



Original Article:

Determination and Correlation of Anticardiolipin Antibody with High Sensitivity C- reactive Proteins and its Role in Predicting Short Term Outcome in Patients with Acute Coronary Syndrome

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Abstract:

Anticardiolipin antibody (aCL) is considered to be an independent risk factor while high sensitivity C reactive protein (hsCRP) is an established marker for coronary artery disease. This study was conducted to determine levels of aCL antibodies and hsCRP, their correlation and role in predicting recurrence of events in patients presenting with Acute Coronary Syndrome (ACS). Sixty patients admitted with Acute Coronary Syndrome were followed up for 7 days or until discharge. Patients were classified into two groups as those having experienced an ischemic event needing intervention within 7 days (Group I) and other having an event free recovery (Group II). aCL antibody and hsCRP levels were estimated and compared in these two groups. Twenty age and sex matched disease free persons served as controls. The levels of aCL were significantly higher in patients with ACS as compared to the controls ($p=0.020$). However the levels of aCL in Group I (13.39 ± 9.46 GPL-U/ml) and Group II (13.51 ± 9.93 GPL-U/ml) were not significantly different ($p=0.838$). The mean hsCRP levels were higher in cases with an event (23.30 ± 10.68 mg/dl) than in cases without an event (20.60 ± 11.45 mg/dl) though it was not significant statistically ($p=0.389$). aCL and CRP were not found to be significantly correlated in causing the recurrence of events ($p=0.178$). Therefore anticardiolipin antibody is an independent risk factor which could be implicated in the pathogenesis of ACS. However it is not significantly associated with recurrence of short-term events in patients with ACS. Also, aCL antibody does not have significant correlation with hsCRP in causing recurrence of events in the patients of acute coronary syndrome.

Key Words: Acute coronary syndrome; Anticardiolipin antibodies; High sensitivity C-reactive protein; Myocardial infarction; Composite end point

Introduction:

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality worldwide. Acute coronary syndrome (ACS) is a constellation of clinical symptoms that encompasses acute myocardial infarction (ST-segment elevation & non ST elevation AMI) and unstable angina (UA). In addition to the well established risk factors like elevated low density lipoproteins (LDL), decreased high density lipoprotein (HDL), sedentary lifestyle, obesity, tobacco, hypertension and diabetes, newer risk factors like elevated high-sensitivity C-reactive protein (hsCRP), antiphospholipid antibodies, hyperhomocysteinemia, elevated fibrinogen, factor VII, plasminogen activator inhibitor-1 (PAI-1) and platelet hyperreactivity are also being evaluated. (1)

Anticardiolipin antibodies (aCL) belong to the group of anti-phospholipid antibodies. They have been found to be associated with increased risk of development of venous and arterial thrombosis and myocardial infarction.(2) An association of anticardiolipin antibodies with coronary artery disease (CAD) has been shown in some (3,4) but not all (5,6) studies. These antibodies have also been shown to possess proinflammatory(7) and procoagulant (8) properties. High levels of IgG aCL (GPL>40) have been strongly associated with both arterial as well as venous thrombosis.(9) Independent correlation of aCL with myocardial infarction and cerebral vascular accidents has been reported.(10) However, there is a paucity of data regarding the association of aCL with outcome in patients with ACS. C-reactive protein (CRP), an inflammatory marker, is a novel and evolving biomarker for the extent and severity of atherosclerotic lesion and provides a useful predictive indicator for subsequent cardiovascular events.(11) CRP is also considered an effective marker to track progress of cardiovascular disease and response to treatment.(12) Blake and

Ridker (13) have also shown that elevated hsCRP can predict risk of cardiovascular events in patients with ACS. Therefore, the present study was planned to investigate the association of aCL and hs CRP levels with 7-day outcome in patients with Acute Coronary Syndrome.

Materials and Methods:

The study was conducted by the Department of Physiology in collaboration with the Department of Internal Medicine and Department of Microbiology, Government Medical College and Hospital, Chandigarh, India. Prior approval from the institutional ethics committee and an informed written consent was obtained from each patient included in the study.

Sixty patients out of 72 patients admitted in the Medical Emergency with a diagnosis of ACS based on the guidelines of American Heart Association task force/ American College of Cardiology (14) were enrolled in the study. Patients of either sex with age more than 20 years and confirmed diagnosis of ACS (based on clinical presentation, ECG findings and/or biochemical markers), presenting within 72 hrs after onset of symptoms were included in study.

Patients not included in study were those presenting with heart failure (overt or ejection fraction <35% on echocardiogram), diastolic BP >110 mmHg or systolic BP <90 mmHg, patients with pacemakers, renal or hepatic dysfunction, presence of infectious and/or autoimmune disease, presence of active *Treponema pallidum* infection or history of intake of drugs likely to alter aCL levels (phenothiazines, hydralazine, procainamide, prednisone). Patients with past history of an episode of thromboembolic event in the past 3 months or history of hemorrhagic stroke, MI in the past 3 months or treatment with anticoagulant drugs like unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in the past 1 month were also excluded from study.

Patients were followed up for 7 days or until discharge and the endpoint were a composite of cardiac death, recurrent angina and AMI needing intervention within 7 days. Patients were classified into two groups as those who attained composite endpoint during recovery (Group I) and other having an event free recovery (Group II). Anticardiolipin antibody (aCL) and high sensitivity C-reactive protein (hsCRP) levels were estimated and compared in these two groups. Twenty healthy age and sex-matched persons served as controls in whom aCL levels were measured.

aCL antibody levels were estimated with standardized ELISA (Enzyme Linked Immunosorbent Assay) (Lab System Company) by using Orgentee Diagnostika GmbH for IgG antibodies. hsCRP levels were estimated using ELISA kit (Calbiotech Inc.).

Statistical Analysis

All data were expressed as Mean ± SD. Unpaired t-test was applied to compare the levels of aCL antibody in patients with ACS and controls and Levels of aCL and hsCRP between Groups I and II. Correlation between aCL and hs-CRP was determined by Pearson's Correlation Coefficient. Logistic regression was applied to correlate the levels of aCL and hs-CRP with short-term outcome in patients with ACS. p- value < 0.05 was considered statistically significant.

Results:

Seventy two patients were evaluated for enrollment in the study out of which 12 did not meet the inclusion/exclusion criteria and were excluded. During the short-term follow-up period of 7 days, 19 patients (Group I) experienced an ischemic event and 41 patients (Group II) remained event free. The levels of anti-cardiolipin antibody were significantly higher in patients with ACS as compared to the controls (p = 0.020) (Fig. 1). However the levels of aCL in Group I (13.39 ± 9.46 GPL-U/ml) and Group II (13.51 ± 9.93 GPL-U/ml) were not significantly different (p = 0.838) (Fig. 2).

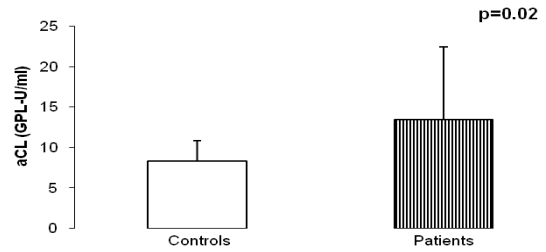


Fig.1: Comparison of Anticardiolipin antibody (aCL) levels in patients and controls

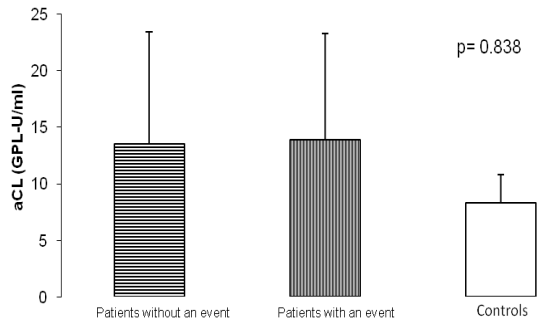


Fig.2: Anticardiolipin antibody levels among patients with and without an event

The mean hsCRP levels were higher in cases with an event (23.30± 10.68 mg/dl) than in cases without an event (20.60±11.45mg/dl) but this was not significant statistically (p = 0.389) (Fig. 3). No significant correlation was found between the levels of aCL and CRP (p = 0.178). Logistic regression analysis showed that there was no statistically significant correlation between the level of anticardiolipin antibody or hsCRP and the recurrence of ischemic events (p = 0.964 and p=0.380 respectively).

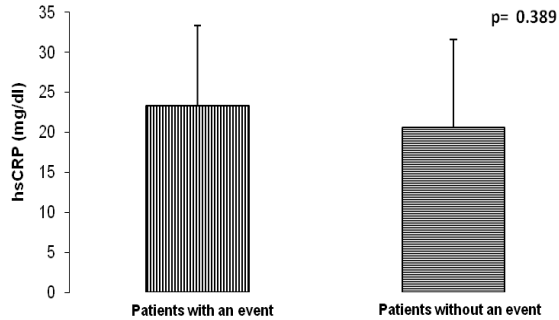


Fig.3: Levels of high sensitivity C- reactive proteins (hsCRP) among patients with and without an event

$r = 0.176$
 $p = 0.178$

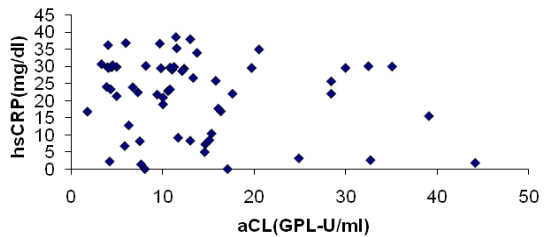


Fig.4: Scatter plot showing correlation between aCL and hsCRP

Discussion:

In the present study, we have demonstrated that levels of aCL in patients with Acute Coronary Syndrome were significantly higher as compared to healthy controls. An association of aCL antibodies with stable Coronary Artery Disease has been shown in several studies. In one study, IgG and IgM aCL levels were found to be higher in patients with ischemic heart disease than healthy controls.(15) Few other studies have also shown a positive association of the IgG aCL with coronary artery disease. (4,16) Our previous study on patients of CAD with stent also supports this view.(17)

It has been observed that the presence of aCL antibodies precede the development of first MI and the aCL titre remained stable for up to 3 months after MI which indicate that the aCL antibodies are not generated by tissue necrosis but rather they participate in the pathogenesis of MI.(18) The proinflammatory and procoagulant properties of aCL have earlier been well established and now there appears to be sufficient clinical evidence to support their role in pathogenesis of CAD. (3,4,16)

However, results of our prospective evaluation failed to demonstrate a predictive role of aCL antibodies in the development of subsequent coronary events in ACS patients. In patients with ACS, plaque disruption and plaque erosion are considered as the underlying cause for the development of ischemic cardiac event.(19) The role of aCL in the development of unstable plaque is not well documented. In a study of 74 male patients with acute and chronic coronary artery disease who underwent coronary angiography, 16 were diagnosed with CAD, 34 had coronary stenosis with prior MI, 14 surviving acute MI and 10 patients revealing no significant coronary narrowing. No significant difference in the level of aCL was found in these four groups.(20) In another study in 80 patients with ACS, no significant association was found between reinfarction and aCL, however, a statistically significant association was observed between aCL and restenosis.(21)

In our study the mean level of aCL were comparatively lower than the reported studies showing association of high titre of aCL with recurrence of coronary events.(21) This could be due to somewhat different patient population. Moreover the recurrence of coronary events can be attributed to many other procoagulant factors like homocysteine, fibrinogen, factor VII, plasminogen activator Inhibitor-I, and platelet hyperreactivity.(1) Some other factors like D-dimer, low apoA-I and high apoB have also recently been advocated in the recurrence of coronary events in the absence of identified risk factors and with standard lipid parameters.(22)

The role of CRP in development of atherothrombotic vascular events is well established.(23) There are data that suggest a direct effect of CRP on endothelial cells, including the upregulation of vascular adhesion molecule, stimulation of proinflammatory mediators and the impairment of vascular NO dependent vasodilation.(24) As per recommendation of American Heart Association, the hsCRP levels of 1 mg/L constitute low risk, 1-3 mg/L as average risk and >3 mg/L as high risk group for assessment of cardiovascular risk.(25) On the same lines, Ridker has also shown association of increased level of hsCRP (>3mg/L) with higher cardiovascular risk.(26) The result of our study showed mean levels of 2.43mg/L in patients with recurrence of event and 2.02 mg/L in those without events. Though the difference in the levels of hsCRP among two groups was not statistically significant but higher levels in patients with recurrence puts them in average risk group. This substantiates role of hSCRp in acute coronary syndrome. However less values of hSCRp obtained in our study could be attributed to small sample size.

In conclusion, anticardiolipin antibodies could be implicated in the pathogenesis of Acute coronary syndrome but are not significantly associated with recurrence of short-term events in patients with ACS. In addition aCL does not seem to have signi-

ficant correlation with hsCRP in determining short term outcome in patients with acute coronary syndrome.

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