

CARDIOVASCULAR FUNCTION FOLLOWING SURGICAL STIMULATION OF PULMONARY PROSTACYCLIN SYNTHESIS. H.B. Hechtman, M.M. Krausz, T. Utsunomiya, L. Levine and D. Shepro*. From the Department of Surgery, Harvard Medical School and Biological Science Center, Boston University*, Boston, MA.

Surgery initiates local wound hemostasis and a systemic reaction which we hypothesize protects against intravascular coagulopathy. This study examines release and systemic effects of prostacyclin (PGI₂) and thromboxane (Tx) in response to surgery. In 10 dogs laparotomy or thoracotomy was followed by a rise in arterial concentrations of 6-keto-PGF_{1α}, the stable metabolite of PGI₂ from 0.02 to 0.26 ng/ml (p < 0.005), a value higher than pulmonary arterial levels (p < 0.05). Tx_{B2}, the stable metabolite of Tx_{A2}, was unchanged. Cardiac output (CO) rose from 3.46 to 4.06 L/min (p < 0.05) whereas mean arterial pressure (MAP) fell from 142 to 122 mm Hg (p < 0.03). ADP induced platelet aggregation decreased from 49% to 28% (p < 0.001). Indomethacin, 5 mg/kg IV, in 5 dogs prevented the rise of 6-keto-PGF_{1α} secondary to surgery, and levels were now higher in mixed venous than arterial blood (p < 0.03). There were no changes in CO, MAP or platelet aggregation. During abdominal aortic aneurysmectomy (14 patients), 6-keto-PGF_{1α} increased from 0.04 to 0.95 ng/ml (p < 0.01) 30 min after incision, but before transfusion or aortic clamping; Tx_{B2} did not change. Cardiac index (CI) rose from 2.72 to 3.04 L/min·m² (p < 0.03) and MAP fell from 100 to 88 mm Hg (p < 0.01). Platelet aggregation decreased from 55% to 40% (p < 0.001) and platelet counts decreased to 166,000/mm³, 24 h postop (p < 0.01). In 9 patients given aspirin (650 mg) by mouth 12 h preoperatively the rise in 6-keto-PGF_{1α} and CI, and fall in MAP and platelet aggregation were prevented. Mean platelet counts were 107,800/mm³, 24 h postop, which was lower than observed in patients not given aspirin (p < 0.005). Surgical trauma stimulates the lungs to secrete PGI₂, which has systemic hemodynamic and hematologic consequences.

ALTERED REGULATION OF PROSTACYCLIN (PGI₂) ACTIVITY IN SEVERE PRE-ECLAMPSIA. G. de Gaetano, D. Marchesi, C. Zoja, A. Schieppati, R. Misiiani, G. Mecca, E. Rossi, M.B. Donati and G. Remuzzi. Istituto di Ricerche Farmacologiche "Mario Negri", Milan; Ospedali Riuniti, Bergamo and University of Milan Blood Transfusion Center, Milan, Italy.

It has been suggested that prostaglandins of the E series play a crucial role in regulation of fetal vascular tone. The discovery of PGI₂ has opened new perspectives for understanding the circulatory physiology of normal pregnancy and the vascular abnormalities of pre-eclampsia. We have bioassayed PGI₂-platelet antiaggregatory activity and confirmed it by RIA of 6-Keto-PGF_{1α} and thin-layer radiochromatography in human umbilical and placental vessels. Fetal umbilical arteries obtained at the end of 9 uncomplicated pregnancies generated significantly more PGI₂ (191 ± 29 ng/mg tissue) than vessels from control non pregnant adults (43 ± 12 ng/mg) (p < 0.01). Placental veins generated PGI₂ similarly to control veins (33 ± 7 and 37 ± 8 ng/mg respectively). This could contribute to maintaining the low peripheral vascular resistance of the fetal circulation with very high cardiac output. Umbilical arteries from 5 women with severe pre-eclampsia generated significantly less PGI₂ (65 ± 12 ng/mg tissue) than the corresponding vessels from women with normal pregnancy (p < 0.01). Similarly placental veins from pre-eclampsia patients generated less PGI₂ (11 ± 2) than normal pregnancy veins (p < 0.01). We propose that in severe pre-eclampsia, placental ischemia and fetal distress could be triggered by deficiency of the adaptive mechanism which maintains high vascular levels of PGI₂ in normal pregnancy. The abnormally high PGI₂-stimulating activity in plasma from patients with severe pre-eclampsia in comparison with plasma from women with normal pregnancy supports the contention that regulation of PGI₂ synthesis is deranged in pre-eclampsia.

THE INTERACTION OF PLATELET ACTIVE DRUGS WITH PROSTACYCLIN *IN VITRO* AND AGAINST BIOLASER INDUCED INTRAVASCULAR THROMBOSIS. J.S. Fleming, B.T. Cornish, J.O. Buchanan and J.P. Buynicki. Pharmacology Dept., Bristol Laboratories, Syracuse, N.Y. 13201.

Prostacyclin and thromboxane A₂, two of the physiologically most important end products of arachidonic acid metabolism, represent a basic control system which modulates platelet function. Decreased vascular prostacyclin is believed to play a role in the increased thrombotic tendency associated with various clinical diseases including diabetes and atherosclerosis. Compounds which either enhance the formation or release of prostacyclin or potentiate the activity of low levels of prostacyclin may be therapeutically useful in ameliorating this associated pathology. We have studied various inhibitors of platelet aggregation for their ability to potentiate the activity of low levels of prostacyclin both *in vitro* and in an *in vivo* model of experimental thrombosis. Anagrelide, aspirin, dipyridamole, sulfinpyrazone and ticlopidine all demonstrated interaction with prostacyclin *in vitro* against collagen-induced platelet aggregation. More limited interactions were observed against ADP-induced aggregation. Using isobolographic analysis most combinations demonstrated additive interaction. However, pronounced supra-additive interaction was observed vs. both aggregating agents in the case of prostacyclin (0.1-1 ng/ml) - anagrelide (8-90 ng/ml) combinations. Dramatic enhancement of the effects of prostacyclin on biolaser-induced thrombosis was also seen in anagrelide (0.5 mg/kg po) pretreated animals. Other inhibitors of platelet aggregation used in combination with prostacyclin produced less spectacular results. These findings suggest that aside from inherent antiaggregatory and antithrombotic activity, certain platelet active drugs may produce equally important effects by virtue of their ability to interact with prostacyclin in a clinically beneficial manner.

ROLE OF ACCELERATED PLASMA DEGRADATION OF PROSTACYCLIN (PGI₂) IN VASCULAR THROMBOSIS. K.K. Wu, Y.C. Chen, E.R. Hall and M.E. Rafelson. Departments of Medicine and Biochemistry, Rush University, Chicago, IL, U.S.A.

To determine whether accelerated degradation of PGI₂ plays a role in thrombosis, we investigated the kinetics of plasma PGI₂ breakdown in 7 normal subjects and 3 patients with small vessel thrombosis (2 with thrombotic thrombocytopenic purpura and one with idiopathic thrombotic stroke). Plasma PGI₂ degradation was evaluated by incubating standard PGI₂ with plasma at 37°C and measuring the PGI₂ activity remaining at serial time intervals. PGI₂ activity was determined by its capacity to inhibit platelet aggregation, and its hydrolysis product, 6-keto-PGF_{1α}, was measured by radioimmunoassay. Plasma PGI₂ survival time of all 3 patients was significantly shorter (<1 min) than that of normals (101 ± S.D.33 min). As 6-keto-PGF_{1α} content in both groups was similar, the shortening of the survival time was attributed to acceleration of PGI₂ hydrolysis. Abnormal degradation of PGI₂ was corrected by adding normal plasma *in vitro*. Moreover, infusion of normal plasma into one of the patients prolonged PGI₂ survival time significantly from a baseline of 50 sec to 55 min 3 days following transfusion, and 80 min 7 days later. Correction of the abnormal PGI₂ degradation by plasma transfusion was associated with improvement of clinical symptoms and blood counts. The disease process tended to relapse at 3-week intervals and could be controlled by transfusion of 3 units of plasma. A deficiency of stimulating factor for PGI₂ production in man contributes to microcirculatory thrombosis, stimulation by patient and normal plasma in bovine endothelial cell culture was investigated. There was no significant difference in PGI₂ production between the patient and normals. The findings indicate that rapid plasma PGI₂ degradation leading to shortened PGI₂ survival plays an important role in the pathogenesis of microcirculatory thrombosis. Correction of the abnormality with plasma suggests the deficiency of a normal plasma factor which protects PGI₂ from rapid degradation.