Prostaglandins potentiate U-46619-induced pulmonary microvascular dysfunction

JOSEPH K. WRIGHT, LAWRENCE T. KIM, THOMAS E. ROGERS, AND RICHARD H. TURNAGE
Departments of Surgery and Pathology, University of Texas Southwestern Medical School and Dallas Veterans Affairs Medical Center, Dallas, Texas 75216

Wright, Joseph K., Lawrence T. Kim, Thomas E. Rogers, and Richard H. Turnage. Prostaglandins potentiate U-46619-induced pulmonary microvascular dysfunction. J. Appl. Physiol. 88: 1167–1174, 2000.—The induction of cyclooxygenase is an important event in the pathophysiology of acute lung injury. The purpose of this study was to examine the synergistic effects of various cyclooxygenase products (PGE2, PG12, PGF2a) on thromboxane A2 (TxA2)-mediated pulmonary microvascular dysfunction. The lungs of Sprague-Dawley rats were perfused ex vivo with Krebs-Henseleit buffer containing indomethacin and PGE2 (5 × 10^-8 to 1 × 10^-7 M), PGF2a (5 × 10^-9 to 5 × 10^-8 M), or PG12 (5 × 10^-10 to 2 × 10^-5 M). The TxA2-receptor agonist U-46619 (7 × 10^-9 M) was then added to the perfusate, and then the capillary filtration coefficient (Kc), pulmonary arterial pressure (Ppa), and total pulmonary vascular resistance (Rt) were determined. The Kc of lungs perfused with U-46619 was twice that of lungs perfused with buffer alone (P < 0.05). The presence of PGE2, PG12, and PGF2a within the perfusate of lungs exposed to U-46619 caused 118, 65, and 68% increases in Kc, respectively, over that of lungs perfused with U-46619 alone (P < 0.03). The Rt of lungs perfused with PGE2 + U-46619 was 30% greater than that of lungs exposed to either U-46619 (P < 0.02) or PGE2 (P < 0.01) alone. When paired measurements of Rt taken before and then 15 min after the addition of U-46619 were compared, PG12 was found to attenuate U-46619-induced increases in Rt (P < 0.01). These data suggest that PGE2, PG12, and PGF2a potentiate the effects of TxA2-receptor activation on pulmonary microvascular permeability.

METHODS

Isolated, Perfused Lung Model

Pathogen-free Sprague-Dawley rats (250–350 g) were anesthetized with pentobarbital sodium (40 mg/kg ip). A median sternotomy was performed, and the pulmonary arterial trunk and left atrium were cannulated via the right and left ventricles, respectively. The heart and lungs were excised en bloc, and the lungs were suspended by a ligature from a force transducer (TSD 125C; Biopac Systems, Santa Barbara, CA) for continuous measurement of lung weight. The lungs were perfused with Krebs-Henseleit buffer containing 3% BSA at 0.04 ml·g body wt^-1·min^-1 and ventilated with room air at a rate of 60 strokes per minute. The Krebs-Henseleit buffer consists of an aqueous solution containing (in mM) 128 NaCl, 4.7 KCl, 1.2 MgSO4, 3.2 CaCl2, 1.2 KH2PO4, 25 NaHCO3, and 6.7 dextrose. The perfusate was bubbled with a 95% O2-5% CO2 mixture to maintain a normal pH (7.40–7.5). Pulmonary arterial pressure (Ppa) and pulmonary venous pressure (Ppv) were continuously measured with pressure transducers (TSD 104A; Biopac Systems) with zero reference at the level of the apex of the lung. These measurements were continuously recorded by a Biopac data acquisition unit (MP100 manager version 3.2.3, hardware version 1.1f, Biopac Systems) interfaced with a personal computer (Dell Computer, Austin, TX). The perfusate was maintained in a 37°C water bath. The first 75 ml of perfusate was discarded to remove blood elements.

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Determination of the effect of indomethacin on U-46619-induced pulmonary microvascular dysfunction. An initial set of experiments (Fig. 1A) was performed to determine the effect of indomethacin on U-46619-induced changes in pulmonary microvascular function. There were four experimental groups defined by the composition of the perfusate: 1) Krebs-Henseleit buffer alone (n = 5), 2) Krebs-Henseleit buffer + U-46619 (n = 7), 3) Krebs-Henseleit buffer + indomethacin (n = 8), and 4) Krebs-Henseleit buffer + indomethacin + U-46619 (n = 6). In this study, indomethacin (100 µM; Sigma Chemical, St. Louis, MO) was added to the perfusate at the beginning of the experiment; 15 min later, U-46619 (7.1 × 10^{-6} M) was added to the perfusate of the appropriate experimental groups. After an additional 15 min of ex vivo perfusion, pulmonary microvascular dysfunction was assessed by measuring the capillary filtration coefficient (Kf), total vascular resistance (RT), and pulmonary vascular pressures as described below.

U-46619 (9,11-dideoxy-11α,9α-epoxymethanoprostaglandin F2α) is a thromboxane-endoperoxide receptor agonist that has been commonly used to mimic the physiological effects of TXA2 (4, 22, 23, 25). The concentration of U-46619 was chosen based on a dose-response curve relating increasing concentrations of U-46619 to increases in Kf in this experimental system (data not shown). This concentration of U-46619 is associated with increases in Kf similar to those seen with in vivo models of acute lung injury (29). Lastly, the increases in Kf associated with U-46619 have been found to be completely inhibited by the thromboxane receptor antagonist SQ-29548 (2 µM; data not shown).

Determination of the effect of PGE2 and PGF2α on U-46619-induced pulmonary microvascular dysfunction. In these and subsequent experiments (Fig. 1B), indomethacin (100 µM) was added to the perfusate of the isolated, perfused lung model to inhibit the generation of endogenous prostanooids (3,
5, 37, 38). This concentration has been previously shown to inhibit the release of TXa2, PGF2α, and PG1 in an experimental model similar to that employed in these experiments (3, 5).

In this particular study, PGE2 (Oxford Biomedical Research, Oxford, MI; 1 x 10^-8 M, 2 x 10^-7 M, 5 x 10^-6 M) or PGF2α (Cayman Chemical, Ann Arbor, MI; 7 x 10^-8 M, 5 x 10^-7 M, 1 x 10^-6 M, 5 x 10^-6 M) was added to the perfusate at the beginning of the experiment; 15 min later, baseline measurements of Ppa and Ppv were obtained. U-46619 (7.1 x 10^-8 M) was then added to the perfusate and allowed to circulate for 15 min, after which Ppa and Ppv were again measured and the Kr, and vascular resistance were determined.

PGE2 and PGF2α were prepared in Krebs-Henseleit buffer according to the supplier's recommendations. The concentrations and mode of administration of PGE2 and PGF2α in these experiments were based on the experience of other investigators utilizing similar experimental models (4, 5, 15, 23, 30, 34). The addition of these substances to the Krebs-Henseleit buffer had no effect on the pH of the perfusate.

Determination of the effect of PG1 on U-46619-induced pulmonary microvascular dysfunction. In this experiment (Fig. 1C), the ex vivo lung model was perfused with a Krebs-Henseleit buffer containing indomethacin (100 µM) for 15 min as described above. PGI2 (Oxford Biomedical Research; 2 x 10^-8 M, 2 x 10^-7 M, 2 x 10^-6 M, 2 x 10^-5 M) was then added to the perfusate, and baseline measurements of Ppa and Ppv were obtained. Immediately thereafter, U-46619 (7.1 x 10^-8 M) was added to the perfusate; 7 min later a second infusion of PGI2 was given as described above. Seven minutes later (15 min after the addition of U-46619), Ppa and Ppv were measured, and vascular resistance and Kr were determined.

The protocol for administering PGI2 was based on its short half-life at a physiological pH (2–3 min). It was prepared in 50 mM Tris buffer (pH 9.0), as recommended by the supplier, and added to the perfusate immediately following reconstitution. The bioactivity of this preparation was confirmed by its ability to inhibit U-46619-induced vasoconstriction (4). The addition of PGI2 to the Krebs-Henseleit buffer as described above had no effect on the pH of the perfusate.

Measurement of Pulmonary Microvascular Dysfunction

Kr. Pulmonary microvascular permeability was quantitated by determining Kr as has been previously described by our laboratory (29) and that of other investigators (11, 39). Briefly, 15 min after the addition of U-46619, the capillary pressure prior to elevating Ppv (Pcpre) was measured using the double occlusion technique (1, 28). Ppv was then elevated 8–10 mmHg by raising the height of the venous reservoir. This results in a two-component weight gain consisting of an initial rapid increase related primarily to recruitment and distension of the vascular bed (minutes 0–1) and a second slow constant weight increase due to fluid filtration across the microvasculature (minutes 1–5). After 5 min of elevated Ppv, Pc was again measured before returning Ppv to baseline (Pcpost). Kr was calculated as shown in Eq. 1.

\[ K_r = \frac{\Delta W \Delta T}{\Delta P} \]  

(1)

where \( \Delta W \) is the change in lung weight between minutes 1 and 5 of partial venous outflow occlusion, \( \Delta T \) is the duration of elevated Ppv during which \( \Delta W \) is measured, and \( \Delta P \) is the difference between Pcpost and Pcpre. Kr is normalized to body weight (expressed as g min^-1 mmHg^-1 100 g body wt^-1). This methodology correlates well with the time 0 extrapolation technique (39).

Pulmonary vascular resistance. Immediately before the addition of U-46619, Ppa and Ppv were recorded and compared with measurements obtained 15 min after the addition of U-46619. Rt was calculated as the total pressure drop across the lung as expressed in Eq. 2.

\[ R_T = \frac{P_{pa} - P_{pv}}{Q} \]  

(2)

where Q is the flow through the isolated perfused lung. In the isogravimetric state, the pulmonary circulation can be represented as a simple linear model in which Ppa is separated from Pc by a precapillary resistance (arterial resistance, Ra) and Pc is separated from Ppv by a postcapillary resistance (venous resistance, Rv) (1). Therefore, where RT is determined in the isogravimetric state, Ra and Rv can be calculated as follows.

\[ R_a = \frac{P_{pa} - P_c}{Q} \]  

(3)

\[ R_v = \frac{P_c - P_{pv}}{Q} \]  

(4)

\[ R_T = R_a + R_v \]  

(5)

All resistance calculations (RT, Ra, and Rv) were normalized for body weight (expressed as mmHg·ml^-1·min^-1·100 g body wt^-1). Rt was also expressed as the absolute difference in determinations of Rt obtained before and 15 min after the addition of U-46619 to the ex vivo lung perfusion. This methodology minimizes variability between lung perfusions in that each lung serves as its own control. Furthermore, this methodology allows determination of the effect of each PG on U-46619-induced vasomotor activity after quantitation of the PG's effect on basal vasomotor tone.

In these determinations of Kr and vascular resistance, Pc was measured with the double occlusion method as described by Allison et al. (1) and Townsley et al. (28). This methodology has been demonstrated to correlate closely with measurements of isogravimetric capillary pressure in both normal and acutely injured lungs (1, 28).

Statistical Analysis

All data are expressed as means ± SE. The sample sizes of the experimental groups ranged from four to eight. The data were compared by ANOVA with a Student-Newman-Keuls test (SigmaStat; Version 2.0; SPSS; Chicago, IL). Statistical significance was considered for a type 1 error of <5%. All P values represent the results of post hoc comparisons. All experiments were approved by the Committee on the Care and Use of Animals at the University of Texas Southwestern Medical School and Dallas Veterans Affairs Medical Center.

RESULTS

Effect of Indomethacin on Pulmonary Microvascular Function

The Kft of lungs exposed to U-46619 in the absence of indomethacin was more than three times greater than that of lungs perfused with Krebs-Henseleit buffer alone (Fig. 2; P < 0.02). The Kft of lungs exposed to U-46619 in the presence of indomethacin (100 µM) was about twice that of lungs perfused with Krebs-Henseleit buffer containing indomethacin but without U-46619.
K_{f} \text{, the presence of PGE}_{2} (5 \times 10^{-8} \text{ M}), \text{PGF}_{2\alpha} (5 \times 10^{-6} \text{ M}), \text{or PG}I_{2} (5 \times 10^{-8} \text{ M}) \text{ within the perfusate significantly enhanced the effect of U-46619 on pulmonary microvascular permeability. These data are shown in Fig. 3. The } K_{f} \text{ of lungs perfused with U-46619 + PGE}_{2}, \text{PGF}_{2\alpha}, \text{or PG}I_{2} \text{ was 118, 65, and 68% greater, respectively, than that of lungs perfused with U-46619 alone (P < 0.03). Furthermore, the } K_{f} \text{ of lungs perfused with U-46619 + PGE}_{2}, \text{PGF}_{2\alpha}, \text{or PG}I_{2} \text{ was 4.4, 2.3, and 2.3 times that of lungs perfused with the respective prostaglandins alone (P < 0.01). In the absence of U-46619, } \text{PG}E_{2}, \text{PGF}_{2\alpha}, \text{and PG}I_{2}, \text{at the same concentrations as used above, had no effect on pulmonary microvascular permeability.}

Concentrations of PGE_{2} < 5 \times 10^{-8} \text{ M} \text{ had no significant effect on U-46619-induced increases in } K_{f} \text{, whereas } 1 \times 10^{-7} \text{ M} \text{ was associated with an increase in } K_{f} \text{ similar to that of } 5 \times 10^{-8} \text{ M}. \text{The } K_{f} \text{ of lungs exposed to U-46619 and } 1 \times 10^{-8} \text{ M PGE}_{2} \text{ was not different from that of lungs exposed to U-46619 alone (0.009 \div 0.0004 vs. 0.011 \div 0.001 g-min^{-1}-mmHg^{-1}-100 \text{ g body wt}^{-1}; n = 4 \text{ and 7, respectively). In contrast, the } K_{f} \text{ of lungs exposed to U-46619 and either } 5 \times 10^{-8} \text{ M PGE}_{2} (0.024 \div 0.004 \div 0.001 g-min^{-1}-mmHg^{-1}-100 \text{ g body wt}^{-1}; n = 6) \text{ or } 1 \times 10^{-7} \text{ M PGE}_{2} (0.0245 \div 0.0044 \div 0.001 g-min^{-1}-mmHg^{-1}-100 \text{ g body wt}^{-1}; n = 4) \text{ was significantly greater than that of lungs perfused with U-46619 alone (0.011 \div 0.001 g-min^{-1}-mmHg^{-1}-100 \text{ g body wt}^{-1}; n = 7; P < 0.05) or indomethacin alone (0.006 \div 0.001 g-min^{-1}-mmHg^{-1}-100 \text{ g body wt}^{-1}; n = 8; P < 0.05). Concentrations of PGF}_{2\alpha} < 5 \mu M (7 \times 10^{-9} \text{ to } 1 \times 10^{-6} \text{ M}) \text{ and concentrations of PG}I_{2} < 5 \times 10^{-8} (2 \times 10^{-8} \text{ M}) \text{ had no effect on U-46619-induced changes in } K_{f}, \text{ whereas concentrations }>5 \times 10^{-8} \text{ M} \text{ had an effect similar to the latter (data not shown).}

Table 1. Effect of indomethacin (100 µM) on U-46619-induced changes in pulmonary vasomotor tone

<table>
<thead>
<tr>
<th>Number of lungs</th>
<th>Krebs Alone</th>
<th>Krebs + U-46619</th>
<th>Krebs + Indomethacin</th>
<th>Krebs + U-46619 + Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure, mmHg</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>19.9 ± 0.30</td>
<td>24.3 ± 1.7*</td>
<td>17.92 ± 0.82</td>
<td>22.54 ± 1.02*</td>
<td></td>
</tr>
<tr>
<td>Capillary pressure, mmHg</td>
<td>8.0 ± 0.5</td>
<td>9.5 ± 0.2*</td>
<td>8.75 ± 0.41</td>
<td>9.9 ± 0.59</td>
</tr>
<tr>
<td>Total resistance, mmHg·ml⁻¹·min⁻¹·100 g body wt</td>
<td>0.58 ± 0.02</td>
<td>0.79 ± 0.04*</td>
<td>0.47 ± 0.04</td>
<td>0.59 ± 0.05†</td>
</tr>
<tr>
<td>Precapillary resistance, mmHg·ml⁻¹·min⁻¹·100 g body wt</td>
<td>0.40 ± 0.02</td>
<td>0.54 ± 0.04*</td>
<td>0.28 ± 0.02</td>
<td>0.37 ± 0.03‡</td>
</tr>
<tr>
<td>Postcapillary resistance, mmHg·ml⁻¹·min⁻¹·100 g body wt</td>
<td>0.18 ± 0.01</td>
<td>0.26 ± 0.01*</td>
<td>0.19 ± 0.02</td>
<td>0.22 ± 0.02</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. lungs perfused with Krebs-Henseleit alone or Krebs-Henseleit + indomethacin, respectively. †P < 0.05 vs. lungs perfused with Krebs-Henseleit + U-46619 (without indomethacin).
Changes in pulmonary vasomotor tone and PGI2 due principally to a 49% increase in Ra over that of U-46619 alone (*P < 0.01). The RT of lungs perfused with PGF2a or PGI2 did not increase Ppa, Pc, or RT over that associated with the prostaglandin itself or that caused by U-46619 alone.

Figure 4 illustrates the effect of PGE2, PGF2a, and PGI2 on U-46619-induced vasoconstriction by comparing the RT of the ex vivo lung model immediately before and 15 min after the addition of U-46619 to the perfusate. In these paired measurements, U-46619 caused a significant increase in RT (P < 0.05) compared with measurements taken immediately before the addition of U-46619. PGI2 attenuated the increase in RT associated with U-46619 (P < 0.01), whereas PGE2 and PGF2a, had no significant effect. Expression of the Ppa data in this manner produced identical results (data not shown).

Discussion

The generation of TXA2 by the lung during acute inflammatory states is often accompanied by the release of PGE2, PGF2a, and PGI2 (9, 14). Although synergism between PGE2 and PGI2 and various proinflammatory substances such as histamine, bradykinin, and interleukin-1 has been well described (2, 34, 35), there have been few studies examining the effect of these prostaglandins on TXA2-mediated changes in pulmonary microvascular permeability. The data presented in this study suggest the following: 1) PGE2, PGF2a, and PGI2 do not alter microvascular permeability when administered individually into an isolated, buffer-perfused rat lung; 2) each of these prostaglandins potentiates the proinflammatory effects of TXA2-receptor activation on pulmonary microvascular permeability; 3) indomethacin (100 µM) attenuates U-46619-induced effects on pulmonary microvascular permeability and vascular resistance; and 4) PGI2 attenuates TXA2-induced vasoconstriction.

Various investigators (12, 20, 21, 27) have examined the individual effects of PGE2, PGF2a, and PGI2 on pulmonary microvascular permeability in normal animal models, including the rat. In contradistinction to lungs exposed to U-46619 alone (P < 0.01). In contrast, PGE2 + U-46619 did not appear to alter either Ppa or Pc when compared with measurements taken in lungs exposed to U-46619 alone. The addition of U-46619 to lungs perfused with PGF2a or PGI2 did not increase Ppa, Pc, or RT over that associated with the prostaglandin itself or that caused by U-46619 alone.

The effect of PGE2 (5 × 10⁻⁸ M), PGF2a (5 × 10⁻⁶ M), and PGI2 (5 × 10⁻⁸ M) on pulmonary vasomotor tone is shown in Table 2. In the absence of U-46619, the addition of PGE2, PGF2a, or PGI2 to the perfusate of the ex vivo lung model had no effect on Ppa or Ppv when compared with those lungs perfused with buffer alone. Of interest, the RT of lungs perfused with PGF2a, or PGI2 was significantly greater than that of lungs exposed to Krebs-Henseleit buffer alone (P = 0.01 for both substances). This appeared to be due principally to a 49% greater Ra in the lungs exposed to these prostaglandins (P = 0.01). The RT of lungs perfused with PGI2 was not statistically different from that of lungs perfused with buffer alone (P = 0.057).

The RT of lungs exposed to PGE2 + U-46619 was significantly greater than that of lungs exposed to U-46619 alone (P < 0.02). This increase appeared to be due principally to a 49% increase in Ra over that of lungs exposed to U-46619 alone (*P < 0.01). In contrast, PGE2 + U-46619 did not appear to alter either Ppa or Pc when compared with measurements taken in lungs exposed to U-46619 alone. The addition of U-46619 to lungs perfused with PGF2a or PGI2 did not increase Ppa, Pc, or RT over that associated with the prostaglandin itself or that caused by U-46619 alone.

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Various investigators (12, 20, 21, 27) have examined the individual effects of PGE2, PGF2a, and PGI2 on pulmonary microvascular permeability in normal animal models, including the rat. In contradistinction to
their very active role in the regulation of local vasomotor tone, the results of the present study, as well as those of other investigators (20, 21, 27), suggest that these exogenously administered prostaglandins do not directly alter pulmonary vascular permeability, at least when administered into a buffer-perfused lung model in the concentrations utilized in this study.

To the authors’ knowledge, there are no studies examining the effect of PGE2 and PGF2α on the TXA2-mediated changes in pulmonary microvascular permeability and only two studies examining the effect of PGI2 (37, 38). In the latter two reports (37, 38), the investigators, utilizing an ex vivo newborn lamb lung model, found that the Kf of lungs exposed to PGI2 and a TXA2-receptor agonist (9,11-epithio-11,12-methano-TXA2) was significantly greater than that of lungs exposed to either PGI2 or TXA2 receptor activation alone. This increase in fluid filtration was accompanied by a reduction in vascular hydrostatic pressure, suggesting that, in addition to a direct effect on microvascular permeability, PGI2 may have increased pulmonary Kf by increasing vascular surface area (37, 38). These results are similar to those of the present study in that the Kf of lungs exposed to PGI2 and U-46619 was nearly 70% greater than that of lungs exposed to U-46619 alone (P < 0.02). Furthermore, this occurred in a setting in which PGI2 prevented U-46619-induced vasoconstriction. Of interest in one of the Yoshimura studies (38), PGI2 alone was found to induce an acute lung injury manifested by “a diffuse hemorrhagic edema.” This is clearly different from the experience reported in the present study [as well as that reported by other investigators (12, 21)] in which PGI2 alone had no effect on Kf. Even in the presence of U-46619, the increase in Kf associated with PGI2 exposure was much more modest than that suggested by Yoshimura et al. (38). The reason for this difference is unclear, although fundamental differences in the experimental models are likely to be important [e.g., a sanguineous perfusate was utilized in the Yoshimura study (38), whereas an asanguineous buffer was used in the present study]. Furthermore, the total amount of PGI2 administered in the Yoshimura study was more than 100 times greater than that of the present study (about 300 µg over 180 min in the Yoshimura study vs. 2.6 µg in the present study).

It is also possible that neutrophils, sequestered within the ex vivo lung model during harvesting, may have contributed to the enhanced microvascular function that characterized exposure of the lungs to U-46619 + PGE2 or PGF2α. The importance of sequestered neutrophils in the microvascular dysfunction of the ex vivo perfused lung model was initially suggested by Seibert et al. (24) in 1993 in a study in which neutrophils sequestered within the perfused lung were found to contribute significantly to the enhanced permeability associated with pulmonary ischemia-reperfusion injury. One may postulate that in the present study perfusion of the lung with U-46619 (and perhaps PGF2α and PGI2 (13, 17, 33, 40)) may have acted on sequestered neutrophils, resulting in the generation of a respiratory burst and, ultimately, a neutrophil-mediated microvascular dysfunction (18, 26). Other more recent studies have suggested that U-46619, as well as PGE2, PGF2α, and PGI2, inhibits neutrophil activation, at least as manifested by increases in intracellular free calcium, leukoaggregation, and the release of superoxide radical, β-glucuronidase, and leukotriene B4 (22, 32, 36). These more recent observations would appear to be inconsistent with the notion that U-46619 or PGE2, PGF2α, or PGI2 increased pulmonary microvascular permeability by activating on neutrophils sequestered within the lung.

Other studies have suggested that activation of the endothelial cell TXA2/PGH2 receptor may directly alter microvascular permeability by changing the endothelial cytoskeletal structure, with resultant changes in cell shape and cell-cell continuity (31). This would suggest a possible second mechanism by which PGF2α and PGI2 may work through the TXA2/PGH2 receptor to enhance microvascular permeability (13, 17, 33, 40). Although these studies clearly suggest that PGF2α and PGI2 may activate the TXA2/PGH2 receptor, the relative affinity of TXA2 receptors for PGI2 and PGF2α is extremely low when compared with that of TXA2 for U-46619 (19, 33, 40). Furthermore, most of these studies were performed using pharmacological doses in vitro models. Lastly, PGE2 has been shown to promote bradykinin-induced edema formation (within the skin), although the mechanism by which this occurs (i.e., whether it is related to neutrophil activation via the EP3 receptor, a direct effect on the microvascular permeability, or an effect of increased blood flow) remains speculative (2, 6, 34, 35). Furthermore, to the investigators’ knowledge, no one has examined the effect of circulating PGE2 on pulmonary vasomotor tone.
PGE2- and PGI2-mediated inhibition of TxA2 release by edema (8), an effect attributed, at least in part, to endotoxin-induced vasoconstriction and pulmonary microvascular dysfunction may contribute to the pulmonary microvascular permeability. In a recent study, the induction of PGE2 and PGI2 release by transfecting a recombinant cyclooxygenase gene into the pulmonary microvasculature was found to attenuate endotoxin-induced vasoconstriction and pulmonary edema (8), an effect attributed, at least in part, to PGE2- and PGI2-mediated inhibition of TxA2 release by the lung itself or inflammatory cells such as neutrophils or platelets sequestered within the lung (8). If a similar mechanism had been operative in the present study, one would have anticipated a reduction, not increase, in Kf. Furthermore, the concentration of TXB2 (the stable metabolite of TxA2) was measured within the perfusate of several of the lungs exposed to PGE2, PGI2, and PGF2α and was found to be no different from that of lungs not exposed to these prostaglandins (data not shown).

The addition of indomethacin to the perfusate of the ex vivo lung model appeared to attenuate, but not prevent, U-46619-induced increases in Kf. Previous investigators have suggested that indomethacin attenuates increases in pulmonary microvascular permeability by inhibiting the release of proinflammatory prostanooids, particularly TxA2, by the lung (16, 39). In the present study, the addition of U-46619 to the perfusate resulted in a small but statistically significant increase in the release of PGE2 and TxA2 by the lung. The presence of 100 μM indomethacin within the perfusate prevented this increase in endogenous PGE2 and TxA2 release (data not shown), suggesting that the “protective” effect of indomethacin resulted from an inhibition of endogenous prostaglandin and/or TxA2 release.

In the present study, the Rτ of lungs perfused with PGI2 was 40% greater than that of lungs perfused with buffer alone (P = 0.007), whereas PGI2 totally prevented the increase in vasoconstriction associated with U-46619 exposure. These results are consistent with those of Zhao et al. (40) and Williams et al. (33), who demonstrated that higher concentrations of PGI2 contract rat pulmonary artery rings or aortic strips (probably via the TxA2/PGH2 receptor (33, 40)), whereas lower concentrations and those given in the presence of vasoconstrictors [e.g., U-46619 (4) or PGF2α (5)] cause vasodilation [possibly via the PGI2/PGH2 receptor (33)]. The results of the present study are consistent with the observations of other investigators who suggested that PGI2 becomes a more potent vasodilator as the tone of the blood vessel is increased (5).

Similar to PGI2, the Rτ of lungs perfused with PGF2α was significantly greater than that of lungs perfused with Krebs-Henseleit buffer (P = 0.01), an increase due principally to vasoconstriction of the precapillary segment. This observation is nearly identical to that published by Barnard et al. (5) using a similar experimental model. In contrast to PGI2, however, PGF2α had no effect on U-46619-induced vasoconstriction. This is perhaps related to the fact that PGF2α competes less effectively for the TxA2/PGH2 receptor than does U-46619 (5, 17, 25).

There is little information available regarding the effect of PGE2 on pulmonary vasoconstrictor function. In the present study, the Rτ of lungs perfused with U-46619 + PGE2 was significantly greater than that of either U-46619 (P < 0.02) or PGE2 alone (P < 0.05), suggesting that PGE2 potentiated the vasoconstriction associated with U-46619. Enthusiasm for this conclusion is limited by the observations that 1) the Ppa of lungs exposed to PGE2 + U-46619 was not different from that of lungs exposed to U-46619 alone and 2) the presence of PGE2 within the perfusate of the lungs did not appear to affect U-46619-induced vasoconstriction when assessed as the absolute change in Rt and Ppa in paired measurements taken immediately before and 15 min after the addition of U-46619 (as shown in Fig. 5).

In summary, these data are consistent with the hypothesis that PGE2, PGI2, and PGF2α potentiate the proinflammatory effects of TxA2-receptor activation on pulmonary microvascular permeability. Although the increase in pulmonary Kf due to PGI2 + U-46619 may result, in part, from PGI2-induced increases in vascular surface area, there is little evidence to support such a mechanism for the increase in Kf due to the combined effects of U-46619 + PGE2 and PGF2α. The synergistic effects of these prostaglandins on TxA2-induced pulmonary microvascular dysfunction may contribute to the lung injury that commonly accompanies systemic inflammatory states.

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Address for reprint requests and other correspondence: R. H. Turner, Dept. of Surgery, Univ. of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235.

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