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INCREASED PROTEIN C AND FIBRINOPEPTIDE A CONCENTRATION IN PATIENTS WITH ANGINA G.F.Gensini,C.Rostagno,R.Abbate,S.Favilla, P.M.Mannucci (1) and G.G.Neri Serneri Clinica Medica I University of Florence and (1) A.Bianchi Bonomi ,Haemophilia and Thrombosis Centre and Institute of Internal Medicine ,University of Milan, Italy

The present study has been designed to investigate protein C (as protein C antigen) and fibrinopeptide A (FpA) concentration in plasma from patients suffering from ischemic heart disease in relation to the frequency of ischemic attacks , in order to estabilish if modifications in protein C levels could contribute to blood clotting activation. Protein C and FpA levels in plasma were measured in 30 controls and in two groups of patients with angina. The first group was formed by 27 patients suffering from spontaneous ischemic attacks (active angina). The second one was formed by patients who previuosly suffered from angina, but were free from myocardial ischemic attacks for at least one month (inactive angina). Protein C (measured by electroimmunoassay) was higher in the whole group of patients than in controls (122.1$\pm$ 20.2 vs. 96.5$\pm$14 $p<0.001$). Moreover significantly higher values were found in patients with active angina in comparison to patients with inactive disease (132.5$\pm$15.7 vs 112.3$\pm$17.6,$p< 0.001$).Similarly patients suffering from active angina had FpA levels higher than patients with inactive angina (8.6$\pm$9.4 vs 5.5$\pm$7.0,$p<0.01$) or controls (1.6$\pm$1.0,$p<0.001$). A high concordance (76%) between protein C and FpA levels exceeding normal limits was found in patients with active angina ($p < 0.05$) but no statistically significant correlation existed between protein C and FpA levels and between protein C or FpA levels and coronary pathoanatomy. These results confirm a significant involvement of blood clotting system in ischemic heart disease and especially in active angina.

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BIOCHEMICAL EVIDENCE OF THROMBUS FORMATION IN PATIENTS WITH PERSISTENT UNSTABLE ANGINA

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Thromboxane released from activated platelets and prostacyclin of the vessel wall may act as potent antagonistic modulators of platelet aggregability and coronary vascular tone. Therefore we studied urinary excretion of their major metabolites, 2,3-dinor-thromboxane B_2 (TX-M) and 2,3-dinor-6-keto prostaglandin $F_{1\alpha}$ (PGI-M), in 16 patients presenting with prolonged angina at rest. The 10 patients who did not improve under vigorous antianginal treatment within 48 hours exhibited higher TX-M excretion than 6 patients responding to therapy (2208 $\pm$ 1542 vs 609 $\pm$ 312 ng/g creatinine; $p<0.01$). Elevated TX-M excretion was also found in 4/8 patients with sustained post-infarction angina. When 9 patients were re-studied in a stable phase after 11 $\pm$ 5 months TX-M was consistently in the normal or high normal range. Excretion of PGI-M was not depressed in any patient but correlated weakly with TX-M ($r=0.408$). Thus, enhanced TX-M excretion as index of platelet activation may identify patients who are at increased risk of active thrombus formation and who could benefit most from anti-aggregatory treatment.

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FIBRINOLYTIC ALTERATIONS AS RISK FACTOR IN PATIENTS WITH CORONARY HEART DISEASE. J. Aznar (1), A. Estellés (1), G. Tormo (2), P. Sapena (2), F. España (1) and V. Tormo (2). Hospital "La Fe" (1) and Hospital General (2). Valencia. SPAIN.

It has been reported that young survivors of myocardial infarction (MI) have elevated plasminogen activator inhibitor (PAI) levels. We have studied several fibrinolytic parameters (euglobulin lysis time, fibrin-plate lysis, tissue plasminogen activator (t-PA) antigen, t-PA activity, PAI activity, plasminogen, α_2 antiplasmin and FDP/fdp in 55 patients with coronary heart disease (CHD), before and after an exercise test. The patients were classified in 4 groups: A) Patients with unstable angina (n=5); B) Patients with stable angina and previous history of MI (n=13); C) Patients with stable angina without previous history of MI (n=11) and D) Patients with MI about 3 weeks before this study (n=26). All the groups were similars in age and life habits. Patients suffering from dislipemia and diabetes were excluded from the study. In basal conditions, PAI activity (U/ml) was high in the 4 patient groups (A: 2.5 $\pm$ 2.8; B: 5.2 $\pm$ 4.9; C: 2.8 $\pm$ 2.6; D: 4.6 $\pm$ 4.6) as compared to a group of 10 healthy volunteers (0.46 $\pm$ 0.5). In all the clinical groups there were a large number of patients (about 60%) whose PA inhibitor level was > 2 U/ml. t-PA antigen (ng/ml) was slightly elevated in all patient groups (A: 12.4$\pm$4.6; B:12.4$\pm$5.6; C:12.5$\pm$4.0; D: 13.3$\pm$4.3) in comparison with control group (10.1$\pm$2.9). The release of t-PA antigen after the exercise test did not differ significantly from one group to another. However, this release was < 3 ng/ml in about 50% of patients in all clinical groups, as compared to the control group, in which the release of t-PA antigen was higher than 3 ng/ml in all the subjects. After the exercise PAI activity remained high in the patient groups. The increased level of t-PA inhibitor activity founded in the patients was partially inhibited by antiserum against PA inhibitor-1 but not by antiserum against PA inhibitor-2. The formation of a complex of about 115,000 daltons between the increased plasma PA-Inhibitor and purified single t-PA was observed by a zymographic fibrin technique. These findings demonstrate that CHD patients have a fibrinolytic hypofunction caused basically by an increase in t-PA inhibitor. This increase in PAI activity is more evident in patient with a previous history of MI.

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INCREASED PLASMA CONCENTRATION OF CROSSLINKED FIBRIN POLYMERS IN ACUTE MYOCARDIAL INFARCTION. C.W. Francis, D.G. Connaghan, W.L. Scott and V.J. Marder. Hematology Unit, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA.

Thrombin cleaves fibrinopeptides from fibrinogen, converting it to fibrin monomer, and activates factor XIII which catalyzes the formation of intermolecular ε-(γ-glutamyl)-lysine bonds to stabilize the fibrin polymer. The formation of factor $XIII_a$-catalyzed fibrin polymers during clotting of plasma and purified fibrinogen in vitro was followed using an SDS agarose gel electrophoretic technique with radiolabeled antifibrinogen antibody overlay. Prior to clot formation an increase in both total amount and sizes of crosslinked fibrin polymers was demonstrated with at least 10 distinct polymeric forms identifiable by a time corresponding to .92 of the clotting time. Soluble polymers were shown to be crosslinked through γ dimer formation by two dimensional electrophoresis with proportionately more dimer in each successively larger polymer. Plasma from patients initially presenting with acute myocardial infarction (MI) showed increases in the plasma concentration of fibrin polymer and in the proportion of total fibrinogen present as polymer, as determined by a quantitative adaptation of the electrophoretic technique. The plasma concentration of crosslinked fibrin dimer in patients with subendocardial or transmural MI showed significant ($p < .005$) increases to 4.0 $\pm$ 1.0% and 3.6 $\pm$ .8%, respectively, as compared to the concentration in normal plasma (.8 $\pm$ .1%). No difference in plasma concentration of fibrin polymer was found in samples from patients with transmural compared to subendocardial MI. This study provides the first direct demonstration and quantitation of factor $XIII_a$ crosslinked fibrin polymers in thrombotic disease and the findings are indicative of increased activity of both thrombin and factor $XIII_a$ in acute MI.