Thromb Haemostas
Volume 73
Number 6
Pages 899-1534
June 1995

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Thrombosis and Haemostasis

Journal of the International Society on Thrombosis and Haemostasis

Abstracts

XVth Congress of the International Society on Thrombosis and Haemostasis
Jerusalem, Israel

June 11–16, 1995

Schattauer

THURSDAY

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FAMILIAL TRANSMISSION OF ELEVATED LEVELS OF FACTOR VII AND ARTERIAL THROMBOTIC DISEASE. G. Castaman, M. Ruggeri, F. Rodeghiero. Hemophilia and Thrombosis Center and Department of Hematology, San Bortolo Hospital, Vicenza, Italy

Factor VII (F VII) plays a key role in in the initiation of blood coagulation. Elevated levels of F VII have been correlated to an increased risk of coronary artery disease (Meade et al, 1986). However, no families with inherited high levels of F VII and arterial thrombosis have been reported. During the recent years, we observed two unrelated families with several members affected by arterial thrombosis at a relatively young age (stroke, myocardial infarction) and consistently elevated F VII levels. The proposita of family 1 suffered from stroke at age 33. F VII activity (140-143 %) and antigen (128-131 %) were grossly elevated. F_{1+2} was 3.6 nMol/L (NV 1.05 ± 0.22). The proposita's mother underwent carotideal arterectomy. Her F VII activity (140-146 %) and antigen (139-166 %) were similarly elevated. F_{1+2} was 2.2 nMol/L. The proposita's daughter had normal F VII and F_{1+2} values. The asymptomatic proposita's son had increased F VII and F_{1+2} (1.85 nMol/L) values. The proposita of family 2 suffered from acute carotideal thrombosis at age 50. Ischemic stroke occured at age 52 while on aspirin. F VII activity and antigen were elevated (135 and 132 %). F_{1+2} was 4.3 nMol/L. Her asymptomatic sister had similarly high F VII and F_{1+2} levels (138 and 137 %; 5.8 nMol/L). The presence of other inherited risk factors were ruled out in both families. The presence of continuous increased activation of coagulation seems really to be associated with high levels of VII, as demonstrated by its occurrence and extent also in asymptomatic subjects with abnormal values. Oral anticoagulation rather than antiplatelet agents should probably best offered to these patients.

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RISK FACTORS FOR FEMOROPOPLITEAL BYPASS GRAFT OCCLUSION FOLLOWING RECONSTRUCTIVE SURGERY Alexander T. Cohen, John B.Wagner, David J. Garrard, Saroj K. Das and Vijay V. Kakkar. Thrombosis Research Institute, Manresa Road, London SW3 6LR

Femoropopliteal (FP) bypass grafting is the most frequently performed surgical procedure for the treatment of patients with disabling claudication and critical lower limb ischaemia. Several risk factors are believed to affect the outcome of surgery but their importance has yet been fully assessed. The affects of potential risk factors including age, sex, indication for surgery, graft material, anastomosis level, number of run-off vessels, smoking, diabetes, hyperlipidaemia and type of therapy used to prevent graft occlusion were considered in this study. In a prospective, multicentre, randomised trial of 208 patients undergoing FP bypass grafting, each patient received, for 3 months, either 5,000 IU subcutaneous injection of 2,500 IU low molecular weight heparin (LMWH) or oral aspirin together with dipyridamole (AD). 300mg aspirin was given once daily and dipyridamole 100mg 8 hourly. Patients were reassessed at 1, 3, 6 and 12 months. Graft surveillance included clinical assessment and bilateral resting Doppler indices. Duplex ultrasonography or angiography was performed when doubt existed about graft patency. Results: Survival analysis using the Kaplan Meier method was used to investigate the effect of risk factors on graft patency. After comparing incidence densities, hazard ratios (HR) and their 95% confidence intervals (95%CI) were calculated. Using multivariate analysis, four risk factors were found to have statistically significant effects: the presence of diabetes, HR=1.97 (95%CI: 1.09 - 3.57); more than one run-off vessel had a protective effect, HR=0.27 (95%CI: 0.12 - 0.60) for one artery and HR=0.46 (95%CI: 0.26 - 0.83) for two or more arteries; treatment with AD was a risk factor when compared to LMWH, HR=1.80 (95%CI: 1.04 - 3.13); surgery for the treatment of critical limb ischaemia was a risk factor when compared to surgery performed for treatment of claudication, HR=2.15 (95%CI:1.25 - 3.70). After multivariate analysis to allow for confounding factors using a Cox Proportional Hazard Model, only two variables were found to have sustained effects: the treatment group and the indication for surgery, taking the LMWH group as a baseline, when surgery was carried out for critical limb ischaemia the use of AD resulted in an HR=3.49 (95%CI: 1.53 - 8.00). In the claudication patients there were no significant differences between the two groups, HR=0.70 (95%CI: 1.3 1.67). Conclusion: The identification of these two independent risk factors should result in an increased vigilance in critical limb ischaemia and a modification of medical therapy

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HEMOSTATIC VARIABLES AND PROGRESSION OF COMMON CAROTID INTIMA-MEDIA THICKNESS IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE. M. Cortellaro, E. Cofrancesco, C. Boschetti, E. Tremoli, D. Baldassarre. University of Milan, Italy.

Changes in common carotid intima-media thickness (CC-IMT), as measured by B-mode ultrasonography, have been used in both population studies and clinical trials to seek risk factors for early atherosclerosis progression and have already been associated with age, high low density lipoprotein cholesterol, leukocytes, hemoglobin, and fibrinogen. However, no information is available on other hemostatic variables.
We investigated the relations between multiple hemostatic and conventional risk factors and CC-IMT changes over 16 months (delta CC-IMT) in 64 peripheral arterial disease (PAD) patients randomly selected from the prospective PLAT study series (1,2).
Samples from 44 (68.7%) patients who presented an increase of CC-IMT during the follow-up period were compared with those from 20 (31.3%) in whom CC-IMT remained unchanged during the same time frame. Conventional risk factors and coagulation variables were similar in the two groups except for higher von Willebrand factor (vWF) (164.6±58.0 vs 133.5±46.6%, p=0.04) and factor VII (FVII) (126.2±32.4 vs 108.0±18.6%, p=0.02) in the patients with increased CC-IMT. Delta CC-IMT correlated positively with plasma levels of FVII (r=0.31, p<0.01) and vWF (r=0.31, p<0.01). Multiple stepwise regression analysis identified FVII as the only independent variable associated with positive changes of CC-IMT (r=0.83, p=.01).
High FVII and vWF might be risk factors for the progression of early carotid atherosclerosis in PAD patients.

1. *Atherosclerosis*, 1991;90:109-18.
2. *Arterioscler Thromb*, 1993;13:1412-17.

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HEIGHTENED THROMBIN FORMATION BUT NORMAL PLASMA LEVELS OF ACTIVATED FACTOR VII IN PATIENTS WITH ACUTE CORONARY SYNDROMES. Piera A. Merlini, Diego Ardissino, Raffaele Coppola, Luigi Oltrona and Pier Mannuccio Mannucci. A. Bizzozero Bonomi Hemophilia and Thrombosis Center, Milan, Division of Cardiology, Niguarda Hospital, Milan and Division of Cardiology, IRCCS Policlinico S. Matteo, Pavia, Italy.

Background. Plaque rupture or fissure with exposure of procoagulant tissue factor is considered a common pathogenetic mechanism in the acute coronary syndromes of unstable angina and myocardial infarction. Activated factor VII (FVIIa), the key enzyme for initiating blood coagulation in resting conditions, is increased in pathological conditions associated with tissue factor exposure. We measured the plasma levels of FVIIa and studied their relationship with signs of coagulation enzyme activation in acute coronary syndromes.
Methods. Plasma FVIIa, prothrombin fragment 1+2 (F1+2) and fibrinopeptide A (FPA) were measured on admission in patients with acute myocardial infarction (N=28), unstable angina (N=32), stable angina (N=17) and in age- and sex-matched healthy individuals (N=33). Measures were also measured after 15 days, 3 months and 6 months.
Results. On admission, patients with unstable angina and myocardial infarction had higher plasma levels of F1+2 ($p<0.001$) and FPA ($p<0.01$) than patients with stable angina or healthy individuals, whereas a difference was seen for FVIIa. During follow-up there was a decrease in FPA, both in patients with unstable angina ($p<0.001$) and myocardial infarction ($p<0.01$), with no changes in F1+2 or FVIIa.
Conclusions. In the acute and chronic phases of myocardial infarction and unstable angina heightened coagulation enzyme activity is not accompanied by an increase of FVIIa. Hence, the measurement of this moiety in plasma does not mirror the enhancement of the tissue-factor coagulation pathway that occurs in patients with acute coronary syndromes, reflected by high levels of activation peptides. Perhaps, the tissue factor bound forms of FVIIa are the trigger of coagulation activation in these conditions.