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Leukotriene Antagonists Attenuate Thromboxane-Inducible Pulmonary Hypertension

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ABSTRACT. Leukotrienes C_4 and D_4 and thromboxane A_2 are potent vasoconstrictors that may mediate pulmonary vasoconstriction in many clinical situations. There is a complex interaction among leukotrienes and thromboxane A_2, because inhibition of thromboxane synthesis prevents some of the hemodynamic effects of exogenous leukotrienes. Similarly, if leukotrienes mediate thromboxane A_2-induced pulmonary vasoconstriction, then leukotriene antagonists should attenuate the effects of a thromboxane A_2-mimetic such as U46619. First, dose response curves for the hemodynamic effects of U46619 were performed on seven spontaneously breathing newborn lambs. Then a putative leukotriene receptor antagonist, FPL57231, 1 mg/kg/min, or a putative leukotriene synthesis antagonist, U60257, 30 mg/kg, was given before infusing U46619 (1 μg/kg/min). U46619 caused significant dose-dependent increases in pulmonary and systemic arterial pressures ($p < 0.05$) and significant dose-dependent decreases in cardiac output and heart rate ($p < 0.05$). A 1 μg/kg/min infusion of U46619 increased pulmonary arterial pressure by 155.4% ± 8.9 and systemic arterial pressure by 8.9% ± 7.7 and decreased cardiac output by 19.7% ± 12.2 and heart rate by 9.9% ± 10.6. FPL57231 attenuated the effects of U46619. U60257 had similar effects. Therefore, the hemodynamic effects of thromboxane A_2, an important mediator of the pulmonary vasoconstriction produced, for example, by group B streptococci and *Escherichia coli*, may be mediated by the secondary production of leukotrienes. (*Pediatr Res* 26: 83–87, 1989)

Metabolites of arachidonic acid may mediate the pulmonary vasoconstriction seen *in utero* (1, 2) and during alveolar hypoxia (3–6). They may also be important mediators of the hemodynamic changes occurring in the adult respiratory distress syndrome (7), endotoxic shock (8–14), and the syndrome of persistent pulmonary hypertension of the newborn (15). The most potent pulmonary vasoconstricting metabolites of arachidonic acid are the peptidoleukotrienes (leukotrienes C_4 and D_4) (16–18), formed via the lipooxygenase pathway, and thromboxane A_2 (8, 10, 11, 13, 14), formed via the cyclooxygenase pathway. There is a complex interaction among these leukotrienes and thromboxane A_2. To date, the evidence suggests that leukotriene C_4 and D_4 stimulate the production of thromboxane A_2 (16, 18–21). These studies would imply that thromboxane A_2 is involved in leukotriene-induced pulmonary vasoconstriction. The purpose of the present study was to investigate the other possibility: that thromboxane A_2 stimulates the production or release of leukotrienes. Because of the instability of thromboxane A_2 and the limited potency of its stable measurable metabolite, thromboxane B_2, we used the specific thromboxane A_2-mimetic, U46619 (Upjohn Co., Kalamazoo, MI) (22–29). In newborn lambs, after characterizing the pulmonary and systemic hemodynamic effects of U46619 by performing dose-response studies, we attempted to block or attenuate the hemodynamic response to U46619 using FPL57231, a putative leukotriene receptor antagonist (Fisons plc, Loughborough, England) (2, 5, 16) and U60257, a putative leukotriene synthesis inhibitor (Upjohn) (1, 6, 30–34).

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MATERIALS AND METHODS

Surgical Preparations. Under local anesthesia with 1% lidocaine hydrochloride, seven newborn lambs at 1 to 3 d of age had polyvinyl catheters placed into a hind leg artery and vein and advanced to the descending aorta and inferior vena cava, respectively. General anesthesia was then induced by having the lamb breathe a mixture of oxygen and halothane. The lamb was then intubated with a 4.5-mm ID endotracheal tube and mechanically ventilated with a Harvard animal ventilator. Anesthesia was maintained with 1–2% halothane.

A left lateral thoracotomy was performed in the fourth intercostal space (35). Polyvinyl catheters were then placed into the internal thoracic artery and vein and advanced to the ascending aorta and right atrium, respectively. The pericardium was incised along the main pulmonary trunk. Teflon cannulae attached to polyvinyl catheters were inserted into the main pulmonary artery and left atrium. A precalibrated electromagnetic flow transducer (CC Instruments, Los Angeles, CA) was placed around the ascending aorta to measure cardiac output (left ventricular output minus coronary blood flow). A chest tube was placed into the pleural space. The thoracotomy incision was closed in layers. The catheters were filled with heparin, plugged, and, along with the transducer cable, brought to the skin, where they were protected in a pouch sewn to the lamb's flank. The lamb was weaned from mechanical ventilation, extubated, and, after recovery from anesthesia, returned to its mother. An intramuscular injection of 1mL of penicillin G procaine and dihydrostreptomycin sulfate suspension was given daily. Three days were allowed for recovery.

Experimental Protocol. U46619 dose response. With the lamb spontaneously breathing and resting quietly in a sling, baseline measurements of the hemodynamic variables (pulmonary and systemic arterial pressures, left and right atrial pressures, heart rate, and cardiac output) and systemic arterial pH and blood gases were made (baseline). Doses of U46619 (0.1, 0.5, 1.0, and 2.0 μg/mg/min) were then infused for 15 min into the inferior vena cava. Each lamb received all doses; the order of doses was

randomly chosen. The doses used were based on previous studies from our and other laboratories (22, 27–29, 36).

The hemodynamic variables were measured continuously and the systemic arterial pH and blood gases were measured after 15 min at the steady state maximal response (U46619). A total of 20 min was allowed between infusions for recovery and return of the hemodynamic variables to baseline. Preliminary data showed that the response to U46619 was reproducible after waiting this time period. Also, there was no evidence for tachyphylaxis.

U46619 infusion during leukotriene antagonism. To determine the role of leukotrienes in producing the hemodynamic effects of U46619, either the putative leukotriene receptor antagonist, FPL57231, or the putative leukotriene synthesis inhibitor, U60257, was given before infusing U46619. The doses used were based on previous studies from our and other laboratories (1–3, 5, 6, 16, 17). First, with the lamb spontaneously breathing and resting in a sling, baseline measurements of the hemodynamic variables and systemic arterial pH and blood gases were made (baseline 1). Then, U46619 (1 μg/kg/min) was infused for 15 min and the effects recorded (U46619). After a 20-min recovery period, measurements were repeated (baseline 2). Then either FPL57231 or U60257, randomly assigned, was administered.

FPL57231 (1 mg/kg/min), a dose previously shown to prevent the hemodynamic effects of leukotrienes (17), was infused for 20 min. After 5 min of infusion, all measurements were repeated (FPL57231) and U46619 (1 μg/kg/min) was then infused as the FPL57231 infusion continued. After 15 more min of infusion of both U46619 and FPL57231, the hemodynamic variables, systemic arterial pH, and blood gases were measured (U46619 + FPL57231). Both infusions were then stopped.

U60257 (30 mg/kg), a dose previously shown to reverse hypoxia-induced pulmonary hypertension in newborn lambs (6) and to increase pulmonary blood flow in fetal lambs (1), was injected intravenously. Then 30 min after this injection, the measurements were repeated (U60257) and U46619 (1 μg/kg/min) was then infused for 15 min. The hemodynamic variables, systemic arterial pH, and blood gases were measured (U46619 + U60257). The U46619 infusion was then stopped. The two studies, using either FPL57231 or U60257, were performed 24 h apart.

Drug Preparation. All drugs were prepared immediately before use. U46619 in ethanol was stored at −70°C and prepared by diluting the compound in 0.9% saline. FPL57231 was prepared as a 1% solution in sterile water. U60257 was stored at −20°C and prepared by diluting the compound in 5 mL of 0.9% saline.

Measurements and Analyses. Pulmonary and systemic arterial and right and left atrial measures were measured with Statham Db23 pressure transducers. Mean pressures were obtained by electrical integration. Cardiac output (left ventricular output minus coronary blood flow) was measured on a Statham SP2202 flow meter. The flow transducers were calibrated *in vitro* using appropriate preformed molds and infusions of normal saline (37). The flow meters were adjusted to zero during diastole when aortic flow was assumed to be zero. Heart rate was triggered from the phasic systemic arterial pressure pulse wave. All hemodynamic variables were continuously recorded on a Beckman multichannel direct writing recorder (Beckman Instruments, Inc.,

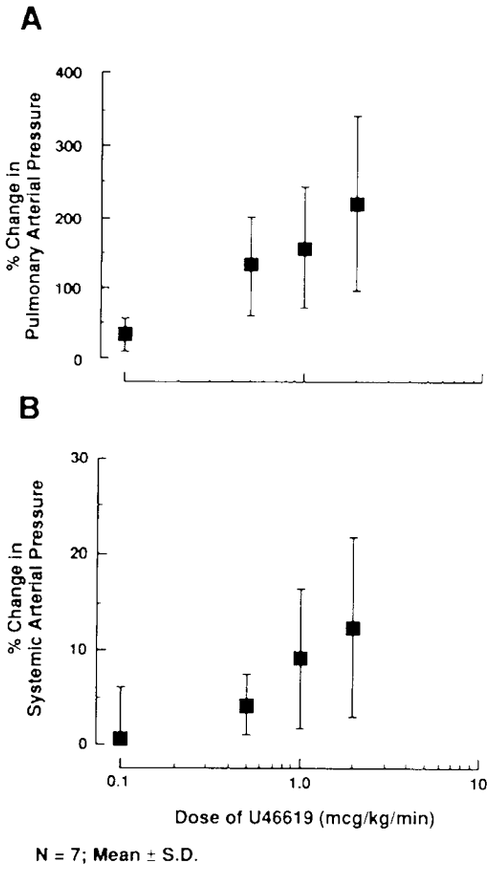

Fig. 1. U46619, a thromboxane A_2-mimetic, causes dose-dependent increases in (*A*) pulmonary [Y = 135.7(X) + 167.6, $r = 0.65$, $p < 0.05$, $S_{Y \cdot X} = 78.5$] and (*B*) systemic [Y = 8.8(X) + 8.6, $r = 0.56$, $p < 0.05$, $S_{Y \cdot X} = 6.4$] arterial pressures.

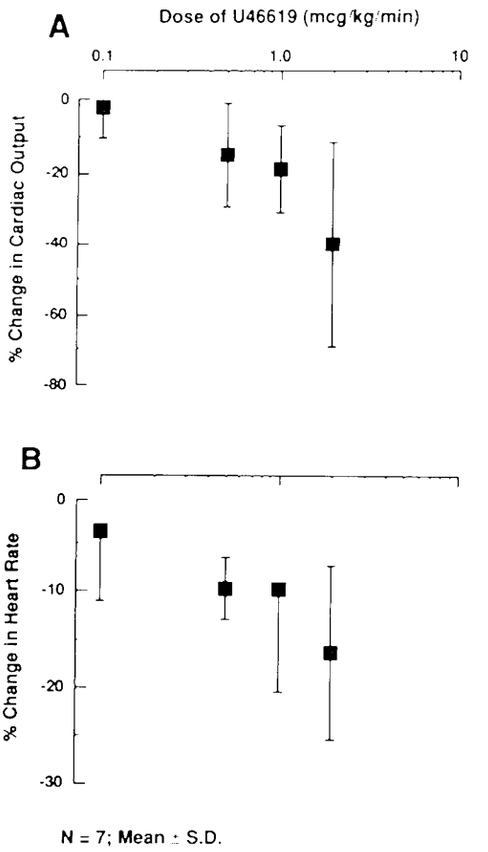

Fig. 2. U46619, a thromboxane A_2-mimetic, causes dose-dependent decreases in (*A*) cardiac output [Y = −26.3(X) − 25.9, $r = 0.60$, $p < 0.05$, $S_{Y \cdot X} = 17.3$] and (*B*) heart rate [Y = −8.5(X) − 11.9, $r = 0.48$, $p < 0.05$, $S_{Y \cdot X} = 7.8$].

Table 1. *Hemodynamic effects of infusions of U46619 in newborn lambs (n = 7, mean ± SD)*

Dose (μg/kg/min)	Pulmonary arterial pressure (mm Hg)		Systemic arterial pressure (mm Hg)		Cardiac output (mL/kg/min)	
	Baseline	U46619	Baseline	U46619	Baseline	U46619
0.1	16.4 ± 4.5	21.4 ± 6.0*	77.5 ± 11.0	77.4 ± 10.4	215.1 ± 44.1	213.6 ± 56.9
0.5	17.3 ± 3.9	37.7 ± 3.6*	75.4 ± 11.3	78.6 ± 13.2	227.9 ± 47.6	187.0 ± 26.0*
1.0	18.2 ± 5.7	42.5 ± 5.3*	74.3 ± 11.1	80.7 ± 12.2*	221.0 ± 27.1	177.6 ± 35.5*
2.0	17.3 ± 5.8	49.2 ± 2.5*	74.6 ± 9.5	83.3 ± 10.3*	229.2 ± 38.3	131.0 ± 60.3*
	Left atrial pressure (mm Hg)		Right atrial pressure (mm Hg)		Heart rate (beats/min)	
0.1	0.2 ± 4.1	1.2 ± 5.0	−0.1 ± 2.7	1.4 ± 2.2	220.3 ± 26.3	213.0 ± 36.5
0.5	0.2 ± 3.2	1.8 ± 4.2*	0.5 ± 1.8	0.9 ± 2.6	226.7 ± 31.1	205.7 ± 32.8*
1.0	0.7 ± 4.1	2.8 ± 5.8	0.4 ± 2.4	2.0 ± 4.7	225.9 ± 31.1	203.7 ± 36.4*
2.0	−0.9 ± 3.4	2.3 ± 5.4*	−0.5 ± 2.3	2.5 ± 3.5	234.0 ± 20.1	196.5 ± 28.0*

* $p < 0.05$ *versus* baseline.

Fullerton, CA). Systemic arterial pH and blood gases were measured at 39°C on a Corning 158 pH/blood gas analyzer (Corning Glass Works, Corning, NY).

Means ± SD were calculated for hemodynamic variables and systemic arterial pH and blood gases before (baseline) and during each infusion of U46619 at the maximum response (U46619) and compared by a paired t test. The dose-dependent effects of U46619, compared as percent change from baseline values, were analyzed using linear regression analysis. The effects of FPL57231 and U60257 on the hemodynamic response to U46619 were compared using analysis of variance techniques and the Newman-Keuls test for multiple comparisons. A $p < 0.05$ was considered statistically significant (38).

RESULTS

U46619 dose response. When plotted on semi-log paper and expressed as percent change from baseline values, U46619 produced dose-dependent increases in pulmonary arterial pressure and systemic arterial pressure and dose-dependent decreases in cardiac output and heart rate (Figs. 1 and 2). Absolute values are shown in Table 1. There was also a significant increase in left atrial pressure ($p < 0.05$). The maximum changes occurred by 1 min and lasted for the duration of the infusion of U46619. All hemodynamic variables returned to baseline values 20 min after the infusion was stopped. Infusion of drug vehicle had no hemodynamic effects. There were some minor changes in systemic arterial pH and blood gases (data not shown).

U46619 infusion during leukotriene antagonism. FPL57231 caused no change in baseline pulmonary and systemic arterial and left and right atrial pressures or systemic arterial pH and blood gases. It did increase cardiac output by 19% ($p < 0.05$). FPL57231 blocked the increase in pulmonary arterial pressure produced by a 1 μg/kg/min infusion of U46619 ($p < 0.05$) (Fig. 3). Similarly, U60257 caused no change in baseline hemodynamic variables or systemic arterial pH and blood gases. U60257 attenuated the increase in pulmonary arterial pressure produced by a 1 μg/kg/min infusion of U46619 ($p < 0.05$) (Fig. 4).

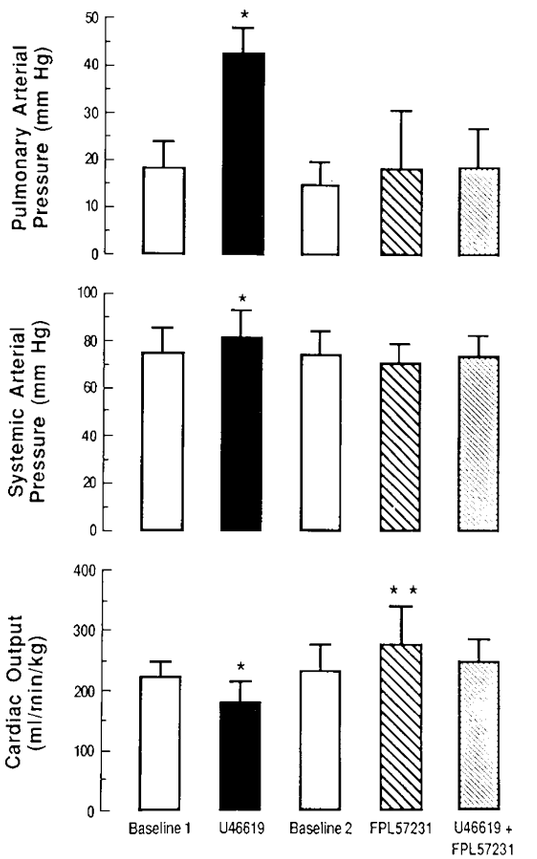

Fig. 3. FPL57231 attenuates the hemodynamic effects of U46619.

DISCUSSION

The results of this study demonstrate that the thromboxane A_2-mimetic, U46619, causes dose-dependent increases in pulmonary and systemic arterial pressures and dose-dependent decreases in cardiac output and heart rate in spontaneously breathing newborn lambs. These hemodynamic effects are attenuated by the putative leukotriene receptor antagonist, FPL57231, and the putative leukotriene synthesis inhibitor, U60257, suggesting that leukotrienes may mediate these effects.

Although U46619 is a chemical analogue of the endoperoxide PGH_2, its biologic activity is identical to thromboxane A_2 (23–29). U46619, like thromboxane A_2, strongly contracts strips of guinea pig lung, dog saphenous vein, and rabbit and rat aorta. It is a weak constrictor or is inactive on strips of guinea pig ileum and stomach, cat trachea, and cat and dog iris sphincter muscles (24–26, 29). Kadowitz and Hyman (28) have previously studied the hemodynamic effects of U46619 on anesthetized adult dogs. In their model, U46619 also increased pulmonary and systemic arterial pressures. However, cardiac output did not change significantly. The hemodynamic effects were blocked by a putative thromboxane A_2 receptor antagonist. Assuming an average dog wt of 10 kg, 0.5 μg/kg injection of U46619 increased pulmonary arterial pressure by 118% and systemic arterial pressure by 15%, compared to 130 and 4%, respectively, in our lamb study (27). The difference in effect on cardiac output is most likely secondary

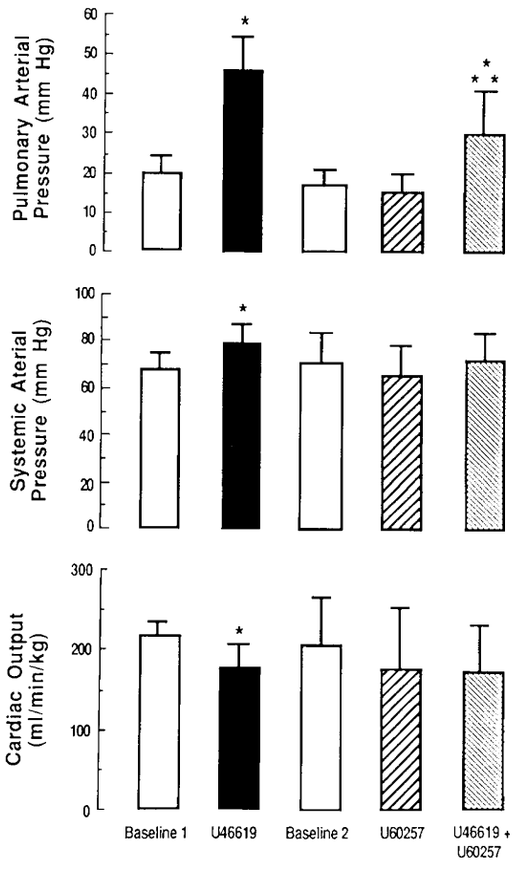

Fig. 4. U60257 attenuates the hemodynamic effects of U46619.

to differences in study design, because in anesthetized lambs, U46619 did not significantly change cardiac output (36).

Thromboxane A_2 is an important mediator of the pulmonary hypertension caused by the infusion of endotoxin or live or heat-killed group B streptococci (8–14). Infusion of *Escherichia coli* endotoxin into lambs and sheep causes a marked early increase in pulmonary arterial pressure associated with an increase in plasma concentrations of thromboxane B_2 (8–10, 12, 39). Similar results have been produced by infusing live group B streptococci into adult sheep and young piglets (13, 14). Administration of indomethacin, imidazole, or other inhibitors of thromboxane synthesis prevents the increase in both pulmonary arterial pressure and the serum concentration of thromboxane B_2 (8, 10, 11, 13, 14).

Other studies have suggested that thromboxane A_2 may also play a role in the pulmonary hypertension caused by leukotrienes. For example, in sensitized guinea pig lungs stimulated by leukotriene C_4, thromboxane A_2 production is increased (19). Similarly, leukotriene C_4 and leukotriene D_4 caused a dose-dependent contraction of isolated perfused guinea pig lungs and an increase in thromboxane production. Both effects were blocked by imidazole, a thromboxane synthetase inhibitor (21). The hemodynamic and airway effects of leukotriene C_4 and D_4 have also been attenuated by inhibition of thromboxane synthesis (16, 18, 20, 28). It is not clear whether the increase in thromboxane is predominantly responsible for the effects of leukotrienes or simply acts as a method of bioamplification. The present study would indicate that this relationship is bidirectional.

Our study shows that the hemodynamic effects of a thromboxane A_2-mimetic, U46619, can be blocked by putative leukotriene antagonists. This implies that thromboxane A_2 causes an increase in the production and the release of leukotrienes. Alternatively, U46619 could be a leukotriene agonist. This is unlikely, because U46619 does not contract guinea pig ileum, a requirement for leukotrienes (25).

FPL57231 and FPL55712 are competitive leukotriene receptor antagonists (40). FPL57231 produces a similar degree of leukotriene antagonism as its parent compound, FPL55712, although it has little antiallergic effects (40). FPL57231 and FPL55712 completely block the hemodynamic effects of exogenously administered leukotrienes in newborn lambs (17) and piglets (41). In isolated perfused rat lungs, FPL55712 blocked the pulmonary hypertensive effects of leukotriene C_4, but not of potassium or angiotensin II (30), although in neonatal piglets, it blocked the effects of leukotriene C_4 and D_4, but not of lysine vasopressin (41).

It is possible that FPL57231 blocked the hemodynamic effects of U46619 because it is a thromboxane receptor antagonist or because it has other nonspecific vasodilating effects. FPL57231 increases pulmonary blood flow in fetal lambs even in the presence of a thromboxane synthesis inhibitor (2, 41). Therefore, FPL57231 is not a thromboxane receptor antagonist. In some studies, FPL57231 has decreased vascular pressures and tended to increase cardiac output (43, 44), but not in others (5, 17). In pump-perfused fetal goat lungs, very large bolus doses of FPL57231 (to 10 mg/kg) prevented the pulmonary pressor response to leukotriene D_4 and lowered normal pulmonary vascular resistance (45). In this model, FPL57231 also blocked the pulmonary pressor response to phenylephrine HCl and U46619 (45). However, in the perfused rat lung, FPL55712 did not block the pulmonary pressor response to angiotensin II (30). In our study, FPL57231 did increase cardiac output without changing vascular pressures. During U46619 infusion, FPL57231 attenuated the hemodynamic effects.

Because FPL57231 may have nonspecific vasodilating effects (46), we also studied the effects of U60257, a putative leukotriene synthesis inhibitor, on the hemodynamic effects of U46619. U60257 inhibits leukotriene synthesis from human leukocytes, antigen-sensitized human lung and rat mononuclear cells at both the 5′ lipoxygenase and leukotriene D_4 synthetase steps (31–34). Although U60257 is an analog of prostacyclin, it does not have any platelet antiaggregating effects (33, 34). The hemodynamic effects of U60257 are therefore likely not mediated by prostacyclin. In fetal lambs, U60257 increases pulmonary blood flow similarly to FPL57231. U60257 blocks hypoxic pulmonary vasoconstriction and leukotriene C_4 production in isolated perfused rat lungs without effect on antiotensin II-induced pulmonary hypertension (4, 30). In our study, U60257 had no effect on baseline vascular pressure or cardiac output. During U46619 infusion, U60257 attenuated the hemodynamic effects. There was a small increase in pulmonary arterial pressure compared to U46619 infusion alone. FPL57231 did completely block the increase in pulmonary arterial pressure. This difference may be due to a time delay in achieving maximal 5′ lipoxygenase inhibition, which may take more than 30 min to be achieved (1). Because U60257, a putative leukotriene synthetase inhibitor and structurally unrelated to FPL57231, thromboxane A_2, or U46619, also attenuated the hemodynamic effects of U46619, it is likely that leukotrienes may mediate many of the effects of U46619.

In conclusion, our study demonstrates that U46619, a thromboxane A_2-mimetic, is a potent pulmonary vasoconstrictor. In addition, the hemodynamic effects of U46619 and, presumably thromboxane A_2, may be mediated in part through the production of leukotrienes.

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