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CARDIOPULMONARY RESPONSE TO SHOCK

ANNUAL PROGRESS REPORT

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Our major hypothesis that clinical events such as endotoxemia and ischemia which could lead to shock stimulate platelet and white blood cell (WBC) secretions which modify cardiopulmonary function has undergone further scrutiny. Particular attention has been paid to the role of arachidonic acid derivatives. Several common events have been found which stimulate the production of Tx such as exposure of blood to foreign surfaces, positive end-expiratory pressure ventilation and pulmonary embolism. The release of TxA2 is associated with the

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formation of a circulating substance which causes a decrease in contractility and abnormalities in myocardial ATPase. Prostacyclin (PGI_2) has been found to be produced in large quantity following surgical trauma. Under these circumstances, endogenous PGI_2 which is formed, increases cardiac output and dilates the systemic vasculature. Further, an infusion of PGI_2 in an experimental setting of severe cardiac depression induced by endotoxemia leads to rapid improvement of cardiac function. Unfortunately, PGI_2 also has adverse effects and may paradoxically stimulate the production of TxA_2 in settings where blood is exposed to an artificial surface.

The problem of permeability in shock states is documented and has been studied in several experimental preparations. It has been found that TxA_2 is centrally involved in the edema of acid aspiration, complement activation and burns. Leukotrienes are also of importance in the biochemical sequence which leads to capillary damage. We have also evaluated the vasoactive agent serotonin (5HT) as a potential culprit in the induction of respiratory failure without pulmonary edema. It was found that platelet entrapment in the lungs with 5HT release can account for the increase in pulmonary vascular resistance, bronchoconstriction and hypoxia noted in acute respiratory failure prior to edema formation.

SUMMARY

The experimental protocols were designed to test the hypotheses that circulating agents were responsible for initiating and perpetuating the adult respiratory distress syndrome. The experimental findings substantiated this thesis and showed that platelet serotonin was responsible for the early bronchospasm, decrease in lung air volumes and hypoxia as well as the increase in pulmonary vascular resistance. Secondly, the data showed that white blood cell recruitment and activation accentuated and generalized the lung injury. The white cell events occured late in the course of respiratory failure. Therapeutic measures directed at reversal of serotonin activity and white blood cell chemotaxis were considered of potential clinical value.

FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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A. Thromboxane (Tx) Mediation of Cardiovascular Instability

Events which lead to shock such as endotoxemia and severe ischemia are thought to stimulate the synthesis and release of Tx, which in turn lead to alterations in cardio-vascular function. It is the latter hypothesis which is the focus of this study, that is the adverse effects of Tx synthesis in cardiodynamics.

1. Prostanoid release and cardiac depression during pressure breathing (1)

Our initial studies did not uniquely identify which prostanoid was involved with hemodynamic instability during lung perfusion. Since we knew that positive end-expiratory pressure (PEEP) led to falls in both mean arterial blood pressure (MAP) and cardiac output (CO) we first tested the hypothesis that prostanoids are important mediators of these events. A support dog was used for ex-vivo perfusion of an isolated left lung lobe (LLL) at a fixed flow. In group I (n = 10) an isolated, isovolumetrically contracting dog heart was placed in circuit between the support dog and LLL. Indomethacin, 5 mg/kg was used to pretreat the support dogs and LLL donors of group II (n = 9); support dogs of group III (n = 5); and LLL donors of group IV (n = 4). This cyclo-oxygenase inhibitor was not used in groups I or V (n = 14). These last two groups were similiar except that a heart was not included in the circuit of group V. In group V, lobe perfusion during simple inspiratory mechanical ventilation led to a fall in support dog MAP from 141 ± 3 mm Hg (x ± SD) to 118 ± 5 mm Hg ($p < 0.01$), and CO from 4.0 ± 0.9 L/min to 2.8 ± 0.8 L/min ($p < 0.01$). Application of PEEP further reduced MAP and CO ($p < 0.01$). In the perfused isolated hearts of group I, Starling curves were shifted downward during PEEP, at five of six left ventricular volumes tested. In group II and III, MAP and CO were unchanged with mechanical ventilation or PEEP and were higher than group I or V, ($p < 0.05$). Radioimmunoassay of the stable degradation products of prostacyclin (PGI_2) and TxA_2 demonstrated low concentrations of these prostanoids in support dogs of group III compared with group V ($p < 0.05$). Blocking the LLL donor dog (group IV) produced hemodynamic results and prostanoid concentrations intermediate between groups I and V. The results show that mechanical ventilation and PEEP can cause a circulating agent(s) to be released which results in a decline in MAP and CO. This is prevented with indomethacin.

2. PEEP, TxA_2 synthesis and decreased contractility (2,3)

PEEP plasmas taken from dogs pretreated with indomethacin (5 mg/kg), aspirin (200 mg/kg), or imidiazole (25 $mg \cdot kg^{-1} \cdot h^{-1}$) were tested by use of an isolated isometrically contracting rat papillary muscle bioassay. The PEEP plasma of untreated control dogs resulted in a depression of the peak developed tension (DTmax) from 5.45 ± 0.78 to 4.82 ± 0.72 g ($p < 0.001$). PEEP plasma from any of the pretreated dogs did not show depression in DTmax. PEEP increased 6-keto prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$, stable metabolite of PGI_2) levels from 0.076 to 0.130 ng/ml ($p < 0.01$) and increased thromboxane B_2 (TxB_2, stable metabolite of TxA_2) levels from 0.088 to 0.211 ng/ml ($p < 0.05$). TxB_2 production was inhibited in both pretreated groups, but 6-keto $PGF_{1\alpha}$ was unchanged in the imidazole group ($p < 0.01$). The in-vitro addition of indomethacin, aspirin, imidazole, or PGI_2 did not cause a depression of DTmax, and even at 1 ng/ml, authentic TxB_2 caused only minimal DTmax depression. Hence, it is unlikely that TxB_2 is the direct causative agent. In addition, PEEP plasma from an isolated perfused lung lobe did not reduce DTmax. These results suggest that prostaglandins are related to

the negative inotropic agent(s) induced by PEEP and that thromboxanes are indirect mediators.

3. Mechanism of decreased contractility with PEEP (4)

This study evaluated the nature of the circulating negative inotropic agent with respect to its action on the coupling of myocardial energy production and contraction. PEEP plama was found to depress Ca^{++}-ATPase activity ($p < 0.025$) when uncubated in our newly developed O_2 consumption chamber (5) with cardiac subfractions obtained from dog and rat myofibrils, sarcolema, and sarcoplasmic reticulum. The miniaturized chamber with a volume of 0.6 ml allowed air bubbles to be easily purged, and temperature rapidly equilibrated. No change in Mg^{++}-ATPase activity was observed. The declines in Ca^{++}-ATPase activity correlate significantly with decrease in left ventricular stroke work, stroke volume, and CO during PEEP treatment. The decrease in Ca^{++}-ATPase with PEEP plasma also correlated with decrease in developed tension of a rat papillary muscle bathed with PEEP plasma. There were no changes in CO in animals who were simply anesthetized; plasma from these animals did not alter developed tension or ATPase. These observations suggest that PEEP plasma and serum contain a negative inotropic agent(s) that may reduce contractility by Ca^{++}-ATPase inhibition.

4. Pulmonary embolism and negative inotropism (6,7)

Pulmonary emboli may impair myocardial performance, causing declines in cardiac index (CI) and right and left ventricular stroke work (LVSW) because of mechanical events. We postulate that embolism also leads to the generation of a humoral factor(s) that may reduce cardiac contractility. Eleven mongrel dogs were infused with 0.5 gm/kg clot. Decreases in CI and LVSW were observed 1 h after embolization. The stable hydrolysis products of PGI_2 and TxA_2 increased within 30 min ($p < 0.005$, $P < 0.001$) and then decreased. These changes did not correlate with the declines in CI or LVSW. Plasma from embolized animals used to bathe an isolated rat papillary muscle reduced developed tension (Tpd) ($p < 0.01$) and decreased calcium ATPase (Ca^{++}-ATPase) activity of a myofibril preparation ($p < 0.001$) obtained from rat cardiac muscle. The correlation between the reduction of Tpd and myofibril Ca^{++}-ATPase was also related to the decreased in cardiac index (CI) ($r = 0.59$, $p < 0.001$) and left ventricular stroke work (LVSW) ($r = 0.57$, $p < 0.001$). Five animals pretreated with indomethacin prior to embolization had no decrease in LVSW as compared with controls ($p < 0.001$). Postembolism plasma did not depress papillary muscle Tpd and did not lower Ca^{++}-ATPase activity of myofibrils. Anesthesia itself did not alter cardiopulmonary function. These results suggest that pulmonary emboli cause the release of a negative inotropic agent(s) into plasma that affects energy availability in the heart and reduces contractility. The production of this agent(s) is inhibited with indomethacin pretreatment.

A second study examined the role of Tx after experimental embolism induced with 0.5 g/kg autologous clot in four groups of five dogs: (a) untreated embolized controls; (b) pretreatment with the Tx synthetase inhibitor, imidazole 25 mg/kg·h i.v., starting 30 minutes before embolization; (c) pretreatment with the cyclooxygenase inhibitor indomethacin, 5 mg/kg, 12 h per os and 1 mg/kg, 1 h i.v. before the experiment; (d) treatment with PGI_2 100 ng/kg·min i.v. for 1 h, 1 h after embolization. Within 30 min, embolization led to increases of 6-keto-$PGF_{1\alpha}$, the stable hydolysis product of PGI_2, from 0.11 ± 0.08 ng/ml (mean ± SD) to 0.33 ± 0.10 ng/ml ($p < 0.005$) and TxB_2, the stable product of TxA_2, from 0.01 ± 0.04 ng/ml to 0.38 ± 0.06 ng/ml ($p < 0.001$). Increases were observed in

total dead space (V_D/V_T) from 0.46 ± 0.03 to 0.61 ± 0.08 ($p < 0.025$), physiologic shunting (Q_S/Q_T) from 16 ± 4% to 38 ± 9% ($p < 0.01$), pulmonary vascular resistance (PVR) from 2.27 ± 0.59 mm Hg·min/liter to 9.21 ± 1.90 mm Hg·min/liter ($p < 0.005$) and mean pulmonary arterial pressure (MPAP) from 14 ± 6 mm Hg to 34 ± 1 mm Hg ($p < 0.001$). CI fell from 139 ± 11 ml/kg·min to 95 ± 17 ml/kg·min in 4 h ($p < 0.025$). Imidazole pretreatment prevented a rise of TxB_2, but not 6-keto-$PGF_{1\alpha}$; indomethacin blocked both. Both agents maintained V_D/V_T at base line and limited increases in Q_S/Q_T and PVR. CI was higher after imidazole pretreatment compared with controls ($p < 0.025$). Indomethacin led to intermediate levels of CI. PGI_2 lowered TxB_2 ($p < 0.025$), V_D/V_T ($p < 0.025$) Q_S/Q_T ($p < 0.025$) and PVR ($p < 0.05$) within 30 min. During PGI_2 infusion, CI was higher than controls. Concentrations of TxB_2 correlated with V_D/V_T, $r = 0.69$ ($p < 0.001$). Treatment of three dogs with the imidazole derivative ketoconazole, 10 mg/kg IV, 30 min after 0.75 g/kg autologous clot resulted in a lowering of V_D/V_T but no other improvement of cardiopulmonary function. These results show that a number of cardiopulmonary abnormalities induced by pulmonary embolism are related directly or indirectly to platelet secretions and that V_D/V_T is closely allied to TxA_2 levels.

B. Prostacyclin Favorably Modifies Cardio-vascular Function

1. Reversal of negative inotropism after experimental endotoxemia (8)

A previous study of endotoxemia in dogs demonstrated that exogenous PGI_2, normally a product of vascular endothelium , restored cardiac index CI to normal and improved survival. To account for these results, a study designed to test whether PGI_2 would alter isolated rat or dog cardiac mitochondrial function following incubation with plasma from endotoxemic animals was undertaken. A group of five animals served as anesthetized controls. A second group of seven mongrel dogs was given 1.75 mg/kg E. coli endotoxin and observed for 5 h without treatment. Anesthesia did not alter cardiopulmonary function; whereas, 30 min after endotoxin, CI decreased from 148 ± 25 (x ± SD) to 111 ± 12 ml/kg·min ($p < 0.05$) and further decreased to 89 ± 20 ml/kg·min after 4 h. Dog plasma obtained 2 h to 5 h after endotoxin infusion, incubated with rat or dog myocardial mitochondria: decreased succinate dihyrogenase (SDH) activity ($p < 0.05$); and depressed mitochondrial respiration in the presence of the substrate succinate and ADP from 180 Natoms to 87 Natoms O_2/mg·protein·min ($p < 0.05$). There was no change in O_2 consumption (V_{O2}) when substrate alone was present, nor did plasma alter the amount of ADP phosphorylation as a function of V_{O2}. A third group of animals ($n = 7$), 30 min after administration of 1.75 ng/kg endotoxin, was treated with 100 ng/kg·min PGI_2 for 3 h. PGI_2 infusion in this group prevented the fall of CI. Plasma obtained during and after PGI_2 infusion did not decrease mitochondrial SDH activity which remained higher than controls ($p < 0.001$); mitochondrial respiration was also not altered. A correlation was observed between CI and SDH activity ($r = 0.58$, $p < 0.001$) and between CI and mitochondrial respiration ($r = 0.61$, $p < 0.001$). In PGI_2 treated dogs, cardiac mitochondria were functionally and structurally normal in contrast to the depression and disruption produced by endotoxin, as observed by enzymatic assay as well as electron microscopy. These results suggest that endotoxemia depresses cardiac mitochondrial respiration, an event related to the fall of CI. In contrast, cardiac function and mitochondrial respiration are maintained with PGI_2 treatment.

2. Cardiovascular effects of endogenous PGI_2 (9)

Wounding initiates local hemostasis and a systemic reaction which we hypothesize protects against intravascular coagulopathy. This study examines release and systemic effects of PGI_2 and Tx in response to surgical trauma. In 10 dogs laparotomy or thoracotomy was followed by a rise in arterial concentrations of 6-keto-$PGF_{1\alpha}$, from 0.02 to 0.26 ng/ml ($p < 0.005$), a value higher than pulmonary arterial levels ($p < 0.05$). TxB_2 was unchanged. CO rose from 3.46 to 4.06 L/min ($p < 0.05$) whereas 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_1 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. These data show that surgical trauma stimulates the lungs to secrete PGI_2, which has systemic cardiovascular and hematologic consequences.

C. Adverse Effects of PGI_2

1. Cardiopulmonary bypass (10,11)

Before proposing patient trials of the use of PGI_2 in cardiopulmonary failure, the response of PGI_2 in settings of platelet and/or WBC activation were studied. PGI_2 was infused into ten dogs during cardiopulmonary bypass (CPB) in an attempt to minimize thrombocytopenia and platelet dysfunction. The animals were anesthetized, placed on mechanical ventilation and underwent thoracotomy. After heparinization with 300 u/kg, animals were assigned to control (n = 5) or PGI_2 treated groups (n = 5). Thoracotomy and then CPB decreased platelet numbers to below $30,000/mm^3$ ($p < 0.05$) and fibrinogen to less than 150 mg/dl ($p < 0.05$). PGI_2 at 100 ng/kg·min was infused for the 2 h period of CPB. PGI_2 infusion did not prevent these changes, but did prevent platelet serotonin (5-hydroxytryptamine, 5HT) release. In the control group after CPB, platelet 5HT fell from the baseline value of 1.11 $ug/10^9$ to 0.35 $ug/10^9$ platelets ($p < 0.05$). In contrast, PGI_2 treatment resulted in a 5HT increase to 2.27 $ug/10^9$ platelets ($p < 0.05$). TxB_2 concentrations of platelets and plasma rose during CPB ($p < 0.05$). Surprisingly, PGI_2 infusion accentuated this rise in platelet and plasma TxB_2 ($p < 0.05$). These data indicate that during CPB, an infusion of PGI_2: 1) does not prevent thrombocytopenia; 2) increases platelet 5HT uptake despite, 3) an associated rise in platelet and plasma TxB_2.

2. In-vitro lung perfusion (12)

To further test the hypothesis that PGI_2 might preserve circulating platelets which had been activated, PGI_2 was added to the perfusate of an isolated perfused canine lung lobe. This setting is known to activate platelets. Platelet count in heparinized controls (n = 7) fell to $44,500/mm^3$ lower than $136,000/mm^3$ seen with 1 ug/min PGI_2 (n = 7) ($p < 0.005$). Surprisingly, with PGI_2 TxB_2 rose from 0.07 to 0.25 ng/ml, a level higher than controls ($p < 0.005$). PGI_2 in comparison to controls also led to higher pulmonary arterial pressure, increase in lobe weight, increase in wet/dry weight ratio, increase in physiologic shunt and decrease in compliance ($p < 0.005$). Further, with PGI_2 there was hemorrhagic edema. Infusion of the PGI_2 hydrolysis product 6-keto-$PGF_{1\alpha}$ (n = 2) led to results similiar to controls. Adverse PGI_2 effects were eliminated by pretreatment with ibuprofen 12.5 mg/kg (n = 5) or an antiplatelet antibody (n = 6). Infusion of PGI_2 into a lobar pulmonary artery of an intact animal was without effect on the lung (n = 2). These results show that

PGI_2 prevents platelet loss from the circulation following activation, but no platelet synthesis of TxA_2. This vasoconstrictor is likely to be the cause of pulmonary hypertension and hemorrhagic pulmonary edema.

D. Permeability Edema

1. Modification of the inflammatory response to acid aspiration with ibuprofen (13,14,15)

Acid injury of the lungs provokes thrombocytopenia and an inflammatory infiltrate that appears to be influenced by PGI_2 and TxA_2. Previous experiments with acid aspiration demonstrated that an infusion of the cyclo-oxygenase inhibitor ibuprofen, alone or in combination with PGI_2, is an effective therapy to restore cardiopulmonary function and decrease pulmonary edema. The present study was designed to clarify the significance of PGI_2 and TxA_2 in acid inflammation of the lungs. Within 30 min, acid injury led to a significant increase in platelet lung entrapment; also, there was an increase in plasma TxB_2, apparently due to platelet TxA_2 production. White blood cell (WBC) synthesis of TxB_2 increased 2 h after acid injury; at this time WBC were entrapped by the lungs. Starting 1 h after aspiration, continuous infusion of PGI_2 for 1 h at 100 ng/kg·min had no effect on thrombocytopenia or WBC sequestration in the lungs. Furthermore, PGI_2 infusion enhanced platelet production of TxB_2 and increased plasma TxB_2 levels. A bolus ibuprofen infusion of 12.5 mg/kg, 1 h after aspiration, inhibited the generation of TxB_2 by platelets and WBC, lowered plasma TxB_2 levels, and although failing to restore circulating platelet counts, prevented WBC sequestration and edema in the lungs. The combination of an ibuprofen bolus (12.5 mg/kg) with a PGI_2 infusion, (10 ng/kg·min) reduced TxB_2 production, restored the number of circulating platelets, stimulated leukocytosis, reversed platelet entrapment and prevented WBC sequestration by the lungs. Evidence of inflammation and pulmonary edema as determined by histological examination was also minimized by ibuprofen alone or in combination with PGI_2. These data indicate that the edema of acid injury is in large part mediated by WBC aggregation and sequestration by the lungs. Secretory activity following platelet and leukocyte adhesion/aggregation appears to be accentuated by circulating PGI_2.

2. Thromboxanes as mediators of edema after aspiration (16)

This second experimental study of aspiration pneumonia tests the hypothesis that the imidazole derivative ketoconazole, a known Tx synthetase inhibitor, will prevent pulmonary leukostasis, hence modifying cardiopulmonary dysfunction. Anesthetized dogs (n = 12) underwent acid aspiration (0.1 N HCl, 3 ml/kg) and were monitored for the next 4 h. After 30 min: CI fell from 121 ml to 104 ml/min·kg ($p < 0.01$); MAP declined from 143 mm Hg to 120 mm Hg ($p < 0.05$); Q_S/Q_T rose from 12% to 26% ($p < 0.01$) and V_D/V_T measured with arterial and end tidal CO_2 rose from 3% to 14% ($p < 0.01$). After 2 h untreated controls (n = 6) entrapped WBC in their lungs (measured by A-V difference). Ketoconazole was given by IV infusion 10 mg/kg·h for 2 h starting 1 h after aspiration (n = 6). There were improvements in all aspects of cardiopulmonary function: CI rose from 106 ml to 138 ml/min·kg ($p < 0.01$) 30 min after therapy was started and remained higher than controls for the next 3 h ($p < 0.05$); MAP was maintained in contrast to controls whose levels were below baseline; Q_S/Q_T rose slowly, but remained 7% to 9% lower than controls ($p < 0.05$); V_D/V_T decreased from 13% to 7% ($p < 0.05$) 30 min after the start of therapy and thereafter remained below controls ($p < 0.05$). After 4 h, untreated animals had drained 127 ml edema fluid via the

endotracheal tube in contrast to 27 ml in the treated group ($p < 0.01$). The results show that Tx directly or indirectly modify the inflammatory response to acid aspiration, and that Tx synthetase inhibitors have beneficial effects on cardiopulmonary function.

3. Inhibition of leukocyte mediated edema with imidazole (17)

Acute respiratory failure (ARF) with permeability edema and increased Q_S/Q_T occurs after complement activation. WBC aggregate, become entrapped in the lungs and release vasotoxic agents. This study of 31 sheep infused with zymosan activated plasma (ZAP) tests the hypothesis that TxA_2 is an intermediate in complement induced ARF. Group I animals (n = 11) were untreated controls. An imidazole infusion, 25 mg/kg·h was started 1 h before a ZAP infusion in group II (n = 10). PGI_2 was given to group III sheep (n = 10) in a dose of 100 ng/kg·min 30 min before the ZAP infusion. Within 5 min, ZAP led to a: fall in the WBC count to 2,900/mm^3 ($p < 0.001$); rise in plasma TxB_2 concentration from 14 to 246 pg/ml ($p < 0.001$); rise in Q_S/Q_T from 13% to 31% ($p < 0.01$); rise in MPAP from 17 to 43 mm Hg. Both imidazole and PGI_2 prevented the increase in TxB_2 and Q_S/Q_T and limited the increase in MPAP to 25 mm Hg and 30 mm Hg respectively, values below untreated controls ($p < 0.05$). Imidazole, but not PGI_2 prevented the increase in lymph flow which in controls increased from 2.2 to 6.0 ml/30 min ($p < 0.01$). The high lymph concentrations of TxA_2 suggests a pulmonary site of production and its bronchoconstrictive action may account for the increase in Q_S/Q_T. However, TxA_2 is only partially responsible for the pulmonary hypertension and apparently unrelated to changes in permeability. The protective action of infused imidazole against increased permeability appears to be independent of its inhibition of Tx synthetase.

4. Role of thromboxanes and leukotrienes (LT) in burn edema (18)

Edema following burn injury is thought to relate to WBC invasion and secretion of permeability factors related to arachidonic acid metabolism. This study was designed to test the ability of TxA_2 synthetase inhibitors and LT receptor antagonist to modify burn edema. Four standard 2 cm^2 burns (100°C for 2 s) were produced on the backs of 400 g to 450 g rats at intervals of ½ h to 1 h. Evans blue dye (5 mg iv) was injected ½ h prior to sacrifice, at which time the burns were 3 h, 2 h, 1 h and ½ h old. In controls (n = 9) water content of unburnt skin was 67.6 ± 0.4% (x ± SE). This rose to 73.2 ± 0.9% ½ h after burning; 71.7 ± 0.9% after 1 h; 71.0 ± 0.8% after 2 h; and 77.7 ± 0.6% after 3 h. Imidazole (25 mg/kg iv bolus) (n = 8) given 1½ h and ½ h after the "3h" and "2h" burns was without effect; however, compared to untreated controls it did reduce blue dye accumulation and edema in the subsequent burns, inflicted ½ h and 1 h after drug administration ($p < 0.05$). Another Tx inhibitor, a pyridine derivative, (OKY 1555, 2 mg/kg iv bolus) (n = 11) was given at the same time as imidazole. It not only prevented edema formation in the skin burned 1 h after the drug was administered (66.4 ± 1.4%, $p < 0.05$), but compared to untreated controls reduced edema to 71.0 ± 0.5% and 68.9 ± 0.7% in the skin burned 1 h, and ½ h before drug therapy ($p < 0.05$). All burns showed reduced bluing. The LT antagonist (FPL 55712, 1.5 mg/kg iv bolus) (n = 5) compared to untreated controls reduced edema and bluing of the skin burned 1 h before therapy (72.8 ± 0.9%, $p < 0.05$) and prevented edema of skin burned after therapy (69.6 ± 1.4%, $p < 0.05$). These results indicate that TxA_2 inhibition can both prevent and treat burn permeability edema, an event mediated at least in part by LT.

E. Cardiopulmonary Activity of Serotonin

1. Vaso and brochoconstrictive actions during embolization (19)

The smooth muscle constricting, platelet amine, 5-HT is theorized to play an important role in the cardiopulmonary dysfunction with accompanies embolization. The present study was designed to examine this hypothesis. Autologous clot, 0.75 g/kg, was injected IV into 14 dogs. After 30 min, one-half of the animals were randomly assigned to the treatment group and received a bolus infusion of 0.15 mg/kg ketanserin, a quinazoline derivative known to be a selective 5-HT receptor antagonist. Five min after embolization there were increases in: MPAP from 12 mm to 48 mm Hg ($p < 0.001$); PVR from 2.2 mm to 12.2 mm Hg·min/L ($p < 0.001$); Q_S/Q_T from 12% to 44% ($p < 0.01$); and V_D/V_T, calculated from end tidal and arterial PCO_2, from 8% to 39% ($p < 0.001$). Within 15 min platelet counts decreased from 186,000/mm^3 to 134,800/mm^3 ($p < 0.05$); 5-HT contained in circulating platelets fell from 1.71 ug/ to 1.44 ug/10^9 platelets ($p < 0.05$). Five min after ketanserin: MPAP declined to 27 mm Hg and was lower than the control value of 41 mm Hg ($p < 0.05$); PVR decreased to 6.2 mm Hg·min/L, lower than 12 mm Hg·min/L in controls ($p < 0.01$); Q_S/Q_T fell to 26% in contrast to 47% in controls ($p < 0.05$); and V_D/V_T declined moderately to 32% ($p < 0.05$), although this value was not different from 38% in control animals. Cardiopulmonary function continued to improve in treated animals until termination of the experiment at 4 h when pulmonary angiograms and perfusion scans demonstrated vascular recruitment compared to untreated embolized control dogs. These data demonstrate that the cardiopulmonary consequences of experimental embolization are primarily determined by the vaso and bronchoconstrictive actions of 5-HT.

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