

THE INDUCTION OF PLATELET AGGREGATES IN HEALTHY SUBJECTS BY VENOUS OCCLUSION. D.A.F. Chamone and J.Vermeylen. Lab. of Blood Coagulation, Dept. of Medical Research, University of Leuven, Belgium.

Circulating platelet aggregates have been observed in various clinical conditions (Wu and Hoak, *Lancet*, 1974, ii, 924). Using a slightly modified method, we have found that platelet aggregates can be induced in vivo in healthy subjects.

Nine volunteers (7 males, 2 females, age 23-38 years) were studied. Blood was drawn from an antecubital vein of one arm immediately before and of the other arm after twenty minutes of occlusion midway between systolic and diastolic pressure. The ratio of the platelet count in platelet-rich plasma (PRP) obtained from blood collected on formalin-EDTA to that from blood collected on EDTA only was 0.934 ± 0.028 (mean \pm S.E.) before and 0.768 ± 0.033 after occlusion ($p < 0.001$). Spontaneous aggregation in PRP, measured as percent increase in light transmission during 10 minutes of stirring in the aggregometer, was 4.20 ± 1.17 before and 3.80 ± 1.69 after occlusion ($p > 0.1$).

This system may help elucidate some of the mechanisms involved in the generation of circulating platelet aggregates. It may also constitute a simple set-up for the in vivo evaluation of drugs affecting platelet function.

COLLAGEN-INDUCED REDUCTION IN RAT CIRCULATING PLATELET COUNT: INFLUENCE OF PLATELET FUNCTION INHIBITORS. I.B. Holmes. Sandoz Ltd, Basle, Switzerland.

The effect on circulating platelet count of repeated intravenous infusions of collagen fibrils was measured in male OFA Sprague-Dawley rats (400-550 g). Citrated blood was pumped from the left carotid artery of anaesthetized animals, via a siliconized double-lumen cannula, into the manifold of a Technicon Autocounter, for continuous registration of platelet count. Native collagen fibrils (Collagenreagent 'Horm') were infused intravenously for 1 min at 15 min intervals. Successive increasing collagen doses (20-320 $\mu\text{g}/\text{kg}$) induced dose-dependent reduction in platelet count, measured as absolute platelet number disappearing from the circulation. Repeated infusion of collagen 160 $\mu\text{g}/\text{kg}$ produced constant, partially reversible, reduction in platelet count. Several known inhibitors of platelet aggregation were investigated in the described test system. Collagen effects were inhibited in a dose-dependent manner to a maximum of 50-60 %, and drug activity was thus quantitated on the basis of dose producing 30 % inhibition (ID30): prostaglandin E_1 (1.6 $\mu\text{g}/\text{kg}/\text{min}$ i.v. infusion); SH-869 (1.1 mg/kg i.v.); aspirin (33.1 mg/kg p.o.); proquazone, a new non-steroidal antiinflammatory compound (5.0 mg/kg p.o.). That part of the collagen response not inhibited might be attributed to the initial phase of platelet adhesion to collagen, known to be relatively refractive to platelet function inhibitors.

THE PRODUCTION OF HEART ATTACKS AND CEREBRAL STROKE BY THROMBOXANE A_2 MIXTURES AND THEIR PREVENTION WITH EG626 (PHTHALAZINOL). T.Shimamoto, M.Kobayashi, T.Takahashi, Y.Takashima, T.Motomiya, S.Murooka and F. Numano. Japan Atherosclerosis Research Institute, Tokyo, Japan.

Thromboxane A_2 (TXA_2) has been implicated as the causative agent in variant angina, myocardial infarction, sudden cardiac death and stroke. In order to verify experimentally such hypothesis, the TXA_2 -mixture was produced by washed rabbit or human platelets stimulated by thrombin (3U for 1.2×10^9 platelets) and the dose of TXA_2 was measured by rabbit aortic strips.

The intracoronary (by our aortic balloon technique) or intracarotid injection of TXA_2 -mixture successfully produced variant angina-like response, fatal or non-fatal myocardial infarction and cerebral infarction resp. in 102 rabbits. The responses were recorded by a movie, polygraphic method including ECG, EEG and histological technique. The effective doses ranged from 1-2 μg of TXA_2 in terms of angiotensin II for the intracoronary and 3 to 6 μg for the intracarotid injection resp. The mixture, kept at 37°C for 5 min, lost TXA_2 and remained without effect, despite the presence of other vasoconstrictors, showing the leading role of TXA_2 for the occlusion of arterioles. The variant angina-like response, myocardial infarction and stroke were statistically significantly prevented by pretreatment of rabbits with therapeutic doses (0.1-1.0 mg/kg, i.v.) of EG626, an orally available potent TXA_2 -antagonistic and cAMP/PDE-inhibiting substance, among drugs tested. The occlusion of arterioles by TXA_2 by its time-matched vasoconstrictive activities after production of platelets aggregates as the plug was prevented by EG626 by reducing the grade of vasoconstriction and platelet aggregation resulting into slipping away of the aggregates and the maintenance of the blood flow. Such facts may show the importance of EG626-type drugs in prevention of heart attacks and stroke as evidenced by its preliminary clinical results.