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Effects of Prostaglandin E_1 and Hydralazine on the Longitudinal Distribution of Pulmonary Vascular Resistance during Vasoconstrictor Pulmonary Hypertension in Sheep

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Pulmonary capillary pressure (Ppc) is dependent upon left atrial pressure, pulmonary venous resistance, and cardiac output. The effects of pulmonary vasodilators on Ppc will therefore depend upon any alterations in the longitudinal distribution of pulmonary vascular resistance (precapillary [arterial] and postcapillary [venous] components). We therefore studied the effects of two pulmonary vasodilators (prostaglandin E_1 and hydralazine) on Ppc and the longitudinal distribution of pulmonary vascular resistance. Pulmonary hypertension was produced in sheep by the continuous administration of the thromboxane A_2–mimetic U46619. Ppc was measured by analysis of pulmonary artery occlusion pressure decay curves. U46619 increased Ppc by 9 mmHg and increased both the arterial and venous components of pulmonary vascular resistance. Subsequent administration of prostaglandin E_1 decreased Ppc by 5 mmHg and decreased both the arterial and venous components of pulmonary vascular resistance (by 50 and 69% respectively). Hydralazine produced smaller decreases in the arterial and venous components of pulmonary vascular resistance (by 35 and 49% respectively) and did not significantly reduce Ppc. We conclude that prostaglandin E_1 but not hydralazine is effective in decreasing Ppc in this experimental model of pulmonary hypertension. (Key words: Anesthetic techniques, hypotension, induced: hydralazine. Complications: pulmonary hypertension. Hormones: prostaglandin E_1. Lungs, blood flow: pulmonary capillary pressure; pulmonary circulation.)

PULMONARY HYPERTENSION may occur from increases in pulmonary arterial (precapillary) resistance (Ra), pulmonary venous (postcapillary) resistance (Rv), or both. Pulmonary capillary pressure (Ppc) is dependent upon pulmonary venous resistance, cardiac output ($\dot{Q}$), and left atrial pressure. The effects of a vasodilator on Ppc will therefore depend upon the overall reduction in pulmonary vascular resistance (Rp) and any alterations in the longitudinal distribution of Rp (arterial and venous components). Although the relative pulmonary and systemic vasodilator effects of many drugs have been studied,[1–3] there has been limited investigation into the effects of vasodilator drugs on the longitudinal distribution of Rp. Since small changes in Ppc may result in marked changes in pulmonary edema during acute respiratory failure,[4,5] changes in the longitudinal distribution of Rp may be clinically important. Hydralazine and prostaglandin E_1 (PGE_1) have been used for the treatment of pulmonary hypertension both with and without respiratory failure.[1,6] We therefore studied the effects of hydralazine and PGE_1 on the longitudinal distribution of Rp in a previously described model of vasoconstrictor pulmonary hypertension in sheep.[2,3]

Materials and Methods

The protocol for this study was approved by the Stanford Administrative Panel on Laboratory Animal Care.

Twenty male sheep weighing 12–30 kg were anesthetized with intravenous sodium thiopental 10–20 mg/kg. After tracheal intubation, the lungs were mechanically ventilated at a tidal volume of 15 ml/kg and a rate adjusted to maintain arterial carbon dioxide tension (Pa_{CO_2}) between 35 and 45 mmHg. Anesthesia was maintained with halothane (1% end-tidal concentration) in oxygen throughout the study. Temperature was maintained at 37.5–39.0° C. After induction of anesthesia, systemic arterial and venous catheters were inserted by femoral cutdown. A triple-lumen balloon-tipped pulmonary artery catheter was inserted *via* the right external jugular vein.

Two hours after catheter insertion, baseline data were obtained, including systemic arterial pressure, pulmonary arterial pressure (Ppa), right atrial pressure, pulmonary arterial occlusion (wedge) pressure (Ppao), and $\dot{Q}$. A minimum of three Ppao profiles were obtained (see below). After baseline measurements, pulmonary hypertension was induced by continuous intravenous infusion of U46619 (9,11-dideoxy-11$_\alpha$, 9$_\alpha$-epoxymethano-prostaglandin $F_{2\alpha}$), a thromboxane A_2–mimetic and pulmonary vasoconstrictor. The U46619 infusion rate was initially titrated until Ppa was approximately 30 mmHg. The infusion rate was then maintained constant for the duration of the experiment. Hemodynamic measurements were obtained 60 min after beginning U46619.

U46619 administration was continued, and the sheep were randomized to receive PGE_1 (n = 7), hydralazine (n = 7), or saline (n = 6) for the next 3 h. PGE_1 and hydralazine were initially administered as continuous intravenous infusions titrated to decrease Rp by 15% (compared to the U46619 value). Measurements were obtained after 30 min of vasodilator drug administration (drug-30). The infusion rate was then sequentially altered to

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decrease Rp by 30, 45, and 60% of the U46619 values, and measurements (drug-60, drug-90, drug-120) were made after 30 min at each condition. The 60% reduction in Rp was then maintained for an additional hour and measurements (drug-150, drug-180) were obtained every 30 min. Vasodilator infusion rates were decreased if necessary to maintain systemic arterial pressure ≥ 55 mmHg. The saline group received saline at 50 ml/h. In all three groups, saline was administered as necessary to maintain Ppao at the predrug value (*i.e.*, the U46619 value).

Measurement Techniques

Intravascular pressures were measured using fluid-filled catheters connected to 53-600F Trantec disposable pressure transducers (American Edwards, Santa Ana, CA), and a Hewlett-Packard 7758B eight-channel monitor and strip-chart recorder. Pressures were referenced to left atrial level and measured at end-expiration. $\dot{Q}$ was measured in triplicate by thermodilution using 10 ml room-temperature saline and a 9520A $\dot{Q}$ computer (Edwards Laboratories, Santa Ana, CA). Arterial blood gas tensions and *p*H were measured with a Corning 168 *p*H/blood gas analyzer (Corning, Medfield, MA).

Ppao decay curves were obtained with rapid balloon inflation during 8–10-s periods of apnea. A minimum of three curves was obtained under each condition. Each pressure decay curve was filtered with a 100-Hz, 24-dB/octave low-pass filter (Krohn-Hite, model 3750, Cambridge, MA) and sampled at 200 Hz with a 12-bit analog-to-digital converter (Data Translations, DT-2801, Marlboro, MA) in an Everex microcomputer (Everex, Hayward, CA), using an 80286 microprocessor (Intel, Santa Clara, CA). In general, occlusion occurred during midsystole, and only curves in which the decay began at a pressure greater than mean pulmonary artery pressure were analyzed. Ppc was derived by analysis of the Ppao decay profiles as previously described.[7] Each decay curve was digitally filtered at 55 Hz with the five-point least squares quadratic and mean pulmonary artery pressure (Ppa) was computed as the mean of the three complete beats preceding the decay. Five seconds of data starting with the decay from mean Ppa were analyzed. A least-squares fit of this data with a biexponential decay ($Ae^{-\alpha t} + Be^{-\beta t} + Ppao$) was obtained with a customized computer program. Using a two-resistance, two-capacitor model of the pulmonary circulation,[7] Ppc was derived from the parameters of the exponential decay. After determining Ppc, Rp was calculated and divided into precapillary or arterial (Ra) and postcapillary or venous (Rv) components, such that

$$Ra = (Ppa - Ppc)/\dot{Q}$$

$$Rv = (Ppc - Ppao)/\dot{Q}$$

and

$$Rp = Ra + Rv$$

Drugs

PGE_1 and U46619 were gifts from Doug McCarter (Upjohn). U46619 stock solution was prepared in absolute alcohol (concentration 5 mg/ml) and diluted to 400 μg/ml in saline. PGE_1 was prepared in 0.2 M phosphate buffer at a concentration of 200 μg/ml. Hydralazine (Apresoline; Ciba) was diluted to 1 mg/ml in saline.

Statistical Analysis

Data are expressed as mean values ± standard errors of the mean. Data were analyzed by two-factor repeated measures (vasodilator drug group × time) analysis of variance followed by the Newman-Keuls' multiple-range test when appropriate. A probability value less than 0.05 was considered significant.

Results

U46619, infused at a rate of $1.4 \pm 0.2\ \mu g \cdot kg^{-1} \cdot min^{-1}$, produced pulmonary hypertension (figs. 1–5). Ppa increased 163%; $\dot{Q}$ decreased 25%; and Rp increased 380%. U46619 affected both the arterial and venous components of Rp (fig. 3). Ra increased 306%; Rv increased 560%; and the relative proportion of Rp that was venous increased slightly (Rv/Rt 0.30 ± 0.03 at baseline *vs.* 0.39 ± 0.03 at U46619; $P < 0.05$). The pulmonary arterial gradient (Ppa − Ppc) increased by 8 mmHg; the pulmonary venous gradient (Ppc − Ppao) increased by 6 mmHg; and Ppc increased by 9 mmHg (figs. 1 and 4). U46619 produced selective pulmonary vasoconstriction so that systemic arterial pressure increased by only 24%, and the ratio of pulmonary to systemic vascular resistance (Rp/Rs) increased by 186% (figs. 2 and 5). In the saline group, the pulmonary and systemic hemodynamic effects of U46619 remained stable throughout the 4-h infusion.

Both PGE_1 and hydralazine decreased Rp (fig. 2). PGE_1 produced dose-related reductions in Rp, and the final desired 60% reduction in Rp was achieved. The development of systemic hypotension limited the hydralazine dose so that Rp could be decreased by only 40%. The mechanism of the reduction in calculated Rp differed between the two vasodilators. PGE_1 decreased Ppa and increased $\dot{Q}$, whereas hydralazine increased $\dot{Q}$ but did not affect Ppa (figs. 1 and 5). PGE_1 produced balanced pulmonary and systemic vasodilation so that Rp/Rs remained unchanged (fig. 2). In contrast, hydralazine produced preferential systemic vasodilation so that Rp/Rs markedly increased.

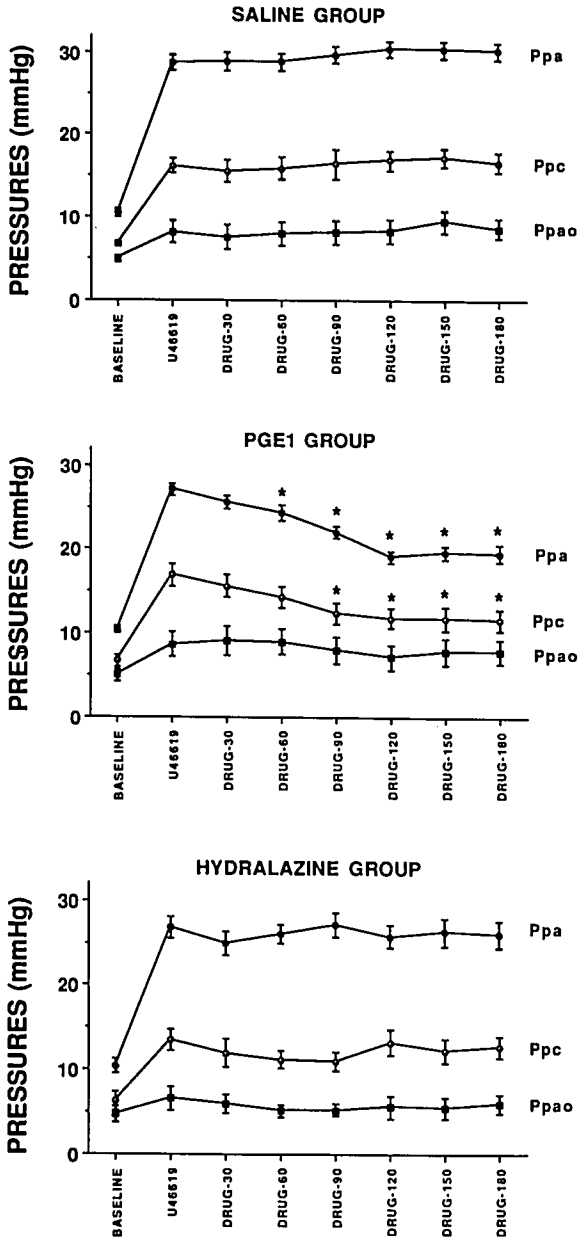

FIG. 1. Pulmonary artery pressure (Ppa), pulmonary capillary pressure (Ppc), and pulmonary artery occlusion pressure (Ppao) at baseline, during U46619 administration, and after 30, 60, 90, 120, 150, and 180 min of saline, prostaglandin E_1 (PGE_1), or hydralazine. Data are expressed as mean values ± SEM. *$P < 0.05$ *versus* the corresponding U46619 values.

Both PGE_1 and hydralazine decreased both components (Ra and Rv) of Rp (fig. 3). PGE_1 decreased Ra 50%, decreased Rv 69%, and did not affect Rv/Rp. Hydralazine decreased Ra 35%, decreased Rv 49%, and did not affect Rv/Rp. PGE_1 decreased the pulmonary arterial gradient (Ppa − Ppc) by 2.3 mmHg and decreased the pulmonary venous gradient (Ppc − Ppao) by 4.5 mmHg (fig. 4). The final dose of PGE_1 resulted in a pulmonary venous gradient only 2.0 mmHg above baseline. In contrast, hydralazine did not affect either (Ppa − Ppc) or (Ppc − Ppao), and the pulmonary venous gradient remained 5.7 mmHg above baseline at the end of the study.

Figure 6 contrasts the effects of the final dose of the two vasodilators on pulmonary vascular pressures. Hy-

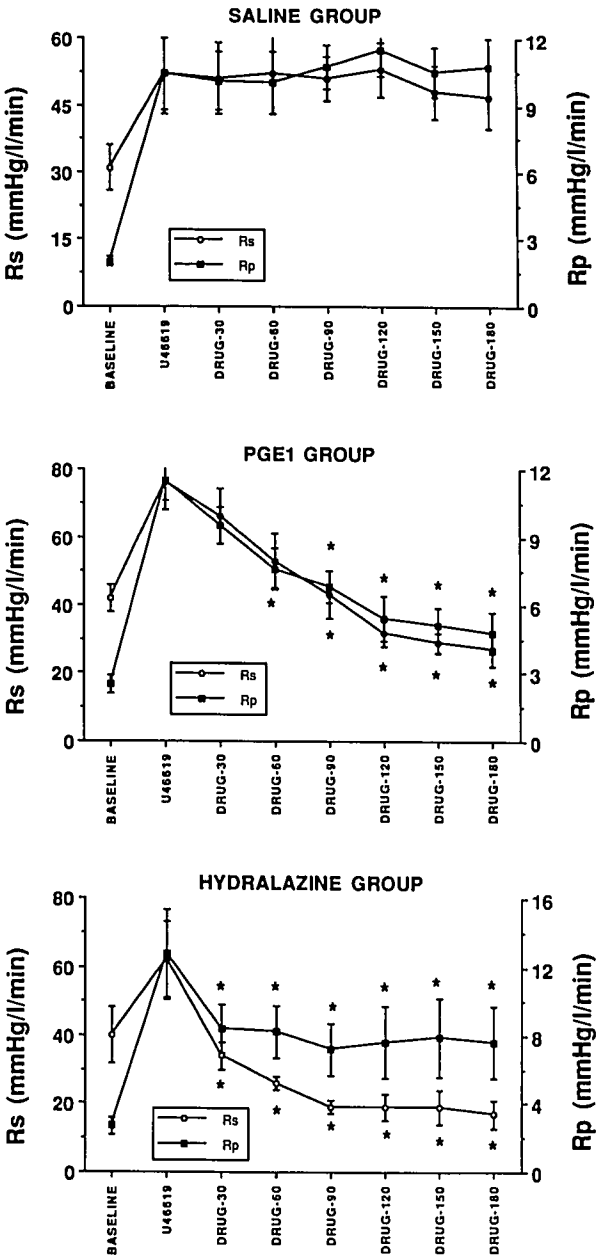

FIG. 2. Systemic vascular resistance (Rs) and pulmonary vascular resistance (Rp) at baseline, during U46619 administration, and after 30, 60, 90, 120, 150, and 180 min of saline, prostaglandin E_1 (PGE_1), or hydralazine. Data are expressed as mean values ± SEM. *$P < 0.05$ *versus* the corresponding U46619 values.

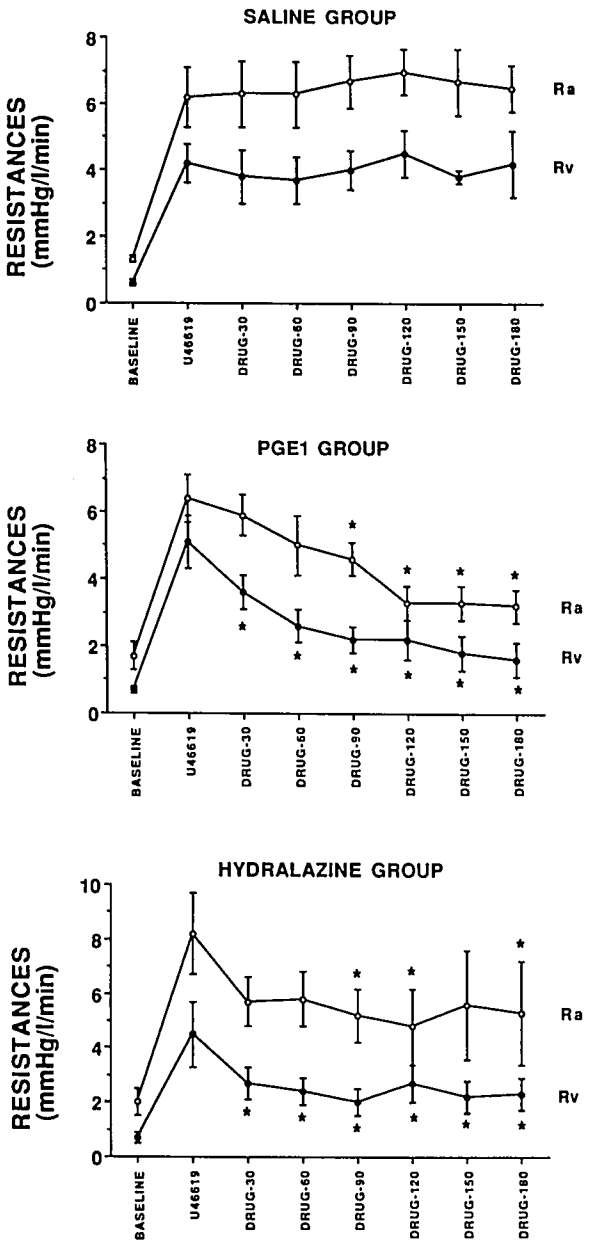

FIG. 3. Arterial (precapillary [Ra]) and venous (postcapillary [Rv]) components of pulmonary vascular resistance at baseline, during U46619 administration, and after 30, 60, 90, 120, 150, and 180 min of saline, prostaglandin E_1 (PGE_1), or hydralazine. Data are expressed as mean values ± SEM. *$P < 0.05$ *versus* the corresponding U46619 values.

dralazine administration had no significant effect on any pulmonary vascular pressure. In contrast, PGE_1 significantly decreased Ppa, Ppc, Ppa − Ppao, and Ppc − Ppao.

Discussion

Increased Rp may result in two distinct problems—namely, pulmonary edema due to increased Ppc, and right ventricular dysfunction due to increased right ventricular afterload. The first problem, elevated Ppc, is usually monitored clinically by measurement of Ppao or left atrial pressure. These pressures equal Ppc only if there is no Rv (postcapillary resistance). However, Rv is normally

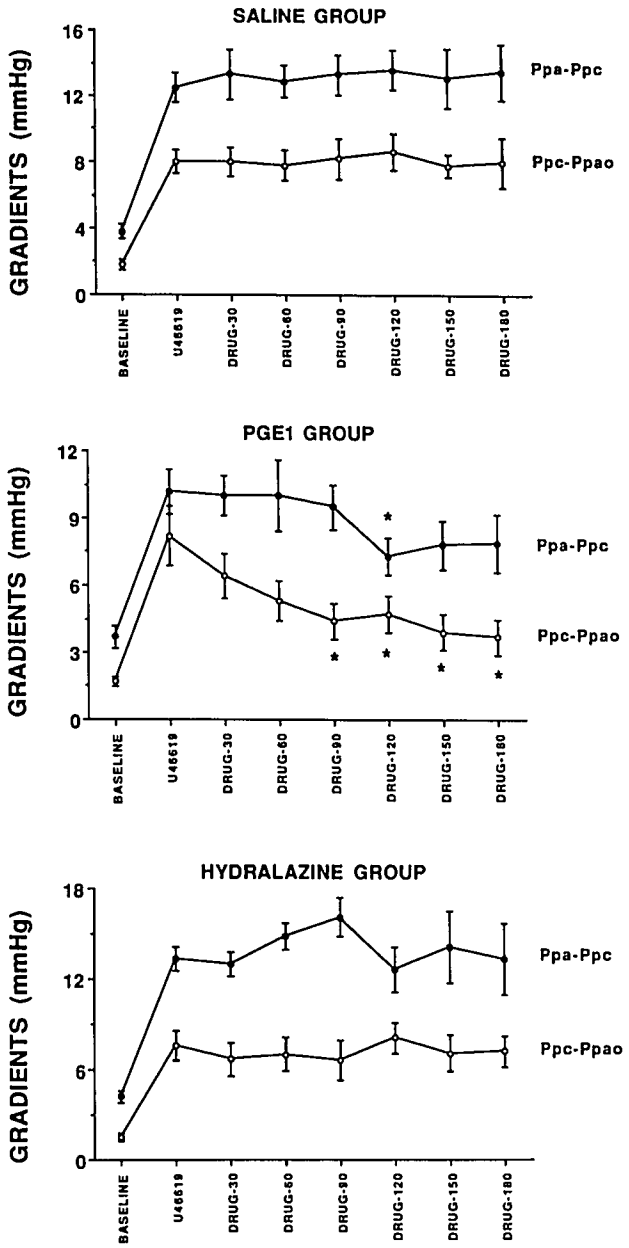

FIG. 4. The pulmonary arterial pressure gradient (pulmonary artery pressure minus pulmonary capillary pressure [Ppa − Ppc]) and the pulmonary venous pressure gradient (pulmonary capillary pressure minus pulmonary artery occlusion [Ppc − Ppao]) at baseline, during U46619 administration, and after 30, 60, 90, 120, 150, and 180 min of saline, prostaglandin E_1 (PGE_1), or hydralazine. Data are expressed as mean values ± SEM. *$P < 0.05$ *versus* the corresponding U46619 values.

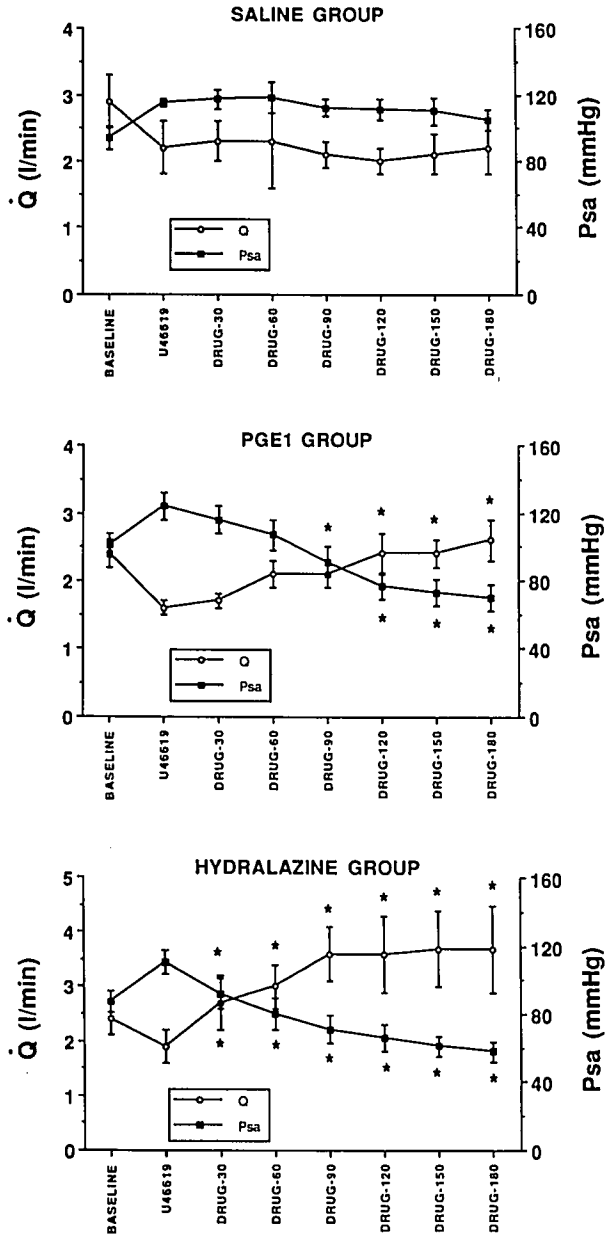

FIG. 5. Cardiac output ($\dot{Q}$) and mean systemic arterial pressure (Psa) at baseline, during U46619 administration, and after 30, 60, 90, 120, 150, and 180 min of saline, prostaglandin E_1 (PGE_1), or hydralazine. Data are expressed as mean values ± SEM. *$P < 0.05$ *versus* the corresponding U46619 values.

40% of Rp[8] and may be increased with disease states and pharmacologic interventions.[9,10] An increase in Rv will increase Ppc if $\dot{Q}$ and left atrial pressure remain unchanged (Ppc = Pla + Rv · $\dot{Q}$, where Pla = left atrial pressure). For example, if Ppa is 40 mmHg and left atrial pressure is 15 mmHg, a normal longitudinal distribution of Rp (*i.e.*, Rv/Rp = 0.40) will result in a Ppc of 25 mmHg. Moreover, when capillary permeability is altered as in adult respiratory distress syndrome, small changes in Ppc may result in marked changes in pulmonary edema.[4,5] Therapy directed toward decreasing Rv should decrease Ppc, thereby decreasing pulmonary edema and promoting lung healing. In contrast, pulmonary arterial vasodilation by itself will not decrease Ppc. In fact, if $\dot{Q}$ increases as a result of systemic vasodilation, pulmonary edema may be exacerbated.[11] In addition, pulmonary arterial vasodilation may worsen ventilation–perfusion matching in patients with lung disease.

Pulmonary hypertension may result from multiple etiologies, each of which may differentially affect pulmonary arterial *versus* pulmonary venous resistance.[12] Similarly, pharmacologic agents may decrease overall Rp by markedly different mechanisms of action.[1] Studies of pulmonary vasodilator therapy have primarily focused on the relative pulmonary *versus* systemic effects of vasodilator therapy.[1–3] In contrast, the relative effects of vasodilators on pulmonary arterial *versus* pulmonary venous resistance have rarely been investigated because of difficulties with measurement of capillary pressure. It is important to note that only decreases in Rv will decrease the gradient between Ppc and left atrial pressure and decrease pulmonary edema.

In the perfused lung, Ppc can be measured by micropuncture[13] or isogravimetric techniques.[8,14–16] Currently, neither method can be used in intact subjects. In the perfused lung, mathematical analysis of the pressure changes following arterial occlusion, venous occlusion, or double vascular occlusion has been used to estimate Ppc by analogy to electrical circuit models of the pulmonary circulation.[9,14–16] The technique of arterial occlusion has been extended to intact subjects by considering pulmonary artery balloon inflation during Ppao measurement

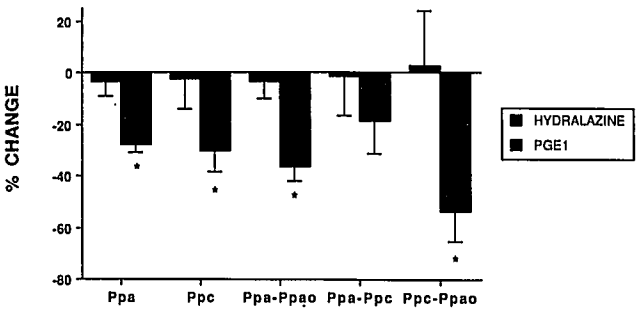

FIG. 6. Effects of hydralazine and prostaglandin E_1 (PGE_1) on pulmonary artery pressure (Ppa), pulmonary capillary pressure (Ppc), the total pulmonary vascular pressure gradient (Ppa − Ppao), where Ppao is pulmonary artery occlusion pressure, the pulmonary arterial pressure gradient (Ppa − Ppc), and the pulmonary venous pressure gradient (Ppc − Ppao). Data are expressed as the percent change in each variable from the U46619 measurement *versus* the final (drug − 180) measurement. *Significant changes ($P < 0.05$).

in these subjects to be analogous to arterial occlusion in the perfused lung.[17–20]

The current study examined the effects of vasodilator therapy on the longitudinal distribution of Rp during U46619-induced pulmonary hypertension. U46619, a stable endoperoxide thromboxane A_2–mimetic, has potent effects on vascular smooth muscle contractility.[21] Thromboxanes have been implicated in a number of pathologic states characterized by abnormal vascular tone. Thromboxane A_2 has been associated with the pulmonary vasoconstriction occurring in association with sepsis,[22] endotoxemia,[23] complement activation,[24] neutrophil activation,[25] and microembolism.[26] In sheep, U46619 infusion has produced sustained pulmonary hypertension without excessive increases in systemic arterial pressure.[2,3] Elevations in Ppa and Rp remain stable for at least 4 h. Vasodilator drug infusion can reduce pulmonary artery pressure and increase $\dot{Q}$, indicating that reversible pulmonary vasoconstriction is present. U46619-induced pulmonary hypertension therefore appears to be a useful model to compare the pulmonary vasodilator properties of drugs. This model has been effective in allowing assessment of the relative pulmonary and systemic hemodynamic effects of different clinically used pulmonary vasodilators.[2,3,27]

In the current study, U46619 increased both Ra and Rv, thereby allowing assessment of the effects of PGE_1 and hydralazine on both components of Rp. U46619 has similar effects on Ra and Rv in the perfused rabbit lung,[28] and another stable thromboxane A_2 analogue has similar effects in the perfused newborn lamb lung.[29] Increased Ppc due to pulmonary venoconstriction is a major factor in the associated pulmonary edema in these models. In sheep, U46619 administration increases lung lymph flow but decreases lung lymph protein concentration, consistent with increased Rv and Ppc.[30]

Vasodilators have been studied for the treatment of both primary and secondary pulmonary hypertension. In general, these studies have focused on the global pulmonary and systemic hemodynamic effects. In contrast, there have been only limited studies of the effect of vasodilators on the longitudinal distribution of Rp. In patients with adult respiratory distress syndrome, PGE_1, nitroglycerin, and prostacyclin each produced decreases in Rp, Ra, Rv, and Ppc with no significant change in Rv/Rp.[6,31] However, the doses of each agent were limited by systemic hypotension, so that only 2–3-mmHg decreases in Ppc and even smaller decreases in Ppc − Ppao occurred. In the current study, both PGE_1 and hydralazine decreased Rp with no significant effect on Rv/Rp. PGE_1 decreased Ppc by 4.4 mmHg, whereas hydralazine had no significant effect on Ppc. The difference in the effects of the two drugs is partially explained by the increased $\dot{Q}$ that occurred with hydralazine administration. In addition, increased sympathetic tone and catecholamine release in response to systemic hypotension may have increased Rp and Rv in the hydralazine group.

One limitation of the current study is the estimation of Ppc (and therefore Ra and Rv) from analysis of Ppao pressure decay profiles. Ppc cannot be directly measured in intact subjects, and the appropriate method for analysis of Ppao pressure decay profiles remains a subject of debate.[32–35] The method used in the current study demonstrated results consistent with the known effects of thromboxane A_2 on the isolated lung and has produced results consistent with data in other animal models of pulmonary hypertension.[7,36] Animal data strongly suggest that the method used in the current study can accurately track changes in Ppc.[37] In addition, the results with PGE_1 (balanced effect on Ra and Rv) are consistent with our findings in the perfused rabbit lung.[38] Since the method of Ppao pressure decay analysis used in the current study results in an estimate of Ppc that is lower than than those produced by the two other commonly used methods,[37] the true changes in Rv and Ppc seen with U46619, PGE_1, and hydralazine may have been even greater than indicated by our results.

In summary, both PGE_1 and hydralazine were effective pulmonary vasodilators in sheep. PGE_1 decreased both Ppa and Rp, whereas hydralazine decreased Rp but not Ppa. Both drugs reduced both components (Ra and Rv) of Rp, but only PGE_1 decreased Ppc and the gradient between Ppc and Ppao. We conclude that PGE_1 is more likely to reduce the hydrostatic component of pulmonary edema during states of pulmonary hypertension.

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