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Vasodilator Therapy in Vasoconstrictor-induced Pulmonary Hypertension in Sheep

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A stable preparation of pulmonary hypertension in sheep was developed using a continuous infusion of the vasoconstrictor U46619, a stable endoperoxide thromboxane A_2-mimetic. Using this model, the pulmonary and systemic effects of nitroglycerin, sodium nitroprusside, hydralazine, and prostaglandin E_1 were compared at doses producing equivalent reductions in systemic blood pressure. Although all four drugs decreased pulmonary artery pressure and resistance, different drug hemodynamic profiles were found. Prostaglandin E_1 demonstrated the greatest pulmonary specificity and resulted in the largest decrease in pulmonary artery pressure (from 33 ± 1 to 23 ± 1 mmHg). Nitroglycerin and sodium nitroprusside demonstrated intermediate pulmonary specificity and did not affect cardiac output. Hydralazine demonstrated the least pulmonary specificity and resulted in a large decrease in systemic vascular resistance, with only a moderate decrease in pulmonary artery pressure and resistance. Rational selection of pulmonary vasodilators for clinical application will vary depending on baseline heart rate and rhythm, pulmonary artery pressure, systemic artery pressure, and cardiac output. (Key words: Blood pressure: hypertension; pulmonary. Heart: vascular resistance. Hormones: prostaglandins. Lung: blood flow; shunt; vascular resistance. Pharmacology: hydralazine; nitroglycerin; sodium nitroprusside.)

THERAPY OF PULMONARY hypertension with associated right ventricular dysfunction remains a therapeutic problem. Clinical use of vasodilators has yielded inconsistent results.[1] Vasodilator therapy may be complicated by systemic hypotension, right ventricular failure, exacerbation of pulmonary hypertension, and arterial oxygen desaturation.[2,3] Active pulmonary vasoconstriction is a significant component of the increased vascular resistance in both acute and chronic pulmonary hypertension.[4] A drug with *preferential* pulmonary vasodilator effect would minimize the risk of systemic complications while effectively lowering pulmonary resistance. Results from clinical studies evaluating pulmonary vasodilators are often in conflict due to small numbers of patients and the heterogeneous nature of human pulmonary hypertension. Extensive human comparative studies are not feasible. We have, therefore, developed an *in vivo* model for pulmonary hypertension in which continuous infusion of U46619, an endoperoxide thromboxane A_2-mimetic, produces stable pulmonary hypertension in sheep. We used this preparation to compare the vasodilator effects of four drugs selected on the basis of: 1) favorable reports suggesting clinical efficacy in pulmonary hypertension,[5-14] 2) mechanism of action *via* either cyclic GMP or cyclic AMP pathways, 3) drug duration of action and available formulations for administration, and 4) primary site of vasodilator activity (arterial, venous, or both). Nitroglycerin (NTG) and sodium nitroprusside (SNP) are short-acting titratable vasodilators which activate guanylate cyclase to increase smooth muscle guanosine 3', 5'-monophosphate (cyclic GMP).[15] Prostaglandin E_1 (PGE_1) is a short-acting linolenic acid derivative which activates adenylate cyclase and increases intracellular cyclic AMP levels.[16] Lastly, hydralazine (HYD) is a long-acting smooth muscle vasodilator which activates guanylate cyclase and, at normal clinical doses, acts primarily on the arterial vascular bed.

Materials and Methods

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

Nine sheep weighing 16–30 kg were anesthetized with thiopental 20 mg/kg iv. Following tracheal intubation, they were mechanically ventilated at a tidal volume of 15–25 ml/kg and a rate adjusted to maintain arterial carbon dioxide tension between 35–45 mmHg. Anesthesia was maintained with halothane (end-tidal 1%) in oxygen. Temperature was maintained at 37.5–39° C with a warming blanket. Following induction of anesthesia, systemic arterial, central venous, and triple-lumen pulmonary arterial catheters were inserted by peripheral cutdown. Heart rate was measured by continuous ECG monitoring. Twenty minutes after catheter insertion, baseline measurements were obtained. Measured hemodynamic variables included heart rate (HR), mean systemic arterial pressure (SAP), central venous pressure (CVP), mean pulmonary artery pressure (PAP), pulmonary artery occlusion pressure (PAOP), and cardiac output (CO). Arterial (ABG) and mixed venous (VBG) blood gas tensions were obtained. Pulmonary hypertension was then induced by infusion of the selective vasoconstrictor U46619 (9,11-dideoxy-11α, 9 α-epoxymethano-prostaglandin $F_2\alpha$). The infusion rate was initially titrated until PAP exceeded 30

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mmHg and CO was reduced by at least 25%; the infusion rate was then maintained constant for the duration of the experiment. Hemodynamic measurements were obtained 30 min later. NTG, SNP, and PGE_1 were then administered to all animals. The order of NTG, SNP, and PGE_1 administration was randomized; each drug was given first in three animals, second in three animals, and third in three animals. Each drug was administered as a continuous infusion titrated to reduce SAP to 70% of each pre-drug value. Hemodynamic and blood gas measurements were obtained prior to each drug infusion and 15 min after a stable drug infusion rate had been obtained. A 45-min stabilization and washout period occurred between drugs. Forty-five minutes after the last randomized drug, HYD was given intravenously over 10–15 min in 3–5 mg increments to produce a 30% reduction in SAP, and data were collected. The extended half-life of hydralazine required that it be administered as the fourth and final vasodilator in all animals.

Measurement Techniques

Intravascular pressures were measured at end-expiration with Hewlett-Packard® quartz transducers (model 1290A) referenced to left atrial level and recorded on a Hewlett-Packard® eight-channel recorder. CO was determined in triplicate by thermodilution technique using 10 ml of room temperature saline injectate and an Edwards 9520A cardiac output computer. Blood gas tensions were analyzed using a Corning® 168 pH/blood gas analyzer. Venous and arterial oxygen saturations were calculated using a Severinghaus slide rule,[17] assuming a P_{50} value of 27 mmHg for sheep hemoglobin.[18] Oxygen content was calculated as: $C = (1.34 \times Hgb \times S_{O_2}) + (0.003 \times P_{O_2})$. Shunt fraction (Qs/Qt) was calculated as: (capillary oxygen content-arterial oxygen content)/(capillary oxygen content-mixed venous oxygen content). Pulmonary vascular resistance (Rp) was calculated as (PAP-PAOP) × 80/CO; systemic vascular resistance (Rs) as (SAP-CVP) × 80/CO; and stroke volume (SV) as CO/HR. The Rp/Rs ratio was calculated to assess the balance of pulmonary to systemic vasodilator effects.

Drugs

Prostaglandin E_1 and U46619 were a gift from Doug McCarter (Upjohn). U46619 stock solution was prepared in absolute alcohol (concentration 5 mg/ml) and stored at −10° to −20° C; aliquots of 0.4 ml were diluted in 50 ml normal saline and infused by Harvard pump for experimental administration. Nitroglycerin (Tridil; American Critical Care) was prepared by diluting 15 mg in 50 ml of 5% dextrose in water. Sodium nitroprusside (Nipride; Roche) was prepared by diluting 10 mg in 50 ml of 5% dextrose in water. PGE_1 was prepared in 0.2M phosphate buffer at a concentration of 0.25 mg/50 ml. Hydralazine (Apresoline; Ciba) was directly administered in intravenous boluses.

Statistical Analysis

Effects of U46619 infusion and the stability of the model over the 3–4-h period of the drug studies were assessed by one-way repeated measures analysis of variance (ANOVA) of five time points. The timepoints were baseline, 30 min of U46619 infusion (prior to infusion of the first drug), and the three other pre-drug times (second drug, third drug, and fourth drug in order). Duncan's multiple range comparison test was used to identify differences among timepoints. Changes among drug effects were analyzed by a one-way repeated measures ANOVA using the change in value during drug therapy. Time-related changes in drug effects were assessed by one-way repeated measures analysis of variance of the change in value during drug therapy at three time points (first drug, second drug, and third drug in order). Probability values less than 0.05 were considered significant. Results are reported as mean values ± standard error of the mean.

Results

The rate of U46619 infusion was 1.4 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. U46619 resulted in pulmonary hypertension with an increase in PAP of 133%, an increase in Rp of 324%, an increase in Rp/Rs of 135%, and a decrease in CO of 24%. These changes remained stable throughout the study (table 1). Arterial P_{O_2} decreased 24% 30 min after U46619 infusion; however, pre-drug arterial oxygen tensions remained greater than 150 mmHg throughout the study (table 2).

Drug infusion rates were 31 ± 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for NTG, 16 ± 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for SNP, and 1.2 ± 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for PGE_1. Total SNP dose did not exceed 1 $mg \cdot kg^{-1}$ during the study, and no animal developed metabolic acidosis concurrent with SNP administration. Hydralazine dose was 0.7 ± 0.1 $mg \cdot kg^{-1}$. SAP decreased 28% with NTG, 31% with SNP, 29% with PGE_1, and 36% with HYD administration. All four drugs decreased PAP (table 3; fig. 1). PAP decreased more with PGE_1 than with HYD ($P < 0.01$), SNP ($P < 0.05$), or NTG ($P < 0.05$). Rp decreased 40% with PGE_1, 33% with HYD, 18% with NTG, and 13% with SNP. PGE_1 ($P < 0.01$) and HYD ($P < 0.05$) decreased Rp significantly more than either NTG or SNP. CO increased 23% with PGE_1 and 24% with HYD; NTG and SNP did not affect CO. Both PGE_1 and HYD increased CO significantly more than NTG or SNP. PGE_1

TABLE 1. Hemodynamic Variables at Selected Times Throughout the Study

Time	HR (beats/min)	$\overline{SAP}$ (mmHg)	$\overline{PAP}$ (mmHg)	CO (l/min)	Rp (dyn·s·cm^{-5})
Baseline	145 ± 12	98 ± 5	14.9 ± 0.9	2.31 ± .17	336 ± 57
30'-U46619	124 ± 6	131 ± 4†	33.4 ± 1.4†	1.73 ± .20†	1293 ± 257†
Pre-drug 2	128 ± 7	121 ± 5†	33.5 ± 1.4†	1.58 ± .18†	1421 ± 280†
Pre-drug 3	131 ± 7	115 ± 3†	34.2 ± 1.5†	1.47 ± .19†	1576 ± 277†
Pre-drug 4	138 ± 12	108 ± 6*	33.6 ± 0.7†	1.66 ± .20†	1386 ± 265†

Values are means ± SEM for nine sheep. HR = heart rate; SAP = mean systemic arterial pressure; PAP = mean pulmonary arterial pressure; CO = cardiac output; Rp = pulmonary vascular resistance

Note: The 30'-U46619 time point is pre-drug 1.
* $P < 0.05$ compared to baseline; † $P < 0.01$.

increased SV 15%; the other three drugs did not affect SV. HR did not significantly change during drug administration. CVP decreased with NTG, SNP, and PGE_1, but did not change with HYD. The decrease with NTG was significantly different ($P < 0.01$) from HYD. PAOP decreased with NTG and PGE_1; there was no change with SNP or HYD. The decrease with PGE_1 was significantly different ($P < 0.01$) from HYD. Qs/Qt increased only with PGE_1, and this effect was significantly different from the other three drugs ($P < 0.01$). There were no significant differences in drug effects on any variable related to the order of administration of the three randomized drugs.

The Rp/Rs ratio (fig. 1) represents relative pulmonary selectivity and was not changed by PGE_1; the other three drugs significantly increased this ratio. HYD was significantly worse than PGE_1 ($P < 0.01$), NTG ($P < 0.05$), and SNP ($P < 0.05$) in this regard.

Discussion

Pulmonary hypertension may develop secondary to a complex interaction between vasoconstriction and structural changes in pre- and post-capillary units of the pulmonary vascular bed. Vasoconstriction occurs in mitral stenosis, adult respiratory distress syndrome,[19] pulmonary embolism,[20] hypoxia,[21] and primary pulmonary hypertension. An ideal pulmonary vasodilator for the treatment of pulmonary hypertension and associated right ventricular dysfunction would decrease pulmonary artery pressure and pulmonary vascular resistance, increase cardiac output, and not worsen systemic blood pressure or pulmonary ventilation-perfusion matching. This study compared the vasodilator effects of four drugs in vasoconstrictor-induced pulmonary hypertension in sheep.

TABLE 2. Oxygenation Variables Related to Drug Therapy

Drug	Arterial P_{O_2} (mmHg)	Venous P_{O_2} (mmHg)	Shunt (%)
Pre NTG	286 ± 57	45.0 ± 4	25.1 ± 4.6
Post NTG	295 ± 52	46.1 ± 5	26.8 ± 5.2
Pre SNP	318 ± 37	49.5 ± 3	24.3 ± 4.1
Post SNP	272 ± 45	48.2 ± 3	24.0 ± 3.2
Pre PGE_1	314 ± 54	46.6 ± 4	22.7 ± 3.9
Post PGE_1	305 ± 60	57.4 ± 7*	32.6 ± 5.5†
Pre HYD	213 ± 45	42.2 ± 4	30.6 ± 4.8
Post HYD	265 ± 52†	51.7 ± 6*	32.9 ± 4.5

Values are means ± SEM for nine sheep. NTG = nitroglycerin; SNP = sodium nitroprusside; PGE_1 = prostaglandin E_1; HYD = hydralazine.
* $P < 0.05$ compared to pre-drug value.
† $P < 0.01$ compared to pre-drug value.

U46619, a stable endoperoxide thromboxane A_2-mimetic, has potent effects on platelet aggregation and vascular smooth muscle contractility.[22,23] Thromboxanes have been implicated in a number of pathologic states characterized by abnormal vascular tone. Recently, thromboxane A_2 has been associated with the pulmonary vasoconstriction seen in sepsis,[24] endotoxemia,[25] complement activation,[26] neutrophil activation,[27] microembolism,[28] and monocrotaline-induced pulmonary hypertension.[29] In our study, U46619 infusion induced sustained pulmonary hypertension without excessive increase in systemic arterial pressure. Elevations in PAP and Rp remained stable throughout the 4-h study period. Vasodilator drug infusion reduced pulmonary artery pressure and increased cardiac output, indicating that reversible pulmonary vasoconstriction was present. U46619-induced pulmonary hypertension, therefore, appears to be of use for comparing the pulmonary vasodilator properties of drugs.

Pulmonary vasodilator therapy may be complicated by systemic hypotension.[1] Vlahakes *et al.*[30] studied right coronary blood flow in adult dogs with acute pulmonary hypertension and increased right ventricular afterload, and demonstrated that right ventricular failure was precipitated by right ventricular free wall ischemia. Infusion of phenylephrine restored myocardial perfusion pressure and right ventricular "coronary driving pressure" and reversed right ventricular failure in that model. A drug with *preferential* pulmonary (*versus* systemic) vasodilator effect minimizes the risk of systemic hypotension, which can result in coronary ischemia and acute right ventricular failure. In our study, the specificity of pulmonary vasodilation was assessed by the

TABLE 3. Hemodynamic Variables Related to Drug Therapy

Drug	HR (beats/min)	$\overline{SAP}$ (mmHg)	$\overline{PAP}$ (mmHg)	CO (l/min)	Rp (dyn·s·cm^{-5})	Rp/Rs
Pre NTG	128 ± 6	125 ± 5	34.1 ± 1.5	1.5 ± 0.2	1467 ± 230	0.214 ± .019
Post NTG	145 ± 8	90 ± 4†	27.1 ± 1.5†	1.6 ± 0.2	1182 ± 190*	0.245 ± .026*
Pre SNP	135 ± 8	120 ± 3	33.7 ± 1.2	1.6 ± 0.2	1408 ± 270	0.224 ± .016
Post SNP	147 ± 8	83 ± 3†	27.1 ± 1.2†	1.5 ± 0.1	1200 ± 209*	0.261 ± .017*
Pre PGE_1	120 ± 4	123 ± 5	33.3 ± 1.3	1.6 ± 0.2	1415 ± 278	0.206 ± .019
Post PGE_1	128 ± 6	87 ± 4†	23.1 ± 1.2†	2.0 ± 0.2*	867 ± 189†	0.209 ± .021
Pre HYD	138 ± 11	108 ± 5	33.6 ± 0.7	1.7 ± 0.2	1386 ± 250	0.249 ± .026
Post HYD	162 ± 14	69 ± 5†	28.3 ± 1.3†	2.1 ± 0.3*	933 ± 160†	0.356 ± .069*

Values are means ± SEM for nine sheep. HR = heart rate; $\overline{SAP}$ = mean systemic arterial pressure; PAP = mean pulmonary arterial pressure; CO = cardiac output; Rp = pulmonary vascular resistance; Rp/Rs = ratio of pulmonary to systemic vascular resistance; NTG = nitroglycerin; SNP = sodium nitroprusside; PGE_1 = prostaglandin E_1; HYD = hydralazine.

* $P < 0.05$ compared to pre-drug value; † $P < 0.01$.

change in Rp/Rs ratio with drug therapy. An ideal pulmonary vasodilator would reduce Rp as much or more than Rs, and thereby decrease this ratio during drug infusion. In our study, PGE_1 demonstrated the greatest pulmonary specificity and did not change the Rp/Rs ratio; the other three drugs all significantly increased (worsened) this ratio.

Pulmonary vasodilator therapy may be complicated by arterial oxygen desaturation and increased pulmonary shunt.[31] Therapy with PGE_1 increased shunt fraction, but did not affect arterial oxygen tension (table 2). PGE_1 also increased cardiac output and mixed venous oxygen tension. HYD resulted in similar increases in cardiac output and mixed venous oxygen tension, but did not increase shunt fraction. Lynch *et al.*[32] demonstrated that shunt fraction varied directly with the mixed venous oxygen tension in an oleic acid injury canine model with intrapulmonary shunt. This effect may explain why drugs such as PGE_1, which cause large increases in CO, may also result in large increases in calculated shunt. Ghignone *et al.*[33] studied the effects of HYD in a canine model of oleic acid injury. As in our study, HYD increased cardiac output and increased mixed venous and arterial oxygen tensions, but did not affect shunt fraction. Caution must be applied when interpreting these results in our study, however, since HYD was the only drug not randomized in order of administration.

Our data suggest different hemodynamic profiles among the four drugs studied in this vasoconstrictor model of pulmonary hypertension. PGE_1 did not affect the Rp/Rs ratio, resulted in the largest decrease in $\overline{PAP}$

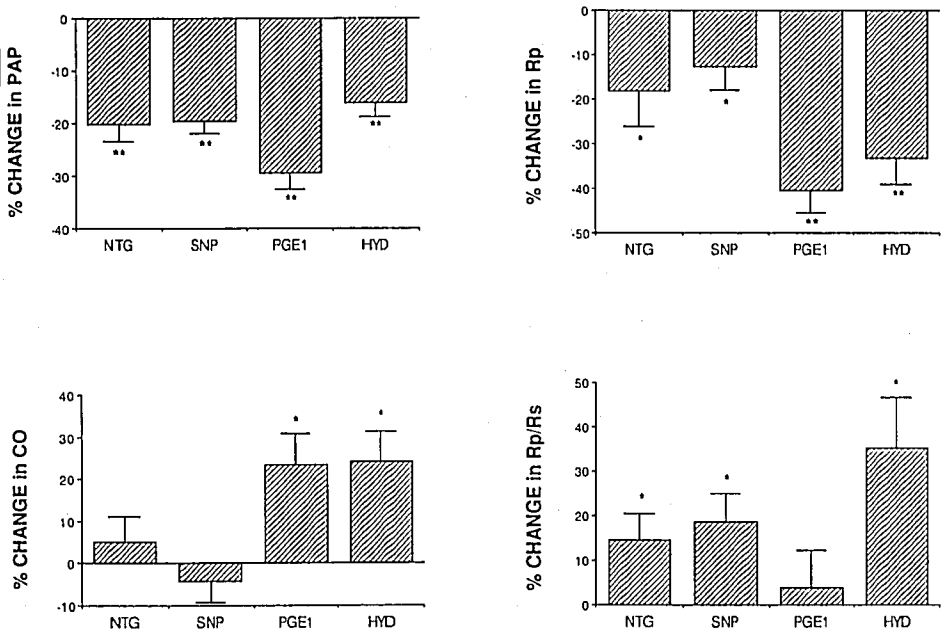

FIG. 1. Per cent change in mean pulmonary artery pressure (PAP), in cardiac output (CO), in pulmonary vascular resistance (Rp), and in the ratio of pulmonary to systemic vascular resistance (Rp/Rs) with the administration of nitroglycerin (NTG), sodium nitroprusside (SNP), prostaglandin E_1 (PGE_1), and hydralazine (HYD). Each value represents the mean ± SEM of nine sheep. * $P < 0.05$ compared to pre-drug value; ** $P < 0.01$ compared to pre-drug value. See text for comparison between different drugs.

of any agent studied, increased CO, and decreased Rp. Endogenous prostaglandins may contribute to the physiologic regulation of pulmonary blood flow, and a deficiency of endogenous prostaglandins has been postulated as a cause of primary pulmonary hypertension.[34,35] PGE_1 has marked pulmonary clearance due to 15-hydroxy-prostaglandin dehydrogenase in the lungs.[36,37] Rapid pulmonary clearance of PGE_1 may decrease the active drug concentration in the systemic circulation and contribute to its selectivity as a pulmonary vasodilator. Metabolism, however, may be altered in abnormal or diseased lungs.[38]

Szczeklik *et al.*[11] studied PGE_1 infusion in 20 patients with pulmonary hypertension due to mitral valve disease. PAP decreased 24%, CO increased 13%, and pulmonary resistance decreased 33%. D'Ambra *et al.*[39] treated five patients with refractory right heart failure and severe pulmonary hypertension in the immediate post-cardiopulmonary bypass period by using central venous infusion of PGE_1 and left atrial infusion of norepinephrine. Rp decreased 85%, and all five patients survived.

In our study, two drugs (NTG and SNP) had intermediate pulmonary specificity as assessed by the change in Rp/Rs ratio (fig. 1). NTG and SNP both reduced PAP 20%, while CO was unchanged by either drug. Pearl *et al.*[6] treated nine patients with chronic pulmonary hypertension with NTG infusion. Stroke volume and cardiac index increased 40%, and both Rp and PAP decreased. Five of six patients treated with long-acting nitrates had sustained improvement. The same investigators utilized NTG and SNP to treat pulmonary hypertension in dogs with increased pulmonary vascular resistance induced by oleic acid injury.[10] NTG increased CO while decreasing PAP and Rp; SNP produced systemic hypotension without changing PAP or Rp. Benoit *et al.*[40] reported a 26% *decrease* in cardiac output when NTG was administered to dogs with oleic acid pulmonary edema. Their protocol produced acute lung injury, but not severe pulmonary hypertension, so that the systemic venodilator and systemic arterial dilator effects of NTG predominated, thereby decreasing left ventricular preload and cardiac output.[41] Hermiller *et al.*[34] reported isosorbide dinitrate to be the only drug to decrease pulmonary artery pressure in ten women with primary pulmonary hypertension. Rp decreased "modestly" but significantly. Identical to our findings, cardiac output did not change. Both NTG and SNP significantly decreased CVP, and the potent venodilator properties of these drugs may limit venous return. This reduction in venous return may be of a sufficient extent that CO does not increase, despite the decrease in right and left heart afterload. The overall effect on cardiac output in this setting is a function of baseline volume status, systemic and pulmonary vascular tone, right and left heart function, and the dose of vasodilator utilized.

In our study, HYD decreased PAP and Rp, increased CO, and produced the largest increase in the Rp/Rs ratio. This last finding must be viewed with caution because HYD was always administered as the fourth drug. Although statistical analysis of pulmonary *versus* systemic vasodilator responsiveness did not demonstrate changes in relation to order of administration of the first three drugs, it is possible that different results might have been obtained if HYD were given earlier in the study. HYD was first used to treat primary pulmonary hypertension by Rubin and Peter in 1980.[8] Four patients treated with oral HYD had decreases in Rp and increases in CO, but no change in PAP. Hemodynamic effects persisted at repeat cardiac catherization 3–6 months later. Other studies with HYD had much less favorable results. Fisher *et al.*[13] treated five patients with primary pulmonary hypertension with HYD. HYD produced no change in PAP or Rp and a variable effect on CO. Moreover, the Rp/Rs ratio increased 35% in these five patients after HYD, similar to our experimental results. Ducas and Prewitt[42] have recently studied the effects of HYD in dogs with pulmonary hypertension induced by autologous blood clot embolization. In these studies, HYD doubled CO, but produced no change in PAP and only a small decrease in Rp. Pressure-flow curves indicated that HYD decreased the effective outflow or downstream pulmonary pressure.

Deleterious side effects of HYD therapy have been well documented. Packer *et al.*[2] studied 13 patients with primary and secondary pulmonary hypertension. HYD decreased Rs 40%, but decreased Rp only 21%. Stroke volume and PAP were unchanged. Four of these patients experienced hypotensive episodes; one developed progressive renal insufficiency and one died. Kronzon *et al.*[43] documented two cases of HYD therapy *increasing* PAP and worsening clinical status. The mechanism was a marked decrease in Rs with a reflex increase in heart rate and CO, but without any change in pulmonary vascular resistance. These two patients experienced dyspnea, chest discomfort, and weakness during HYD therapy. Although HYD decreased pulmonary artery pressure and increased cardiac output in our study, systemic vascular resistance always decreased significantly more than pulmonary vascular resistance. This decrease in the Rp/Rs ratio could precipitate myocardial decompensation in clinical use. The large increase in cardiac output seen with HYD may be related to direct and reflex cardiostimulating effects of HYD,[44] including a direct inotropic stimulation mediated *via* the beta adrenergic system.

In summary, we have developed stable pulmonary hypertension in sheep utilizing the vasoconstrictor

U46619. Four vasodilators were examined in this setting to determine their potency and relative specificity for the pulmonary vasculature. Prostaglandin E_1 was the most selective pulmonary vasodilator. PGE_1 also caused the largest decrease in pulmonary artery pressure. NTG and SNP were intermediate in pulmonary selectivity and did not affect CO. HYD demonstrated the least favorable pulmonary Rp/Rs profile with systemic vasodilator activity significantly more potent than pulmonary vasodilator activity. The limited clinical experience with pulmonary vasodilator therapy is consistent with our experimental findings, but caution must be exercised in extrapolating our findings directly to the clinical situation. Human pulmonary hypertension includes a complex heterogenous spectrum with marked pathologic abnormalities. This study has been limited to the examination of four vasodilators titrated to a single hemodynamic endpoint during U46619-induced vasoconstrictor pulmonary hypertension. Different vasodilator characteristics might be observed as these drugs are cautiously titrated through their full range of activity. Rational drug selection for clinical application will depend on baseline hemodynamic parameters, such as heart rate and rhythm, systemic and pulmonary arterial pressure, arterial oxygenation, and cardiac output.

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