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Research Article

Humoral factors released from platelets during pulmonary embolism may be the cause of several attendant cardiopulmonary abnormalities. This study examines the role of thromboxanes (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 \cdot h i.v., starting 30 min 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 prostacyclin (PGI₂) 100 ng/kg \cdot min i.v. for 1 h, 1 h after embolization. Within 30 min, embolization led to increases of 6-keto-PGF_{1α}, the stable hydrolysis product of PGL, from 0.11±0.08 ng/ml (mean±SD) to 0.33±0.10 ng/ml (*P* < 0.005) and TxB₂, the stable product of TxA₂, from 0.10±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 from 14±6 mm Hg to 34±1 mm Hg (*P* < 0.001). Cardiac index (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 [...]



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Thromboxane Mediation of Cardiopulmonary Effects of Embolism

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ABSTRACT Humoral factors released from platelets during pulmonary embolism may be the cause of several attendant cardiopulmonary abnormalities. This study examines the role of thromboxanes (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 \cdot h i.v., starting 30 min 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 prostacyclin (PGI₂) 100 $\eta g/kg$. min i.v. for 1 h, 1 h after embolization. Within 30 min, embolization led to increases of 6-keto-PGF_{1 α}, the stable hydrolysis product of PGI₂, from $0.11\pm0.08 \eta g/ml$ (mean \pm SD) to 0.33 \pm 0.10 η g/ml (P < 0.005) and TxB₂, the stable product of TxA₂, from 0.10 \pm 0.04 η g/ml to $0.38\pm0.06 \eta g/ml$ (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 (\dot{Q}_s/\dot{Q}_T) from $16\pm 4\%$ to $38\pm 9\%$ (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 from 14±6 mm Hg to $34\pm1 \text{ mm Hg}$ (P < 0.001). Cardiac index (CI) fell from $139\pm11 \text{ ml/kg} \cdot \text{min to } 95\pm17 \text{ ml/kg} \cdot \text{min in 4 h}$ (P < 0.025). Imidazole pretreatment prevented a rise of TxB₂, but not 6-keto-PGF_{1 α}; indomethacin blocked both. Both agents maintained V_D/V_T at base line and limited increases in \dot{Q}_s/\dot{Q}_T and PVR. CI was higher after imidazole pretreatment compared with controls (P < 0.025). Indomethacin led to intermediate levels of CI. PGI₂ lowered TxB_2 (P < 0.025), V_D/V_T (P < 0.025), \dot{Q}_s/\dot{Q}_T (P < 0.025) and PVR (P < 0.05) within 30 min. During PGI₂ infusion, CI was higher than controls. Concentrations of TxB₂ correlated with V_D/V_T , r = 0.79 and \dot{Q}_s/\dot{Q}_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 physiologic dead space, 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 TxA₂ levels.

INTRODUCTION

Pulmonary embolism produces cardiopulmonary dysfunction that may result directly from mechanical obstruction of the pulmonary vasculature as well as indirectly by humoral factors (1). It is believed that platelet interaction with a clot leads to platelet release reaction, which may be responsible for several of the attendant cardiopulmonary abnormalities such as pulmonary hypertension and increase of venous admixture (2, 3). Platelet aggregation is inhibited by prostacyclin (PGI₂),¹ which is largely produced by the vascular wall (4), whereas thromboxane $(Tx) A_2$, a potent proaggregator, is produced by platelets (5). The ratio of circulating PGI₂:TxA₂ is likely to be significant in controlling platelet-endothelial interaction (5), and therefore, aggregation and release of vaso- and bronchoactive agents. The present study was designed to

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¹ Abbreviations used in this paper: CI, cardiac index; CO, cardiac output; 5-HT, 5-hydroxytryptamine; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PGI₂, prostacyclin; PVR, pulmonary vascular resistance; Tx, thromboxane.

evaluate the cardiopulmonary functional abnormalities after embolism, moderated by PGI₂ and TxA₂.

METHODS

20 mongrel dogs of either sex weighing 17-34 kg were anesthetized with pentobarbital sodium 15 mg/kg i.v. and paralyzed with pancuronium bromide, 2 mg i.v. The dogs were intubated and ventilated with room air at a tidal volume of 15 ml/kg and rate of 12 cycles/min. The animals were placed supine and catheters positioned in the right atrium and femoral artery via a groin cutdown. A 7 Fr thermistortipped, pulmonary arterial catheter (Instrumentation Laboratory, Lexington, MA) was introduced through the external jugular vein. Strain gauge transducers were used to measure the following pressures: mean arterial (MAP), mean pulmonary arterial (MPAP), and pulmonary arterial wedge (PAWP). Cardiac output (CO) determined by thermodilution was performed in triplicate and divided by body weight to obtain cardiac index (CI). Pulmonary vascular resistance (PVR) measured in millimeters of mercury per minute per liter was obtained from the ratio MPAP-PAWP/CO

Blood gases, pH, oxygen saturation, and hemoglobin of arterial and mixed venous blood were measured with Clark and Severinghaus electrodes and by spectrophotometry using extinction coefficients specific for dog blood (Instrumentation Laboratory, models 813 and 282). The PCO₂ of mixed expired gas was also measured. Physiologic shunting (\dot{Q}_s/\dot{Q}_T) was calculated from the Berggren equation (6)

$$\frac{\dot{Q}_{s}}{\dot{Q}_{T}} = \frac{C_{c}O_{2} - C_{s}O_{2}}{C_{c}O_{2} - C_{v}O_{2}} \times 100,$$
[1]

where C_aO_2 and C_vO_2 are oxygen contents in arterial and mixed venous blood. Capillary oxygen content, C_cO_2 , was derived from the alveolar gas equation with the assumption that the respiratory quotient was one. \dot{Q}_T is blood flow exiting the lung with the same oxygen content as mixed venous blood. Dead space, including anatomic and physiologic components, (V_D/V_T) was derived from a modified version of the Bohr equation

$$\frac{V_{\rm D}}{V_{\rm T}} = \frac{P_{\rm a} CO_2 - P_{\rm E} CO_2}{P_{\rm a} CO_2},$$
[2]

where the subscripts "a" and "E" indicate arterial blood and mixed expired gas. Platelets were counted in arterial blood by means of phase microscopy.

Prostaglandin assay. TxB_2 and 6-keto-PGF_{1a}, the stable derivatives of TxA_2 and PGI₂, respectively, were measured by radioimmunoassay (7–9). Arterial blood was collected in cooled plastic syringes containing heparin. The blood was immediately centrifuged at 1,500 g for 20 min at 4°C. Plasma was separated and stored at -20°C until testing.

Specific rabbit Tx and PG antisera were stored in 0.5-ml vol at -80° C until use when the antiserum was thawed. The Tx antiserum was diluted 1/10,000, and the PG antiserum was diluted 1/4,000 using isogeltris composed of 0.1% gelatin, 0.9% NaCl in 0.1 M tris (hydroxymethyl) amino methane-HCl (Tris-HCl) (Sigma Chemical Co., St. Louis, MO) buffer (pH 7.3). Test plasma (0.2 ml), dilute rabbit Tx or PG antisera (0.2 ml), and [³H]TxB₂ or [³H]6-keto-PGF_{1α} tracer (New England Nuclear, Boston, MA) were incubated for 1 h at 37°C. The added tracer (0.1 ml) had an activity of 6,000-7,000 cpm. A control assay was run where isogeltris (0.2 ml) was substituted for test plasma. A blank assay was also used where isogeltris (0.2 ml), rabbit plasma or serum

(0.1 ml, mixed 9 to 1 with 0.1 M ethylene diamine tetraacetic acid) were incubated with Tx or PG tracer (0.1 ml). After 1 h of incubation, the reaction was stopped by the addition of rabbit plasma (0.1 ml) for the TxB₂, or rabbit serum (0.1 ml) for the 6-keto-PGF_{1 α} assay. Goat anti-rabbit gamma globulin (0.1 ml) (Arnel Products Co., Brooklyn, NY) was added and precipitation allowed to proceed overnight. Then 0.1 M ethylene diamine tetraacetic acid (0.5 ml) was added. The precipitate was collected by centrifugation at 1,200 g for 20 min, dissolved in 0.1 ml Protosol and mixed with 2 ml scintillation fluid (Biofluor, New England Nuclear). The scintillation counts from test plasma, control and blank assays were used to calculate percent inhibition from the formula

% inhibition =
$$1 - \left(\frac{\text{test-blank}}{\text{control-blank}}\right) \times 100.$$
 [3]

The acceptable inhibitory range was between 15 and 85%. The lower limit permitted the minimum detectable amount of TxB_2 and 6-keto-PGF_{1 α} to be 6 or 10 pg, respectively.

Studies were performed to assess the serologic specificities of the antisera used in the radioimmunoassays. In the TxB₂ system 28 pg TxB₂ inhibited homologous binding by 50%; PGD₂, PGE₂, 13,14-dihydro-15,keto-PGF₂, PGF₂, and 6keto-PGF₁ crossreacted <1%. In the 6-keto-PGF₁ system, 140 pg 6-keto-PGF₁ inhibited homologous binding by 50%; 6-keto-PGE₁ crossreacted 3% while PGD₂, PGE₂, 13,14dihydro-15-keto-PGE₂, PGF₁, PGF₂, and TxB₂ crossreacted <1%.

Embolization. Autologous blood was clotted with thrombin 10 U/ml blood. The clot was cut into 3- to 5-mm cubes, washed with saline, and 0.5 g/kg embolized intravenously to the lungs. Previous experience with this preparation using ¹³¹I-fibrinogen to label the clot has shown the disappearance rate of ¹³¹I activity to range between 3.2 and 5.3%/h during the 4-h observation period (10). Pulmonary angiograms at 4 h demonstrated peripheral emboli in all lobes.

Animals were divided into four groups of five dogs in each: (a) untreated embolized controls; (b) pretreatment with the thromboxane synthetase inhibitor, imidazole 25 mg/kg·h i.v., starting 30 min before embolization; (c) pretreatment with the cyclooxygenase inhibitor, indomethacin, 5 mg/kg per os 12 h before the experiment and 1 mg/kg indomethacin i.v. 1 h before embolization; (d) treatment with PGI₂ 1 h after embolization; PGI₂ 100 $\eta g/kg \cdot min$ was infused intravenously for 1 h. The PGI₂ was stabilized in Tris-HCl buffer at a pH of 10. An ice water-jacketed syringe maintained temperature of the infusate at 2 to 3°C. An additional three dogs received a larger mass of clot, 0.75 g/kg. 30 min later an intravenous bolus of the imidazole derivative, ketoconazole, 10 mg/kg was given to observe the effects of reducing TxA₂ concentration in this more extreme setting of cardiopulmonary dysfunction. In unpublished observations of seven dogs this dose of ketoconazole given 1 h after embolization led to a fall in TxB_2 levels to 0.02 $\eta g/ml$ within 30 min. All measurements except V_D/V_T were the same. To eliminate the anatomic component and directly estimate physiologic dead space (V_{D_p}/V_T) , end tidal (ET) CO₂ concentration was measured by infrared analysis (Instrumentation Laboratory, model 200). After converting Co₂ concentration to end tidal PCO2, this value was substituted for PECO₂ in Eq. 2 to obtain V_{D_p}/V_T . Our experience in 18 anesthetized dogs has yielded an average base-line value of 7%.

All data in the table and text are presented as the mean ± 1 SD. The standard error is used in figures. Statistics are based on an analysis of variance, and when differences between groups were found a nonpaired t test was used for intergroup



FIGURE 1 The increase in pulmonary vascular resistance 1 h after embolization was significantly less in imidazole and indomethacin-pretreated dogs (P < 0.005). PGI₂ lowered PVR, but not significantly.

comparisons. Linear regression is used to examine the relationship between variables.

RESULTS

Pulmonary embolization in five control animals caused an increase in MPAP from 14 ± 6 mm Hg to 34 ± 1 mm Hg (P < 0.001) within 30 min. By 2.5 h MPAP had stabilized at 29 ± 4 mm Hg. PVR promptly rose from 2.27 ± 0.59 mm Hg·min/liter to 9.21 ± 1.90 mm Hg· min/liter (P < 0.005, Fig. 1). After 1 h PVR stabilized.

Arterial oxygen tension (PaO_2) fell from 85 ± 4 mm Hg to 69 ± 5 mm Hg (P < 0.01) by 30 min and then increased to 72 ± 7 mm Hg at 4 h. Initially, at 30 min \dot{Q}_S/\dot{Q}_T rose from $16\pm4\%$ to $38\pm9\%$ (P < 0.01, Fig. 2) and V_D/V_T rose from 0.46 ± 0.03 to 0.61 ± 0.08 (P < 0.025, Fig. 3). Thereafter, \dot{Q}_S/\dot{Q}_T and V_D/V_T decreased, and at 4 h were $28\pm8\%$ and 0.57 ± 0.04 , respectively. There were no significant changes in the base-line MAP of 134 mm Hg and PAWP of 7 mm Hg through the 4-h period of observation (Table I). For the first 1 h, CI was unchanged. Thereafter, it decreased and at 4 h was 60% of base line (P < 0.025, Fig. 4).

Platelet counts decreased 30%, 30 min after embolization (P < 0.025) and then remained stable (Table I). There was an increase in 6-keto-PGF_{1α} from $0.11\pm0.08 \eta g/ml$ to $0.33\pm0.01 \eta g/ml$ (P < 0.005, Fig. 5) and TxB₂ from $0.10\pm0.04 \eta g/ml$ to $0.38\pm0.06 \eta g/ml$ (P < 0.001, Fig. 6). Both cyclooxygenase prostanoids then decreased, and at 4 h were $0.18\pm0.09 \eta g/ml$ and $0.14\pm0.06 \eta g/ml$, respectively.

Imidazole infusion blocked the production of TxA_2 . TxB₂ levels did not increase with embolization, while



FIGURE 2 Relative to untreated control animals, the rise in \dot{Q}_s/\dot{Q}_T after imidazole or indomethacin was transient. PGI₂ rapidly restored \dot{Q}_s/\dot{Q}_T to base line.

6-keto-PGF_{1a} rose to values similar to untreated controls. In further contrast to controls, \dot{Q}_{s}/\dot{Q}_{T} rose transiently from 16±2% to 31±6% (P < 0.025) and then returned to base line (Fig. 2); V_{D}/V_{T} remained unchanged through the experiment (Fig. 3); MPAP rose from 20±4 mm Hg to 37±3 mm Hg (P < 0.001), and at 3 h had fallen below control values (P < 0.05); the rise in PVR was less than controls at all time periods (P < 0.05, Fig. 1); and CI was higher than con-



FIGURE 3 Imidazole and indomethacin prevented a rise in V_D/V_T , while PGI₂ rapidly restored this variable to base line. A transient increase in V_D/V_T occurred after cessation of PGI₂.

| | | Hours | | | | | | | | |
|-------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--|--|
| | Base line | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 4.0 | | |
| MAP, mm Hg | | | | | | | | | | |
| Control | 134±15 | 133±9 | 124 ± 14 | 127 ± 11 | 132 ± 14 | 134 ± 17 | 134±16 | 140±16 | | |
| Imidazole | 133 ± 8 | 125 ± 10 | 124 ± 12 | 123 ± 10 | 126 ± 10 | 126 ± 11 | 128 ± 7 | 127±5 | | |
| Indomethacin | 133 ± 5 | 132 ± 14 | 131 ± 13 | 135 ± 12 | 137 ± 11 | 144 ± 12 | 145±16 | 137±18 | | |
| PGI₂ | 138 ± 25 | 140±19 | 129 ± 22 | 96±19° | 97±18° | 137±19 | 141±18 | 142 ± 18 | | |
| MPAP, mm Hg | | | | | | | | | | |
| Control | 14±6 | 34±1 | 31±3 | 33±5 | 30±3 | 29±4 | 29 ± 3 | 29±4 | | |
| Imidazole | 20±4 | 37±3 | 33±2 | 29± 1 | 27 ± 2 | 26±3 | 25±3° | 27±3 | | |
| Indomethacin | 18±4 | 32±6 | 26±3° | 26±6 | 26 ± 4 | 26 ± 6 | 29 ± 5 | 29±6 | | |
| PGI ₂ | 17±2 | 33±4 | 30 ± 2 | 25±2° | 24±4° | 25± 3 | 24±2° | 25±4 | | |
| PAWP, mm Hg | | | | | | | | | | |
| Control | 7±2 | 9±2 | 7±2 | 8±2 | 7±2 | 7±2 | 8±3 | 8±3 | | |
| Imidazole | 9±2 | 10±4 | 10±3 | 10±3 | 10±3 | 10 ± 2 | 11±1 | 11±2 | | |
| Indomethacin | 8±2 | 9±1 | 9±2 | 8±2 | 8±2 | 8±2 | 9±2 | 10±2 | | |
| PGI2 | 8±3 | 9±3 | 8±3 | 8±3 | 6±4 | 8±4 | 8±4 | 8±5 | | |
| Platelets, $\times 10^3/mm^3$ | | | | | | | | | | |
| Control | 212 ± 65 | 151 60 | 151 ± 55 | 135 ± 42 | 135 ± 11 | 131 ± 26 | 150 ± 45 | 150±70 | | |
| Imidazole | 199 ± 56 | 160 40 | 146 ± 54 | 142 ± 59 | 131±49 | 147±49 | 154±40 | 139±36 | | |
| Indomethacin | 186 ± 48 | 110 27 | 122 ± 50 | 115±65 | 117±66 | 102 ± 36 | 103 ± 53 | 110±64 | | |
| PGI ₂ | 208±68 | 145 54 | 144 ± 40 | 131 ± 38 | 132 ± 47 | 149±51 | 153 ± 80 | 149±58 | | |

 TABLE I

 Cardiovascular and Platelet Response to Embol

P < 0.05 compared with controls.

trols (P < 0.05, Fig. 4). Platelets decreased after embolization in a manner similar to controls (P < 0.05, Table I).

much lower than that of other groups (P < 0.001). After embolization, the concentration did not change (Fig. 4). TxB₂ concentration was also lower than that

In indomethacin-pretreated dogs, the base-line value of 6-keto-PGF_{1 α} was 0.008±0.001 $\eta g/ml$, which was





FIGURE 4 Cardiac index gradually decreased after embolization, an event prevented by imidazole and less well by indomethacin. After cessation of PGI₂, the CI approached control values.

FIGURE 5 Embolization caused a rise in concentrations of 6-keto-PGF_{1a}, which was prevented with the cyclooxygenase inhibitor indomethacin, but not the thromboxane synthetase inhibitor imidazole. Infusion of PGI₂ led to a 10-fold increase in concentrations of 6-keto-PGF_{1a}.



FIGURE 6 Imidazole given just after the first sample was drawn (30 min prior to embolization) and indomethacin given 12 and 1 h before the experiment inhibited the rise in TxB₂, while an infusion of PGI₂ led to its rapid lowering. 30 min after cessation of PGI₂, there was a significant increase in TxB₂ (P < 0.05).

of other groups (P < 0.005, Fig. 5). After embolization, levels of TxB₂ rose from 0.014 ± 0.003 $\eta g/ml$ to 0.023 ± 0.005 $\eta g/ml$ (P < 0.05), which was still significantly below controls. Embolization led to an insignificant decrease of PaO₂; after 3 h, PaO₂ had fallen to 75±5 mm Hg (P < 0.025). \dot{Q}_S/\dot{Q}_T and V_D/V_T were not significantly changed by embolization (Figs. 2, 3). The increase in MPAP was similar to controls. PVR rose; at 1 h it was significantly lower than controls and reached equivalency at 3 h. CI was well maintained within the first 2 h, but then decreased in the next 2 h to a value 79% of base line (Fig. 4). Platelets decreased in the same fashion as controls.

PGI₂ infusion was started 1 h after embolization. The plasma concentration of 6-keto-PGF_{1a} rose to $4.51\pm3.25 \ \eta g/ml$ at the end of the infusion period. After cessation of PGI₂, the concentration returned to base line in 30 min. After 30 min, PGI₂ lowered TxB₂ concentration (P < 0.005), reducing the value below control animals (P < 0.025). However, 30 min after cessation of PGI₂, TxB₂ levels rose above control (P < 0.05). PGI₂ infusion reversed the fall in PaO₂ and rise in \dot{Q}_s/\dot{Q}_T (P < 0.025, Fig. 2). V_D/V_T also decreased 30 min after the start of PGI₂ infusion (P < 0.025) to levels lower than control (P < 0.05). However, 30 min after cessation of PGI₂ infusion, V_D/V_T rose (P < 0.025) concomitant with the increase of TxB₂. Arterial and MPAP were also lowered during PGI_2 (P < 0.05), as was PVR (P < 0.05). CI was maintained during the infusion (P < 0.05), but 30 min later dropped to values similar to controls. Platelet numbers were not restored by PGI₂ infusion.



FIGURE 7 A significant relation exists between TxB_2 and V_D/V_T (P < 0.001). Data from control and PGI₂ groups are plotted before the PGI₂ infusion was started.

 V_D/V_T and TxB_2 concentration in control and PGI_2 groups correlated well (r = 0.79, P < 0.001, Fig. 7). The \dot{Q}_S/\dot{Q}_T was also related to TxB_2 (r = 0.69, P < 0.001). 30 min after embolization, the increase of TxB_2 related to a decrease of platelets in control and PGI_2 groups (r = -0.64, P < 0.001).

Ketoconazole given 30 min after embolization to three dogs, appeared to influence only V_{D_p}/V_T . 2 h after embolus, V_{D_p}/V_T was 22% (Table II), while

TABLE II Cardiopulmonary Effects of Ketoconazole Given 0.5 h after Embolization (n = 3)

| | Hours | | | | | | | | | |
|-------------------------------|-----------|------|-----|-----|-----|-----|--|--|--|--|
| | Base line | 0.5 | 1.0 | 2.0 | 3.0 | 4.0 | | | | |
| MPAP, mm Hg | 11 | 49 | 37 | 30 | 31 | 30 | | | | |
| CI, ml/kg·min | 127 | 117 | 116 | 107 | 110 | 99 | | | | |
| PVR, mm Hg• | | | | | | | | | | |
| min/liter | 1.8 | 11.7 | 8.8 | 7.0 | 6.8 | 8.2 | | | | |
| \dot{Q}_{s}/\dot{Q}_{T} , % | 11 | 52 | 44 | 30 | 29 | 24 | | | | |
| V_{D_p}/V_T , % | 7 | 37 | 27 | 22 | 23 | 30 | | | | |

 V_{D_p}/V_T was $34\pm3\%$ in a series of seven untreated dogs given 0.75 g/kg autologous clot. After 2 h MPAP was 30 mm Hg and PVR was 7.0 mm Hg·min/liter. These values were within one standard deviation of those in untreated dogs where MPAP was 29 ± 5 and PVR was 10.3 ± 4.5 mm Hg·min/liter. Finally, the decline of \dot{Q}_s/\dot{Q}_T from 52 to 30% at 2 h was similar to untreated animals whose level at 2 h was $30\pm15\%$.

DISCUSSION

Pulmonary embolism obstructs the pulmonary vasculature and causes a rise in dead space and hypoxemia. These effects are not entirely explicable in terms of mechanical obstruction. A humoral agent(s) released by the clot has been thought to contribute to the cardiopulmonary distress (1, 11, 12). Present investigations show that emboli cause production of the antiaggregator and vasodilator PGI₂, as well as the proaggregator and constrictor, TxA₂. PGI₂ is produced by vessel walls, while TxA₂ is synthesized in platelets and perhaps lung parenchyma (4, 13, 14). Our observation that the concentration of TxB₂, the stable degradation product of TxA₂ is temporally related to the fall in platelet count (r = -0.64) suggests that in this setting TxA₂ may originate in platelets that have aggregated. Inhibition of TxA₂ synthesis with imidazole, but not the thrombocytopenia, indicates that aggregation after embolization is independent of TxA_2 .

Induced thrombocytopenia or inhibition of platelet function by indomethacin has in the past been shown to modify the effects of microembolism (15, 16). Present data suggest that TxA_2 , directly by smooth muscle constriction or indirectly by promoting release of smooth muscle constrictors such as platelet serotonin (5-hydroxytryptamine, 5-HT), is responsible for at least some of the cardiopulmonary abnormalities after experimental pulmonary embolism. Inhibition of TxA_2 synthetase by pretreatment with imidazole and inhibition of cyclooxygenase by pretreatment with indomethacin (Figs. 5, 6) modified the rise in \dot{Q}_S/\dot{Q}_T and prevented any increase in V_D/V_T (Figs. 2, 3). The CI was better maintained along with lower PVR (Figs. 3, 4).

Infusion of PGI₂ led to decreased concentration of TxA₂ and prompt reductions of \dot{Q}_S/\dot{Q}_T , V_D/V_T , MPAP, and PVR with maintenance of CI. These salutary cardiopulmonary effects of PGI₂ have been reported and have been related to a direct action on pulmonary arterial smooth muscle causing vasodilation as well as enhanced fibrinolytic activity (10, 17). The very prompt reduction in \dot{Q}_S/\dot{Q}_T and V_D/V_T excludes PGI₂induced clot lysis as the mechanism of action. A selective PGI₂ effect of vaso- and bronchodilation has been suggested by our finding that a PGE₁ infusion will reduce MPAP to levels lower than PGI₂, but surprisingly, will worsen \dot{Q}_s/\dot{Q}_T and V_D/V_T (18). Other actions of PGI₂ are to antagonize the vaso- and broncho-constriction induced by 5-HT infusion (19) and to lower plasma 5-HT levels after experimental pulmonary embolization (20). Since PGI₂ modifies plasma and platelet 5-HT transport, it is possible that PGI₂ not only acts directly to relax vascular and bronchial smooth muscle, but also acts indirectly in inhibiting the synthesis and/or release of the platelet agents, TxA₂ and 5-HT, which mediate smooth muscle constriction. The present data support the postulate that release of platelet secretions can be modified by PGI₂, and that this event is related to improvement in cardiopulmonary function.

Obstruction of the pulmonary vasculature by emboli leads to ventilation without perfusion. That this rise in V_D/V_T could be prevented or reversed with inhibitors of TxA₂ synthesis was unexpected since this functional abnormality has usually been considered to be a simple mechanical event. It is likely that inhibition of TxA₂ secretion by platelets layering onto the embolus prevents intense constriction distal to the clot. As long as there is some perfusion through these embolized segments, the measured V_D/V_T will appear unchanged (21). This is related to the method of measurement, using the very soluble gas CO₂, which is sensitive only to very high ventilation/perfusion ratios.

The PGI₂ group illustrates the close association of TxA₂ and V_D/V_T. When PGI₂ with t₄ of 2-3 min was stopped, TxA₂ concentrations rapidly rose along with V_D/V_T (Figs. 3, 6). As TxA₂ decreased, so did V_D/V_T. The excellent correlation of TxB₂ with V_D/V_T in control and PGI₂ studies strongly suggests a causal relationship (Fig. 7). The ability of ketoconazole given after embolization to reduce TxB₂ and V_{Dp}/V_T adds further support to this thesis.

The fact that MPAP was little altered and PVR only moderately reduced in the treatment groups after embolization shows that significant reductions in the cross-sectional area of the pulmonary vascular bed still existed despite normal V_D/V_T . It is likely that other vasoactive platelet secretions are involved in the control of PVR. Serotonin is important. Administration of the antagonist cyproheptadine before embolization, using the same preparation as reported in this study prevented any rise in PVR (20).

There are a number of possible causes of the decline in CI after pulmonary embolism. Most noteworthy is right ventricular failure secondary to pulmonary hypertension. In addition, TxA_2 has been reported by our laboratory to be associated with a circulating agent that causes reduction in cardiac output and cardiac contractility (22, 23). The present results do not permit identification of the mechanism whereby PG and TX manipulations maintain CI.

One of the most perplexing events after emboliza-

tion is hypoxemia. Mechanical effects of the clot cannot explain the increase in \dot{Q}_s/\dot{Q}_T that is caused by perfusion of poorly or nonventilated lung segments. Our observation that the concentration of TxB₂ correlates with \dot{Q}_s/\dot{Q}_T (r = 0.69) indicates that TxA₂ may directly or indirectly induce bronchoconstriction. An indirect role is suggested by the observation that neither imidazole nor indomethacin completely prevented the increase in \dot{Q}_{s}/\dot{Q}_{T} (Fig. 2), and also that ketoconazole was without beneficial effect. Further, PGI₂-infused animals maintained a low \dot{Q}_s/\dot{Q}_T even after cessation of PGI₂, a time when TxA₂ concentrations rose transiently. Other bronchoconstrictors, particularly serotonin, may also participate in producing the hypoxemia of embolization (24). An infusion of 5-HT will lower arterial oxygen tension that can be restored by a simultaneous infusion of PGI_2 (19). In this setting, PGI₂ may be acting both as a bronchodilator as well as a promotor of rapid 5-HT clearance by platelets (20). Pretreatment with imidazole and indomethacin inhibits TxA₂ synthesis (Fig. 6), and although these drugs did not inhibit platelet sequestration and loss, it is possible that they modified platelet 5-HT release accounting for the attenuated rise in \dot{Q}_{s}/\dot{Q}_{T} . Posttreatment with ketoconazole did not alter Qs/QT. At this time, after platelet sequestration, it is unlikely that the drug influenced 5-HT release.

These results suggest that many of the cardiopulmonary effects of embolism are related to platelet secretions. However, extrapolation of these data to the clinical setting must be done with caution. Our experimental use of fresh clot divided into small fragments permitted embolization of peripheral vessels. This varies from the usual findings in patients where older and larger clot fragments with less surface area for platelet activation are the rule. It is possible that patients suffer quantitatively fewer humorally mediated effects of embolism than those noted in this study.

Cardiopulmonary function has also been shown to be altered in other states where platelets are entrapped in the lungs such as microembolism, sepsis, and abdominal aortic aneurysm repair (1, 11, 14, 15, 25, 26). In addition to platelet synthesis of TxA_2 , the observation that lung parenchyma can be stimulated by antigen antibody reaction to release thromboxanes (27) indicates that pulmonary metabolic events may also influence cardiopulmonary function.

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