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WARFARIN INDUCED FIBRINOLYSIS: THE EFFECT OF RECOVERY WITH AND WITHOUT VITAMIN K. N.A. Marsh, Department of Physiology, Queen Elizabeth College (University of London), London W8 7AH, England.

We have previously shown that fibrinolysis in the rat is enhanced by levels of warfarin administration sufficient to produce moderate anticoagulation. This effect is mediated largely by an increase in plasma plasminogen activator. Plasminogen levels are decreased and fibrin(ogen) degradation products raised confirming the presence of a systemic hyperfibrinolytic state. In order to investigate this phenomenon further we have measured fibrinolytic components in rats recovering from warfarin administration. Groups of male Hooded rats received 14 µg warfarin/100 g body weight /day by mouth for one to two weeks. The animals were then allowed to recover without further treatment or following a single 50 µg dose of vitamin K_1. Euglobulin lysis time, one stage prothrombin time, plasma plasminogen activator (fibrin plate method), plasma plasminogen (caseinolytic method), plasma fibrinogen (clot weight method) and plasma fibrinolytic inhibitors were measured at intervals after the end of the warfarin treatment. In animals recovering without vitamin K prothrombin time returned to normal within one week. However fibrinolysis remained elevated with plasma plasminogen activator concentrations of more than twice the control value. Plasma inhibitor levels were depressed and fibrinogen levels elevated. After two weeks all fibrinolytic components had returned to normal. Following vitamin K_1 administration a different pattern emerged; prothrombin time returned to normal within 24 hours but fibrinolysis was diminished. The latter effect was due to a marked increase in plasma fibrinogen and moderate fall in plasma plasminogen activator both of which contributed to a prolonged euglobulin lysis time. These results indicate that fibrinolysis and coagulation in the rat are not linked in a 'dynamic equilibrium' like that proposed for man. The enhanced fibrinolysis rather than being a result of the fall in vitamin K dependant clotting factors may be due to the direct action of warfarin. The 'fibrinolytic shutdown' following vitamin K remains unexplained.

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THE EFFECT OF EXERCISE AND ORAL CONTRACEPTIVE AGENTS ON HEMOSTATIC AND FIBRINOLYTIC MECHANISMS IN TRAINED ATHLETES. I.A. Huisveld, J.E.H. Hospers, B.N. Bouma, J.L. Zevenbergen M.J.E. Bernink and W.B.M. Erich. Dep.of Physiology and Dep. of Haematology, State Univ. of Utrecht, The Netherlands.

Exercise increases hemostatic and fibrinolytic activity in humans. The same has been reported for oral contraceptive agents (OCA). We studied the combined effects of strenuous exercise and OCA in twenty highly trained female athletes. Ten of the subjects had been using the pill (30 mcg ethinylestradiol) for more than a year (users). The other ten females not using OCA served as a control (non users). All subjects were exercised to exhaustion which was attained within 10-16 min. by means of an increasing workload test on a bicycle ergometer. Tests were performed during morning hours and only in the first half of the therapeutic or menstrual cycle. Hemostatic and fibrinolytic components were determined in pre and postexercise plasma samples. Changes in plasma volume that occurred with exercise were calculated and postexercise results were corrected for these changes. Procoagulant activity of Factors XII, XI and VII were determined using partial thromboplastin time assays. HMWK, α_2-macroglobulin and C1-INH were quantified by an immunodiffusion technique using monospecific antisera. Synthetic chromogenic peptide substrates were used for the determination of plasminogen, prekallikrein, α_2-antiplasmin and AT III amidolytic activities. Comparison of resting values showed an increase in F XII and plasminogen concurrent with a decrease in C1-INH level in the group of users. The combination of exercise and OCA induced a decrease of all plasma components except F VII in the users. Postexercise decreases in F XII, HMWK, prekallikrein and the two inhibitors α_2-macroglobulin and α_2-antiplasmin were seen in the non users. Results indicate that hemostatic and fibrinolytic changes due to strenuous exercise are potentiated by OCA in trained females. The relevance of corrections for changes in plasma volume is demonstrated.

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SUPPRESSION OF EXERCISE-INDUCED PLASMINOGEN ACTIVATOR AND PLASMA RENIN ACTIVITY FOLLOWING ASPIRIN INGESTION. D.H. Osmond, A.M. Hedlin, A.Y. Loh, D. Sakac and R.R. Topp. Department of Physiology, University of Toronto, Toronto, Canada.

The influence of aspirin on the fibrinolytic and renin systems was studied in 10 healthy young men, who served as their own controls. Basal blood samples were obtained after a 15-minute rest, immediately after exercise, and following a 15-min post-exercise rest. Later, (7-14 days) 1250 mg aspirin was ingested 1 hr. before test samples were obtained, as before. Exercise on a bicycle ergometer induced doubling of the resting heart rate within 2 min., and was continued for 3 min. longer. Aspirin induced a significant reduction in the level of plasminogen activator, before and after exercise, and also some decrease in hemoglobin and hematocrit levels. Exercise almost doubled the basal plasma renin activity (PRA, angiotensin I, ng/ml plasma/hr., by radioimmunoassay) in the control and aspirin experiments. Aspirin did not significantly blunt this exercise-induced rise in PRA. However, after 15-minute rest, the control PRA remained elevated, while the post-aspirin PRA was 37% below it ($p < 0.025$). After cold activation of the plasmas (-4°C, 72 hr.), the PRA increment over corresponding non-activated samples was used to estimate "prorenin". Prorenin as % of active renin before aspirin was 347.2, 210.5, and 210.8, for the basal and 2 post-exercise periods respectively; after aspirin the values were 460.5, 354.9, and 353.4. Clearly, exercise depresses the proportion of prorenin, suggesting an exercise-induced enhancement of prorenin conversion, possibly related to the exercise-induced stimulation of the fibrinolytic system. After aspirin, all 3 prorenin percentages are higher, implying that it interferes with prorenin conversion. Thus, exercise increases both fibrinolysis and PRA. The increase in PRA could be due in part to fibrinolytic enzyme conversion of prorenin (plasmin activates prorenin in vitro). Aspirin suppresses plasminogen activator, and thus prorenin activation.

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HYPOXIA AND ACIDOSIS INDUCE THE RELEASE OF PLASMINOGEN ACTIVATOR FROM VESSEL WALLS. L. Tappy and F. Bachmann. Laboratoire Central d'Hématologie, CHUV, CH-1011 Lausanne, Switzerland.

The mechanisms, which induce the release of vascular plasminogen activator (VA), are not fully understood. To test the effects of hypoxia and of acidosis on the liberation of VA from the vessel wall, we have used the isolated pig ear perfusion system described by Markwardt and Klöcking. Pig ears, collected at the slaughterhouse, were kept on ice for a maximum of 4 hours. A catheter was placed into the main artery and the ear flushed with oxygenated HEPES-Tyrode's solution pH 7,4 for 30 min at 37 °C. Baseline activities in effluent fractions from time 30-42 min, averaged 0,95 U UK/ml. Assays were performed on plasminogen rich fibrin plates. From 43 to 65 min, pig ears were perfused with oxygenated HEPES-Tyrode's solution pH 7,4 (controls) or pH 6,7 (acidosis), or within the same buffer (pH 7,4) pretreated by extensive nitrogen bubbling (hypoxia).

VA concentrations in controls remained fairly constant until 65 min. The hypoxia stimulus resulted in an increase of PA activity of 180% over basal activity ($p < 0,001$). Acidosis led to a mean increase of PA activity of 240% ($p < 0,001$).

These experiments suggest that acidosis and hypoxia, if present distally to venous segments occluded by a thrombus, may represent powerful stimuli for the secretion of plasminogen activator from vessel walls.