# ACTIVATED PROTEIN C RESISTANCE IN MYOCARDIAL INFARCTION

(Received 3 October, 1996)

**B. S. Cebeci, M.D.*** / B. Y. Cingözbay, M.D.***** / A. Öztürk, M.D.******
**M. Coşkun, M.D.* / N. Üskent, M.D.****

* *Professor, Department of Cardiology, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, İstanbul, Turkey.*
** *Professor, Department of Hematology, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, İstanbul, Turkey.*
*** *Associate Professor, Department of Cardiology, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, İstanbul, Turkey.*
**** *Assistant Professor, Department of Hematology, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, İstanbul, Turkey.*
***** *Resident, Department of Cardiology, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, İstanbul, Turkey.*

## ABSTRACT

**Objective:** The aim of this study is to investigate the role of activated protein C resistance (APCR) as a contributing factor in the pathogenesis of myocardial infarction.

**Methods:** Forty patients with acute myocardial infarction (AMI) who have been followed by the Cardiology Department of Gülhane Military Medical Academy Haydarpaşa Training Hospital and 30 healthy individuals were included in this study. Patient group consisted of 27 males and 13 females, (mean age 47.9 (23-81) control group composed of 16 males and 14 females, (mean age 46.1 (24-63) Whole blood count and routine biochemical work up were performed and activated protein C resistance (APCR) ratio, and activated partial thromboplastin time were evaluated in both groups.

**Results:** Two patients and three controls had APCR. Mean APCR ratio was 2.56 ± 0.56 in the control and 2.74 ± 0.67 in the patient group and there was no statistically significant difference between the two groups ($p>0.05$).

**Conclusion:** Although APCR is a major risk factor for venous thrombosis, its role in the pathogenesis of AMI is not clearly understood.

**Key Words:** Activated protein C resistance, Acute myocardial infarction

## INTRODUCTION

Occlusive thrombus, which develops secondary to injury on atherosclerotic plaque and which causes variable degrees of luminal stenosis, is the essential mechanism in the pathogenesis of acute myocardial infarction (1). Local events on vascular wall and balance of procoagulant and anticoagulant factors determine the amount and stability of thrombus (2-4). Protein C resistance which develops due to a point mutation in factor V gene in more than 90% of the cases has been found 5-10 times more common when compared to the deficiency of the protein C, protein S and antithrombin III in patients with venous thrombosis (5,6). Protein C resistance has been detected in 30% of patients examined for venous thromboembolism by Dahlback et al. and 52-64% of patients with juvenile or recurrent venous thrombosis by Griffin (6,7). Protein C resistance was found in 5% of normal healthy population (7). Leiden mutation causing protein C resistance has been reported with an incidence of 1.7% in English population and 1,7-2% in Dutch population (8).

Although the role of protein C resistance in thrombophilic diseases is well known, there are few studies investigating its role in the pathogenesis of acute myocardial infarction. In this study we investigated the role of active protein C resistance as a risk factor in acute myocardial infarction.

## MATERIAL AND METHODS

The study has been performed at the Cardiology and Hematology departments of Gülhane Military Medical Academy Haydarpaşa Training Hospital. Forty patients (13 females and 27 males) with acute myocardial infarction (AMI), (mean age 47.9 (23-81) were studied. Thirty healthy individuals (16 male, 14 female) aged between 24-63 (mean 46,1) were included in the study as the control group. Diagnosis of AMI was confirmed according to the World Health Organization (WHO) criteria (9). Characteristics of the patient and the control groups are shown in Table-I. Patients with a history of venous thrombosis, pregnancy, chronic hepatic or renal disease and patients who are on medication that affect hemostatic parameters and those with active infection were excluded from the study.

Following a fasting period of 12 hours, venous blood samples of patients and controls were drawn between 8:30 to 9 a.m., whole blood count, fasting blood glucose level, BUN, creatinine, uric acid, AST, ALT, alkaline phosphatase, total cholesterol, trigliceride, fibrinogen, prothrombin time, activated partial thromboplastin time (aPTT) and activated protein C resistance (APCR) were measured.

Activated protein C resistance measurement: Coatest APC resistance (choromogenix AB. Taljegardsgaten 3, S-431 53 Möndal, Sweden 822643-63/8 serial) kit was used for APCR measurement (10). Principle of the study: 100 µl aPTT solution and 100 µl patient plasma were incubated for 5 minutes. Coagulation started with the addition of 100µ CaCl2 with and without APC on Behring coagulameter and aPTT was recorded. Time period with APC and without APC were used to get a ratio (Rs). This ratio was (Rs±SD) 2.56 ± 0.56 in the control group and value of ratio <2 was accepted as APCR.

Statistical analysis: Student's t test was used to compare mean values of the patient and the control groups.

## RESULTS

APCR levels of both groups were shown in Table-I. In the patient group two patients were found to have APCR and APCR ratios were 1.38, 1.81, respectively. Activated protein C resistance was detected in 3 controls, whose APCR ratios were less than 2. Mean APCR ratio was 2.74 ± 0.67 in the patient and 2.56 ± 0.56 in the control group. There was no statistically significant difference between the two groups ($p>0.05$).

## DISCUSSION

Activated protein C resistance was found by Dahlback et al in 1993 (11). The etiologic factor was detectable in only 15-20% of patients with primary venous thrombosis prior to finding of APCR and afterwards, this ratio increased to 50% (5-7,12,13). It is important that APCR could be detected in a significant number of patients with secondary venous thrombosis (5,14). Constructive thrombus which would spoil the resting demand-supply balance or an occlusive thrombus which develops secondary to injury on an atherosclerotic plaque is the main pathogenesis in AMI and unstable angina pectoris (1-4). That is why participants of hemostatic system are important in the pathogenesis of AMI. The balance between procoagulant and anticoagulant system is the main factor which determines the clinical outcome. There is a recent interest in the effects of APCR in arterial system, especially in its role in the thrombus development in the coronary arteries after obvious description of the role of APCR in the development of venous thrombosis. Two young subjects who had homozygote APCR and myocardial infarction were presented by Holm et al in 1994. They performed an epidemiologic case controlled study in order to determine whether the f-V mutation was a risk factor for myocardial infarction (15). Samani et al searched for an arginine-glysine mutation for APCR by performing f-V DNA analysis in 60 patients who were followed-up due to AMI in coronary intensive care unit between 1993-1994 and they showed that prevalance was not increased in patients with AMI (16). In this study we did not find statistically significant difference in terms of APCR between the control and the patient groups. Although APCR is a major risk factor for the development of venous thrombosis, its role in the pathogenesis of AMI is not clear.

**Table I.** Characteristics and mean value of APCR ratio of patient and control groups

| | Patients | Controls |
|---|---|---|
| Number | 40 | 30 |
| Sex (M/F) | 27/13 | 16/14 |
| Mean age | 47.9 | 46.1 |
| Mean APCR ratio | 2.74±0.67 | 2.56±0.56 |
| APCR | 2 | 3 |

## REFERENCES


1. Davides MJ, Thomas A. Thrombosis and acute coronary artery lesions in sudden ischemic death. N Eng J Med 1984;310:1137-1140.
2. Fuster V, Balmidon L, Cohen M, et al.Insights into the pathogenesis of acute ischemic syndromes. Circulation 1988;77:1213-1220.
3. Gotah K, Minamino T, Katoh O, et al. The role of intracoronary thrombus in unstable angina angiographic assessment and thrombolytic therapy during ongoing anginal attacks. Circulation 1988;77:526-534.
4. Zalewski A, Shi V, Nardone D, et al. Evidence for reduced fibrinolytic activity in unstable angina at rest. Circulation 1991;83:1685-1691.
5. Bauer K. Hypercoagulability a new cofactor in the protein C anticoagulant pathway. N Eng J Med. 1994;330:566-567.
6. Svensson PJ, Dahlback B. Resistance to activated protein C as a basis venous thrombosis. N Eng J Med 1994;330:517-522.
7. Griffin JH, Evatt B, Wideman C, et al. Anticoagulant protein C pathway definitive in majority of thrombophilic patients. Blood 1993;82:1989-1993.
8. Nicholas J, Dalay ME, Hampton KK, et al. High prevalance of a mutation in the factor V gene with in UK population relationship to activated protein C resistance and familial thrombosis. Br J Heamotol 1994;88:219-222.
9. Tunstall-Pedeo H, Kuulasmaa K, Amouyel P, et al (WHO MONICA Project). Myocardial infarction and coronary deaths in the World Health Organization. MONICA Project. Circulation 1994;583-612.
10. Rosen S, Johansson K, Lilnderg K, et al. Multicenter evaluation of a kit for activated protein C resistance on various coagulation instrument using plasmas from healthy individuals. The APC Resistance Study group. Thromb Haemostasis 1994;72:255-260.
11. Dahlback B, Carlson M, Svensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C prediction of a cofactor to activated protein C. Proc Nat Aca Sci, USA 1993;90:1004-1008.
12. Koster T, Rosendaal FR, de Ronde A, et al. Venous thrombosis due to poor anticoagulant response to activated protein C. Leiden Thrombophilia Study. Lancet 1993;342:1503-1506.
13. Sun X, Evat B, Griffin HJ, et al. Blood coagulation factor V an abnormality associated with resistance to activated protein C in venous thrombophilia. Blood 1994;83:3120-3125.
14. Matsude J, Gohchi K, Isukamoto M. Resistance to activated protein C in systemic lupus erythematosus patients with antiphospholipid antibodies (letter). Eur J Haematol 1994;53(3):188-189.
15. Holm J, Zöller B, Svensson PJ, et al. Myocardal infarction associated with homozygous resistance to activated protein C (letter). Lancet 1994;344:952-953.
16. Samani NJ, Lodwick D, Martin D, et al. Resistance to activated protein C and risk of premature myocardial infarction (letter). Lancet 1994;344:1709-1710.