maximum 24 hours duration are registered in the emergency department and are included in the study (ACC/AHA Guidelines, 2002).Chief Complaints considered were 1) Chest pain or severe epigastric pain, non-traumatic in origin with components typical of myocardial ischemia . 2) Central or substernal compression or crushing chest pain, pressure, tightness, heaviness, cramping, burning achy sensation. 3) Unexplained indigestion, belching, epigastric pain. 4) Radiating pain in neck, jaw, shoulders, back, one or both arms. 5) Associated dyspnoea. 6) Associated nausea / vomiting. 7) Associated diaphoresis. Special Considerations were noted in Women, who may present more frequently than men with atypical chest pain and symptoms.Patients with angina pectoris (or equivalent type of ischemic discomfort) with at least one of three features (reporting within 12 hours):

a) Occurs at rest or with minimal exertion usually last for more than 20 minutes (if not interrupted by NTG)

b) Severe and described as a new onset pain (i.e. within 1 month)

c) Crescendo pattern

Patients are considered to have unstable angina or NSTEMI on the basis of serial electrocardiogram and determination of CK-MB. If markers are negative, with a reference limit of the 99th percentile of the normal population, the patient with ACS may be considered to have experienced unstable angina. In the latter condition, ECG, ST segment or T wave changes may be persistent, whereas they may or may not occur in patients with unstable angina and if they do, they are usually transient. Markers of myocardial injury may be detected in the blood stream hours after the onset of ischemic chest pain, which allows the differentiation between unstable angina (i.e. no markers in circulation, usually transient, if any, ECG changes of ischemia) and NSTEMI (i.e. elevated biochemical markers).

The diagnosis of acute MI is based on the presence of at least two of the following criteria:

a)Typical ischemic chest pain lasting for more than 30 minutes for the first time with no such history of similar episode.b)New appearance of abnormal Q waves with evolutionary ST and T wave changes in serial ECG tracings. and c)Enzymatic evidence i.e: a rise in CK-MB to at least twice the upper limit of normal values.

RESULTS

In the present study, 91 subjects were recruited from medical emergency department. Of the total 91 subjects 30 were of STEMI (Group 1), 15 were of NSTEMI (Group 2), 16 were of unstable angina (Group 3) and 30 were controls (Group 4).

In group 1 out of 30 cases 26 were males and 4 were females. In Group 2 out of 15 cases 13 were males and 2 were females, in Group 3 out of 16, 13 were males and 3 females, in group 4 of total 30 controls 25 were males and 5 females (p=0.976).

Mean age in Group 1 was 52.73±10.22 years, mean age in Group 2 was 55.80±11.40 years, mean age in Group 3 is 59.40±8.55 years, and in Group 4 mean age was 56.60±13.24 years (p=0.265).

In this study , out of total 30 cases of STEMI 11 had inferior wall Myocardial Infarction (MI), 5 had Anteroseptal wall MI, 11 had Anterior wall MI, 2 had Anterolateral wall MI and 1 had Apical wall MI.

Of 31 patients with NSTEMI / UA, 26 patients had abnormal ECG, and 5 patients had no ECG changes. Of 26 patients with abnormal ECG, 6 patients had fresh changes; rest of the 20 patients had old abnormal ECG changes. All the 30 cases of STEMI were thromoblysed, as there were no contraindications for its use. In NSTEMI / UA, STK was not given and all the three groups were given treatment as per ACC / AHA 2002 guidelines.

Table 1: Levels of hs-CRP, CKNAC, CKMB, HDL-C, LDL-C and TG in study groups

Variables	Group 1	Group 2	Group 3	Group 4	Significance (one way ANOVA)
hs-CRP (mg/dl)	1.01±0.37	0.95±0.36	1.07±0.38	0.64±0.35#	<0.001*
CKNAC (IU/l)	749.65±791.02	745±495.56	68.88±24.29	87.80±28.19	<0.001*
CKMB (IU/l)	62.96±63.81	105.13±69.70	17.31±3.61	17.47±9.16	<0.001*
HDL-C (mg/dl)	34.27±6.01	40.47±16.91	41.00±8.23	43.17±5.09	0.002*
LDL-C (mg/dl)	151.0±36.74	193.73±90.95	146.87±43.39	140.83±22.13	0.006*
TG (mg/dl)	132.83±51.11	163.00±97.53	157.50±67.94	97.67±19.19	0.001*

Table 2: Correlation between MPO, hs-CRP and CPKMB in prognosis of ACS

Dependent factor	Independent factor	r-value	Significant factor	p-value (t-test)
Complications	MPO, hs-CRP, CKMB	0.508	MPO	<0.001*

In our study hs CRP levels, though moderately elevated as compared to controls, showed no association with clinical complications arising within 7 days. Similarly CK-MB levels was not associated with complications.

Correlation test showed that:

1) MPO, hs-CRP and CK-MB are not related to each other
2) Hs-CRP and CPK MB independently have no correlation with prognosis

There were two deaths in our study, one was in group 1 and one in group 3, and both deaths were due to ventricular fibrillation and shock. Both patients died within 24 hours.

One patient in group 3 (UA) developed atrial fibrillation on second day which was transient and responded to DC cardioversion.4 patients of group 1 and one patient of group 2 developed recurrent post MI angina which was not responding to nitrate and other conventional therapy. They were later referred to higher centers for angiography.One patient in group 1 developed shock on second day. In this patient angiography was done in higher center, which was showing triple vessel disease. Later bypass grafting was done and patients survived. 3 patients in group 1 developed bradycardia and hypotension on day one. Of the 3, one patient was of inferior wall MI group and he responded to IV fluids and atropine. In rest of the two patients bradycardia and hypotension was transient. Similarly two patients in group 2 and one in group 3 developed hypotension on first day and they responded to IV fluids. One patient of group 3 (UA) developed frank STEMI after two days.

DISCUSSION

C-reactive protein (CRP) was identified by Tilet and Francis (1990) in the plasma of patients with pneumonia, and was named for its ability to bind and precipitate the C-polysaccharide of pneumonococcus[7,8]. It is an alpha globulin with a molecular mass of identical subunits, which are noncovalently assembled as a cyclic pentamer[9]. CRP is syntheized in the liver and is normally present as a trace constituent of serum or plasma at levels of less than 0.3 mg/dl[8,10,11,12].

CRP is one of the acute-phase proteins, the serum or plasma levels of which rise during general, non-specific response to a wide variety of diseases. This includes infections by gram-positive and gram-negative organisms, acute phase of rheumatoid arthritis, abdominal abscesses, and inflammation of the bile duct[9]. CRP may also be found in patients with Guillain-Barre syndrome and multiple sclerosis, certain viral infections, tuberculosis, acute infectious hepatitis, many other necrotic inflammatory diseases, burned patients and after surgical trauma[9,13,14].

Although the detection of elevated levels of CRP in the serum is not specific for any particular disease, it is a useful indicator of inflammatory processes[15]. CRP levels rise in serum or plasma within 24 to 48 hours following acute tissue damage, reach a peak during the acute stage and decrease with the resolution of inflammation or trauma[7,16,17]. Levels of C-reactive protein are elevated in patients with unstable angina, a condition that is probably dependent on coronary thrombosis of atherosclerotic plaques, but not in those with variant angina caused by vasospasm. Therefore, elevated C-reactive protein levels in patients with acute coronary syndromes likely reflect inflammation in the coronary artery rather than in the ischemic myocardium. In acute coronary syndrome CRP predicts recurrent MI independently of troponin, which suggests it is not merely a marker for the extent of myocardial damage. Recent data also suggest that hsCRP may be a marker for risk of restenosis.

Elevated hs-CRP levels also seem to predict prognosis and recurrent events in patients with stroke and peripheral arterial disease. However, CRP levels are not very sensitive in MI and ACS as several factors have been identified as being associated with increased to decreased levels of CRP.

Table 3: Factors affecting CRP levels in blood

Increased levels	Decreased levels
• Elevated BMI • Smoking Elevated BP • Metabolic syndrome / DM • Low HDL / elevated triglycerides • Estrogen, progesterone and other hormone use • Chronic infection (gingivitis & bronchitis) • Chronic inflammatory disease (rheumatoid arthritis)	• Moderate alcohol consumption • Increased activity and exercise • Weight loss • Medication • Statins • Fibrates • Niacin

In patients presenting with stable or unstable angina, CRP has additive and independent predictive value to a troponin assay for both short- and long-term CV events[18,19,20]. CRP predictive value is additive to the cholesterol-to-HDL ratio and total cholesterol levels[21]. In the Physician's Health Study[21], the multivariate adjusted relative risk for future MI was 2.3 for elevation of cholesterol and 1.5 for elevation of CRP, but 5.0 for elevation of both cholesterol and CRP.

CRP retains its predictive value even when adjusted for the extent of atherosclerosis by coronary angiography[22]. After angiography, CRP may be especially useful in interpreting the significance of a "normal" coronary angiogram or minimal CAD in a patient with angina, as a highly elevated CRP would suggest that the absolute risk for death or MI may be as high as that of some patients with severe CAD. Although some studies have defined elevated CRP as low as 0.3 mg/dL in patients with CAD[18,23] another study showed no significant difference in patients with low CRP (<0.2 mg/dL) and moderate CRP elevations (0.2-1.0 mg/dL). Thus, the most common definition of 1.0 mg/dL, used in patients with CAD, appears to be a reasonable cut-point to separate risk.

CONCLUSION

In this present study of 91 subjects we concluded that in patients of ACS, there was no significant association between MPO, hs CRP & CK-MB when taken together to predict complications. Individually MPO is an early marker of plaque, destabilization in the overall spectrum of atherogenesis, it was postulated that it will be extremely useful in risk stratification of patients with chest pain, thereby preventing complications with help of timely intervention.

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