Effects of Indomethacin on the Pulmonary Vascular and Air Way Resistance Responses to Pulmonary Microembolization[1] (37289)

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Clarke, Graf and Nadel (1) showed that pulmonary microembolization with $BaSO_4$ solution causes a marked bronchoconstriction in dogs. Recently, Piper and Vane (2) and Lindsay and Wyllie (3) found that pulmonary embolism due to a variety of substances causes the release of prostaglandins from the lung in animals. It has been well-established that prostaglandin E_2 (PGE_2) decreases and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) increases both pulmonary vascular and airway resistances in many species of animals (4). From these observations, it is tempting to speculate that the bronchoconstriction induced by pulmonary microembolization is due to the increased synthesis and release of $PGF_{2\alpha}$ in the bronchial smooth muscle (4, 5). Very recently, Vane (6) postulated that the pharmacodynamic effects of both aspirin and indomethacin are due to their inhibitory effect on the prostaglandin synthesis in the lesion. The present study was undertaken to examine whether indomethacin would influence the changes in pulmonary vascular and airway resistances caused by pulmonary embolization in dogs.

Methods. Sixteen dogs weighing between 15 and 22 kg were anesthetized by the intravenous (iv) administration of sodium pentobarbital (30 mg/kg). Under artificial respiration with a Palmer respirator, the left hemithorax was opened. Systemic and pulmonary arterial pressures and left atrial pressure were continuously measured with Statham pressure transducers (P23AA and P23D) connected to catheters placed in the left subclavian artery through the left mammary artery, in the pulmonary artery through a small branch of the left pulmonary artery and in the left atrium through a small branch of a pulmonary vein. Pulmonary airway resistance was evaluated by measuring the intratracheal (pulmonary airway) pressure with a Statham pressure transducer (P23D) through a side branch of the inflow tract of the respirator tubing. The respiratory tidal volume was maintained at an average of 15 ml/kg and the end-expiratory pressure was kept at zero atmospheric pressure throughout the experiments. All of the parameters measured were recorded continuously with a Grass polygraph (Model 7).

PGE_2, $PGF_{2\alpha}$ and indomethacin were generously given by Dr. J. E. Pike, Upjohn Co., Kalamazoo, MI and Dr. T. Y. Shen, Merck, Sharp & Dohme Co., Rahway, NJ, respectively. Each prostaglandin was dissolved in 95% ethanol (10 mg/ml) and further diluted with 0.9% NaCl solution to make a 100 μg/ml solution prior to the experiment. Indomethacin (5 mg/kg) which was diluted with 95% ethanol (50 mg/ml), was given intravenously to 8 dogs and the solvent solution was given to 8 additional dogs as controls. In order to produce pulmonary microembolization, barium sulfate, USP (Mallinckrodt Chem. Work, St. Louis, MO) was diluted with distilled water to make a 30% aqueous suspension, and was rapidly injected intravenously in doses of 10–120 mg/kg to both groups of dogs. The data in this paper were evaluated statistically employing the *t* test (7).

Results. The effects of the iv injection of increasing (cumulative) doses of $BaSO_4$ on

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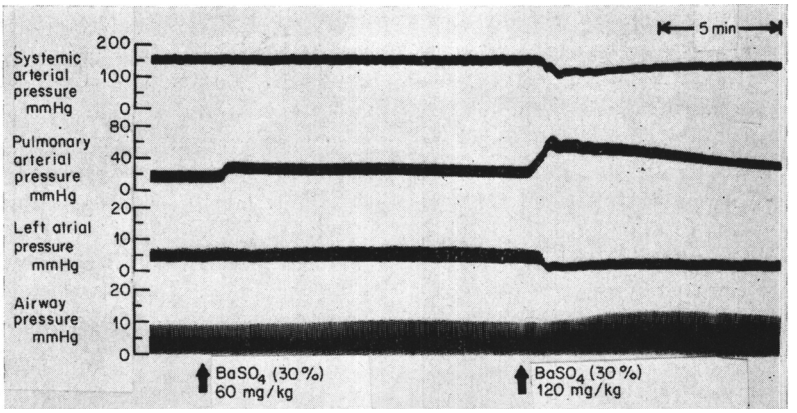

FIG. 1. Effects of the iv injection of barium sulfate ($BaSO_4$) on the systemic arterial pressure, pulmonary arterial pressure, left atrial pressure and pulmonary airway pressure in a dog.

systemic and pulmonary arterial pressures, left atrial pressure and pulmonary airway pressure were studied in 8 control dogs and 8 indomethacin-treated dogs. Tracings of representative experiments are illustrated in Figs. 1 and 2, and the average results are summarized in Fig. 3. As seen in Fig. 1, shortly after the iv injection of $BaSO_4$ (60 mg/kg), pulmonary arterial pressure rapidly increased by 10 mm Hg and then gradually decreased while both systemic arterial pressure and left atrial pressure remained essentially unchanged. After approximately a 3–4 min delay, pulmonary airway pressure increased slowly, the maximum increase being 1.5 mm Hg. When an additional dose (60 mg/kg; cumulative dose 120 mg/kg) was given, both systemic arterial pressure and left atrial pressure rapidly decreased by 40 and 5 mm Hg, respectively, as pulmonary arterial pressure increased by 32 mm Hg. Again pulmonary airway pressure slowly but progressively increased, the maximum increase being 4.8 mm Hg.

Figure 2 shows that the iv injection of $PGF_{2\alpha}$ (10 μg/kg) increased systemic and pulmonary arterial pressures, and pulmonary airway pressure as left atrial pressure fell transiently (8–10). The slow iv injection of indomethacin (5 mg/kg for 5 min) caused no significant change in the hemodynamic and respiratory parameters. Approximately 45 min after the injection of indomethacin, the same dose (10 μg/kg) of $PGF_{2\alpha}$ caused

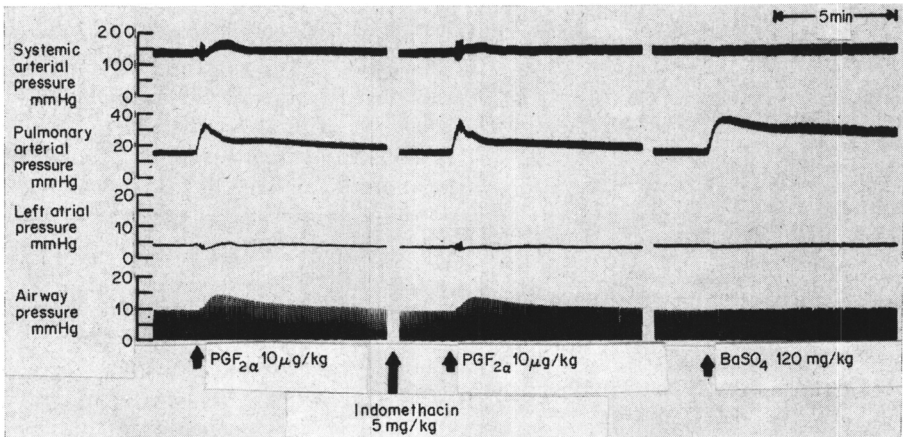

FIG. 2. Effects of the iv injection of $PGF_{2\alpha}$ and $BaSO_4$ on the systemic arterial pressure, pulmonary arterial pressure, left atrial pressure and pulmonary airway pressure in a dog before and 45 min after the iv injection of indomethacin.

essentially similar changes in the hemodynamic and respiratory parameters. In contrast, the iv injection of $BaSO_4$ (120 mg/kg) after indomethacin increased pulmonary arterial pressure markedly, but caused no significant change in airway pressure, indicating that the bronchoconstrictor response to pulmonary embolization with $BaSo_4$ was almost completely abolished. As summarized in Fig. 3, there was no significant difference in the hemodynamic changes induced by $BaSO_4$ between control dogs and in indomethacin-treated dogs. However, stepwise (cumulative) increasing doses of $BaSO_4$ increased pulmonary airway pressure progressively in control dogs but caused no significant change in indomethacin-treated dogs.

Discussion. From the present study, it is evident that pulmonary microembolization with $BaSO_4$ increases pulmonary arterial pressure and pulmonary airway pressure whereas systemic arterial pressure and left atrial pressure decrease. The prior administration of indomethacin before $BaSO_4$ causes no significant change in the pulmonary arterial pressure response, but almost completely abolishes the pulmonary airway pressure response to pulmonary microembolization with $BaSO_4$. As confirmed by this study, it is known that $PGF_{2\alpha}$ increases both pulmonary arterial pressure and airway pressure in dogs (8–10). Furthermore, pulmonary embolization with a variety of particles previously was found to increase the biosynthesis and release of prostaglandins from the lung (2, 3). Hence, it is tempting to conclude that the respiratory changes induced by $BaSO_4$ microembolization are due to the release of prostaglandins, especially $PGF_{2\alpha}$ from the lungs, and that the potent prostaglandin synthetase inhibitor, indomethacin (6), blocked the formation of $PGF_{2\alpha}$ and its bronchoconstrictor action. The pulmonary hypertensive response to pulmonary embolization appears mostly to be due to a mechanical obliteration of the pulmonary vascular bed since indomethacin caused no significant change in the pulmonary hypertensive response to $BaSO_4$.

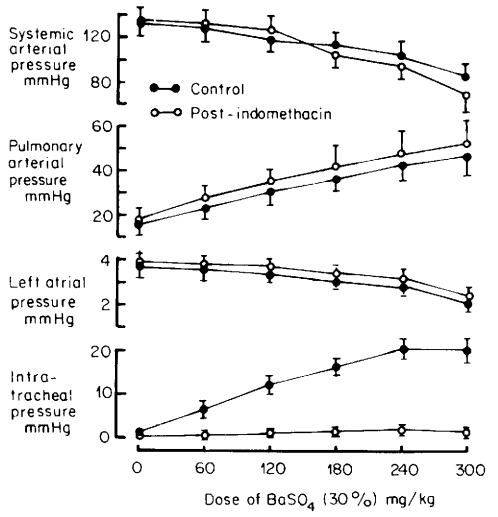

FIG. 3. Summary of the effects of the iv injection of progressively increasing (cumulative) doses of $BaSO_4$ on the systemic arterial pressure, pulmonary arterial pressure, left atrial pressure and pulmonary airway pressure in 8 control dogs and 8 indomethacin-treated dogs.

Unlike catecholamines, serotonin and histamine, prostaglandins are not stored in the tissue (9, 10). Instead, prostaglandin precursors such as arachidonic acid exist as a moiety of the phospholipids in the cell membrane. A variety of pathophysiological stimuli including pulmonary embolism appear to trigger through unknown mechanisms the activation of phospholipase A which cleaves arachidonic acid from arachidonyl phospholipids (11, 12). Since prostaglandin synthetase is abundantly present in most tissues, the cleavage of arachidonic acid causes the rapid formation of prostaglandins. Thereafter, as prostaglandins exert their various biological actions in different tissues, they are rapidly inactivated by prostaglandin dehydrogenase either at the site of their action or by the lung after a single circulation (10, 12–14).

Using a bioassay method, Lindsay and Wyllie (3) showed that pulmonary embolism increases the release of a PGE_2-like substance from the lung. It remains uncertain whether $PGF_{2\alpha}$ is also increased in this condition since their method cannot differentiate the type of prostaglandin in the biological fluids. It has been stated that the prostaglandins

in the human bronchial and tracheal smooth muscles are mostly PGE_2, a bronchodilator, while $PGF_{2\alpha}$, a bronchoconstrictor, is usually undetectable (4). However, using a radioautography method, ^3H-$PGF_{2\alpha}$ given iv was found to distribute to the bronchi as well as the lung in mice (15). Lands, Lee and Smith (16) demonstrated *in vitro* that more PGE_2 than $PGF_{2\alpha}$ is formed from arachidonic acid when glutathione is added to the incubation media containing seminal vesicle microsomal fraction. Hence, it was postulated that in certain pulmonary disorders such as asthma and pulmonary embolism, $PGF_{2\alpha}$ is more predominantly formed than PGE_2 from the common precursor, arachidonic acid, thereby causing a marked bronchoconstriction in these disorders (4, 5). However, in recent preliminary studies in our laboratory, the injection of an equi-mixture of PGE_2 and $PGF_{2\alpha}$ still exerts a marked bronchoconstrictor and pulmonary hypertensive action, together with a systemic hypotensive action in dogs. This observation would strongly suggest that a proportionally increased formation of both PGE_2 and $PGF_{2\alpha}$ is sufficient to induce potent bronchoconstriction in pulmonary embolism.

From the recent studies made by Vane (6) and others (17–19), it is evident that either aspirin or indomethacin inhibits the formation of prostaglandins in the lung and other tissues. Hence, when animals were pretreated with indomethacin, subsequent stimuli such as pulmonary embolization do not result in the formation of prostaglandins nor in the hemodynamic and respiratory changes, although the tissue is still responsive to prostaglandins given exogenously. These findings are essentially in agreement with the hypothesis of Vane that aspirin-like drugs inhibit prostaglandin synthetase, thereby inhibiting a variety of pathological processes including inflammatory and immunological reactions. Although both PGE_1 and PGE_2 exert vasodilator and bronchodilator actions in the lung, both E prostaglandins were found to be ineffective in ameliorating the clinical manifestations of pulmonary embolism in dogs (20). It remains uncertain whether indomethacin would be effective in the treatment of patients with pulmonary embolism.

Summary. The effects of indomethacin on the circulatory and respiratory responses to $BaSO_4$-induced pulmonary microembolization were studied in anesthetized dogs. It was found that indomethacin blocks the bronchoconstrictor response but not the circulatory responses to pulmonary embolization. It is suggested that indomethacin blocks the formation and release of prostaglandins due to pulmonary embolization.

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