

EPIDEMIOLOGICAL ASPECTS OF ANTITHROMBIN-III, SELENIUM AND LIPOPROTEIN COMPONENTS IN CORONARY DISEASE.

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The known risk factors for coronary disease can only "explain" a proportion of the incidence of the disease. Looking for supplementary risk factors we thus selected for detailed study both a group of patients with normal levels of risk factors (normotensives, non-smokers with normal serum cholesterol) and a group with high conventional risk factors, comparing both groups with an age and sex matched control group. Subgroups were formed by individuals aged below (young) and above (old) 60 years.

Total- and HDL-cholesterol, apo-lipoproteins A-I and B and triglycerides showed co-variation with each others and with fatty acids in serum. With "factor analysis" seven "factors" were extracted and the factor scores for sub-groups were calculated. Two factors discriminated between young, high risk patients and controls. One was a positive risk factor and the other a negative one. The factors may be dependent on the existence of two unknown sub-groups of serum lipoproteins which were characterized by high concentrations of certain fatty acids.

Coronary patients were found to have 9.1% higher antithrombin-III (AT-III) activity in their plasma than controls ( $p=0.037$ ). Plasma selenium levels were slightly less in patients than in controls. There was a slight, but significant ( $r=0.29$ ,  $p=0.015$ ) positive correlation between selenium and AT-III concentrations. Multivariate statistical analysis indicated that selenium was significantly negatively correlated with disease.

It is concluded that antithrombin-III tend to be high and that plasma selenium levels are relatively sub-normal in some coronary patients. It is also suggested that fatty acid analysis may be useful in the characterization of lipoproteins that are involved in the development of atherosclerosis.

## THROMBOLYSIS: GENERAL

Thrombolytic Properties of Pro-Urokinase, Plasminogen Proactivator (PPA). Y. Iga, K. Tanaka, M. Tsukada, S. Kameyama, S. Morichi and T. Suyama. Green Cross Corp., Osaka, JAPAN.

Thrombolytic properties of highly purified plasminogen activator (PPA) isolated from culture medium of human kidney cells were compared with those of human urinary urokinase (u-UK). When 125-I-PPA or u-UK was added to whole blood perfusion medium containing preformed thrombi made from whole blood by Chandler loop method, the rates of uptake by the thrombi of PPA and u-UK for 4 hrs were only 2.5% and 2.7% respectively. Using the same thrombi and perfusion medium, an in vitro thrombolytic effect of PPA was examined over a 4 hr period. In early perfusion time, a lag phase was observed in the lysis-time curve of PPA, but not of u-UK. After the lag phase, the lysis by PPA increased linearly without early reaching a low level plateau that was characteristic of the lysis by u-UK. At 4hr, the PPA percent lysis was higher than the u-UK figure. Half lives in rabbit of 125-I-labelled PPA and u-UK iv doses were  $5.1 \pm 0.2$  min and  $7.3 \pm 0.2$  min respectively. The thrombolytic ability of PPA in vivo was evaluated in rabbit pulmonary embolism induced by iv 125-I-fibrin suspension as well as cynomolgus monkey femoral vein thrombosis produced by formation of 125-I-fibrinogen labelled clot in an isolated segment of the vein. In both models, PPA was as effective in thrombolysis as u-UK. However conversion to active UK form, consumptions of plasminogen and PI, fibrinogenolysis and prolongation of APTT in plasma were minor in the PPA group, but not in the u-UK group. It is thus suggested that PPA may cause a local activation limited on the fibrin to lead to a lysis of the thrombi without incurring systemic fibrinolysis.

a) Pulmonary embolism in rabbits ( $n=3$ , 100,000 IU/kg IV.)

Agent	Lysis percent		UK (IU/ml)		Plg (%)		Fibg (%)	
	6min	30min	6min	30min	30min	120min		
1% Albumin	$5.2 \pm 2.9$	$19.7 \pm 9.0$	0	0	100	100		
PPA	$43.0 \pm 4.3$	$46.0 \pm 5.0$	$41 \pm 22$	$1 \pm 2$	$72.9 \pm 0.4$	$82.6 \pm 6.5$		
u-UK	$46.4 \pm 2.4$	$45.1 \pm 2.9$	$559 \pm 41$	$24 \pm 15$	0	$46.8 \pm 15.7$		

b) Femoral vein thrombosis in monkeys ( $n=3$ , 100,000 IU/kg IV.)

Agent	Lysis (%)	UK (IU/ml)	UK (ng/ml)	Plg (%)	PI (%)	APTT (min)	Fibg (%)
Saline	0	0	0	100	100	$22 \pm 3$	100
PPA	$75 \pm 12$	$71 \pm 6$	$1776 \pm 1144$	$67 \pm 11$	$73 \pm 21$	$22 \pm 1$	$88 \pm 9$
u-UK	$88 \pm 15$	$422 \pm 92$	$1584 \pm 1130$	$30 \pm 8$	$26 \pm 9$	$36 \pm 6$	$22 \pm 19$

THE EFFECT OF HEPARIN AND FIBRIN ON THE ENZYMIC EFFICIENCIES OF THROMBOLYTICS IN VITRO. R. Fears. Beecham Pharmaceuticals Research Division, Biosciences Research Centre, Epsom, Surrey KT18 5XQ, U.K.

Selective fibrinolysis may be achieved physiologically by the binding of both endogenous plasminogen activator (t-PA) and plasminogen to fibrin. It has been suggested that t-PA may also exhibit fibrin-selectivity when used at therapeutic doses for acute myocardial infarction whereas the other principal thrombolytics, urokinase (UK) and streptokinase (SK).plasminogen, are not bound. However, in the present kinetic studies it was found that plasminogen activation by SK.lys-plasminogen was enhanced by soluble fibrin (the effect mainly on  $K_m$ ), the affinity of binding to fibrin was similar to t-PA (dissociation constant approx. 100 nM) and the reaction mechanism appeared similar (Rapid Equilibrium Ordered Bireactant). When evaluating the *in vivo* significance of fibrin-enhancement, variation in the form of the substrate (i.e.,  $glu_{1-}$  or  $lys_{77-}$  forms) and the contribution of heparin must also be considered. Both t-PA and UK activities were potentiated by heparin (the effect mainly on  $K_m$ ) but in the presence of fibrin the effect of heparin on t-PA was attenuated; SK.plasminogen enzymatic activity was unaffected by heparin. Thus, in the presence of heparin, *in vivo*, there may be an exacerbation of the systemic action of t-PA. As differences in fibrin binding and enhancement between t-PA and intact SK.plasminogen - the activator that is produced from APSAC (tminase) - are relative rather than absolute, therapeutic activity will be influenced more by the dosage regimen and the clearance rate.