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MULTITHERAPY PRETREATMENT IMPROVES HEMODYNAMIC FUNCTION IN EXPERIMENTAL ENDOTOXEMIA.

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To evaluate the cardiopulmonary response to a new regimen of therapy in endotoxemia, ten pigs were infused with endotoxin 0.01 mg/kg over three hours. Five animals (treatment group) received therapy starting 30 min prior to endotoxin infusion consisting of repeated doses of protease inhibitor concentrates (C1-esterase inhibitor 2000 IU, antithrombin III 500 IU, aprotinin 2 mill KIU), methylprednisolone 100 mg/kg, antihistamine (promethazin 1 mg/kg), a serotonin antagonist (ketanserine 2 mg/kg) and an opiate antagonist (naloxone 0.06 mg/kg). Five animals were untreated. Eight animals (control group) were anaesthetized and observed without endotoxin or treatment. The observation time was five hours. Two untreated animals receiving endotoxin died. Endotoxin caused a decrease in cardiac function with decreased left ventricular stroke work (LVSW). Endotoxin resulted in a marked increase in pulmonary vascular resistance (PVR) and oxygenation was impaired. With multiherapy cardiac output increased. Systemic vascular resistence was decreased in the treatment group while it increased steadily in the untreated group. LVSW was significantly better maintained in the treated animals. Pulmonary vascular resistence was unaltered in the treatment group. Pulmonary gas exchange was not different between the endotoxin infused groups. Endotoxin infusion caused no metabolic changes in this short time model as oxygen consumption was not different between the three groups. Overall cardiopulmonary function was improved in treated animals compared to both untreated endotoxin infused animals and controls as mixed venous oxygen saturation was higher in the treatment group.

Multitherapy has a protective effect on cardiopulmonary functions in experimental endotoxemia.

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ENDOTHELIAL BASEMENT MEMBRANE PROTEOGLYCAN (PG) ALTERATIONS IN DEOXYCORTICOSTERONE (DOCA)-NaCl -INDUCED HYPERTENSIVE RAT MESENTERIC ARTERIES.

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Hypertension is associated with increased endothelial permeability. This has been previously associated with endothelial desquamation or alterations in junctional architecture. To determine if this increase in endothelial permeability was associated with changes in the basement membrane, especially the heperan sulphate (HS) PG, ruthenium red-stained sections of the superior mesenteric arteries of DOCA-NaCl treated rats were examined by transmission electron microscopy. After 3 weeks of treatment, some rats were hypertensive (DOCA-H), but some remained normotensive (DOCA-N). The intimal PG distribution was compared between DOCA-H, DOCA-N, and untreated normotensive controls. Compared to untreated controls, in DOCA-H arteries there was a reduction in basement membrane, including HS, and a small increase in other PGs. In DOCA-N arteries there was a much smaller change in PG disribution. In the DOCA-H rats, there was evidence of increased endothelial permeability as shown by sub-endothelial oedema, and an increase in the wet/dry weight ratio of the kidneys.

It is therefore possible that hypertension induces changes in endothelial cell metabolism which affect the production or maintenance of the basement membrane. Since the changes were not observed in the DOCA-N arteries they are not a result of the treatment. HS is generally accepted to be involved in the control of endothelial permeability, thus the observed loss of HS from hypertensive arteries may result in the increased endothelial permeability.

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EFFECTS OF INTRAVENOUS ADMINISTRATION OF A TISSUE-TYPE PLASMINOGEN ACTIVATOR (AK-124) IN ACUTE MYOCARDIAL INFARCTION, INCLUDING CHANGES IN BLOOD COAGULATION AND FIBRINOLYTIC ACTIVITY. – PRELIMINARY REPORT.

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We administered a tissue-type plasminogen activator (t-PA) intravenously to 10 patients with acute myocardial infarction (AMI), within 6 hours after the onset of symptoms, and then examined the state of reperfusion by coronary arterio graphy (CAG), and observed changes in blood coagulation and fibrinolytic activity to evaluate the drug effects. AK-124 (produced by Asahi Chemical Industry and Kowa Co., Ltd. in collaboration), a t-PA produced the by tissue culture of normal human lung cells, was given in a dosage of 48,000–576,000 A.K. units by intravenous infusion over 30–45 minutes. In 7 patients who received t-PA, a reflow or improved flow was detected on CAG. In t-PA treated patients, euglobulin lysis activity clearly increased, euglobulin lysis time clearly shortened, and D-dimer increased. After t-PA treatment, the levels of circulating fibrinogen and α_2-plasmin inhibitor decreased by an average of 12%, and 14% of base-line values respectively, but plasminogen showed no detectable change. A hematoma at the site of the catheter insertion was observed in one patient. These observations suggest that t-PA has a higher specificity for fibrin bound plasminogen than for plasma plasminogen, and produces coronary thrombolysis without causing systemic fibrinolysis, at least with the above dosage.

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EFFECT OF TREATMENT WITH STREPTOKINASE AND HEPARIN ON FIBRINOGEN, FIBRIN AND RELATED PROTEINS IN ACUTE MYOCARDIAL INFARCTION (AMI) PATIENTS.

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The properties of fibrinogen and fibrin, the levels of fibrinopeptide A (FPA) and fibrin(ogen) degradation products (FDP) were studied in 34 patients with AMI who were undergoing thrombolytic and heparin therapy. They were classified into 6 groups according to their stage of treatment: group 1, before intravenous administration of 800.000 U streptokinase over 30 min; group 2, after administration of SK but before administration of heparin; group 3, during 24 h of the 5 mg/h heparin continuous infusion; group 4, during 48-72 h of the 16.6 mg/h heparin continuous infusion; group 5, after 1 week of administration of SK and with a bolus inyection of 50 mg heparin every 4 h; group 6, patients who were undergoing only heparin treatment. The Fg I/ Fg II ratio varies during treatment with SK and heparin. In group 1 a slight increase (2.5) is observed. Group 2 shows a significant decrease (0.6) as a result of fibrinolysis. In group 3 the ratio reaches normal value (1.8) while in the fourth group it is twice the normal value (4). The value for group 5 is nearly normal (2.1), and in group 6 it reaches values similar to those obtained in group 4, which implies that the rise in the FgI/FgII ratio is not a result of fibrinolytic treatment. The FPA level shows and increase in patients with AMI (group 1,126 ng/ml). When SK treatment is applied (group 2), FPA decreases to 52 ng/ml. Later treatment with heparin (group-3, 82; group-4, 44 and group-5, 81 ng/ml) does not neutralize thrombinic activity. Patients treated only with heparin (group 6) show an FPA value of 19 ng/ml, which is lower than in the other groups. All of this indicates that thrombin is activated after fibrinolytic treatment. FDP values show a significant increase in the six groups (1, 53; 2, 430; 3, 128; 4, 270; 5, 139 and 6, 141 ug/ml), which indicates that during treatment with heparin the fibrinolytic activity persists. The formation of highly cross-linked fibrin is altered in groups 1,2,3 and 4, as a consequence of circulating FDP effect and fibrinogenolysis. The permeability of the fibrin clot decreases in groups 1 (0.42), 2 (1.3), 4 (1.1) and 5 (0.5 ml/s/mg) and increases in group 2 (23.2 ml/s/mg) with respect to the normal plasma value (3.2 ml/s/mg). The decrease in permeability must be related to the existence of hypercoagulability resistant to heparinization. FPA values, the FgI/FgII ratio, and fibrin permeability can be used to evaluate the degree of thrombin activity during thrombolytic treatment in AMI.