Title: VASODILATOR THERAPY IN A VASOCONSTRICTOR MODEL OF PULMONARY HYPERTENSION IN SHEEP

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Introduction. Therapy of pulmonary hypertension with associated right ventricular dysfunction remains a therapeutic problem. Clinical use of vasodilators has produced inconsistent results.[1] Extensive comparative human studies are not feasible. We therefore developed a vasoconstrictor model of pulmonary hypertension in sheep and used this model to compare the vasodilator effects of seven drugs clinically used for therapy of pulmonary hypertension.

Methods. Eighteen male sheep weighing 16-30 kg were anesthetized with thiopental, 20 mg/kg iv, intubated and mechanically ventilated to maintain arterial PCO_2 at 35-45 mm Hg. Anesthesia was maintained with halothane (end-tidal 1%) in oxygen. Systemic and pulmonary arterial catheters were inserted. Measured and derived hemodynamic variables included heart rate (HR), cardiac output (CO; by thermodilution), stroke volume (SV), mean systemic arterial (SAP), mean pulmonary arterial (PAP), pulmonary artery wedge, and central venous pressures, pulmonary and systemic vascular resistances (SVR; PVR), arterial and mixed venous blood gas tensions, and shunt fraction (Q_s/Q_t). Following baseline measurements, the pulmonary vasoconstrictor U46619, a thromboxane A_2 mimetic, was infused at 0.8-1.7 ug/kg/min. The rate was initially titrated to achieve PAP > 30 mm Hg and a 20% or greater decrease in CO; the infusion rate was then maintained constant. In 9 sheep prostaglandin E_1 (PGE_1), sodium nitroprusside (SNP), and nitroglycerin (NTG) were then administered in random order with a 45 min stabilization period between drugs. Each drug was titrated to reduce SAP by 30%. Hemodynamic and blood gas data were obtained prior to each drug and 15 min later when a stable infusion rate had been obtained. Following completion of the 3 drug infusions and a 45 min stabilization period, HYD was administered in 3-5 mg boluses to reduce SAP by 30%; final measurements were then obtained. In the other 9 sheep, PGE_1, prostacyclin (PGI_2), isoproterenol (ISO) and nifedipine (NIF) were similarly studied; nifedipine was administered by continuous infusion. Drug effects were assessed by repeated measures analysis of variance and the Newman-Keuls' multiple range test.

TABLE

	HR (beats/min)	SAP (mm Hg)	PAP (mm Hg)
Baseline	138±10	98±5	14±1
U46619	119±5	127±4+	31±1+
Pre NTG	128±6	125±5	34±1
NTG	145±8	90±4+	27±1+
Pre SNP	135±8	120±3	34±1
SNP	147±8	83±3+	27±1+
Pre HYD	138±11	108±5	34±1
HYD	162±14	69±5+	28±1+
Pre PGE_1	118±5	122±4	32±1
PGE_1	127±5	87±3+	22±1+
Pre ISO	119±6	121±4	30±1
ISO	182±10+	110±6	25±2+
Pre PGI_2	118±4	118±3	30±1
PGI_2	145±8+	85±2+	25±2*
Pre NIF	113±3	108±4	31±1
NIF	123±9	74±3+	29±1+

Values are means ± SEM for nine sheep;

CO (L/m)	PVR (d·s·cm^{-5})	PVR/SVR	Qs/Qt (%)
2.6±0.2	266±40	.09±.01	17±1
1.7±0.2+	1164±171+	.21±.01+	19±2
1.5±0.2	1467±230	.21±.02	25±5
1.6±0.2	1182±190*	.25±.03*	27±5
1.6±0.2	1408±270	.22±.02	24±4
1.5±0.1	1200±209*	.26±.02*	24±3
1.7±0.2	1386±250	.25±.03	31±5
2.1±0.3*	933±160+	.36±.07*	33±4
1.6±0.2	1345±207	.20±.02	20±4
2.2±0.2+	740±135+	.21±.02	28±5+
1.8±0.1	996±90	.20±.01	18±2
3.2±0.2+	573±55+	.20±.02	23±2+
1.7±0.2	1085±90	.21±.01	16±3
3.1±0.3+	570±90+	.24±.02*	23±2+
1.6±0.1	1200±100	.23±.02	19±4
2.4±0.3*	810±110+	.32±.02+	25±3*

*p <0.05 compared to pre-drug value; +p < 0.01

Results. U46619 increased PAP 128%, PVR, 338%, and the PVR/SVR ratio 138%, and decreased CO 35% (Table). These effects remained stable throughout the study. All drug doses except ISO were limited by the 30% decrease in SAP; ISO dose was limited by tachycardia and dysrhythmias. All 7 drugs decreased PAP, PVR, and SVR. All drugs except NTG and SNP increased CO; SV increased only with PGE_1, PGI_2, and NIF. All drugs except PGE_1 and ISO increased the PVR/SVR ratio. With the exception of HYD, all drugs which increased CO increased Q_s/Q_t. All drugs which increased CO increased mixed venous PO_2. Arterial PO_2 increased with HYD, ISO, and NIF and remained unchanged with the other drugs.

Discussion. Although all 7 drugs decreased PAP and PVR, distinct hemodynamic profiles were found. As assessed by the PVR/SVR ratio, PGE_1 and ISO demonstrated the greatest pulmonary specificity. PGE_1 resulted in the largest decrease in PAP; ISO resulted in the smallest decrease in SAP and the largest increase in HR. NTG, SNP, and PGI_2 demonstrated intermediate pulmonary specificity. PGI_2 resulted in a large increase in CO while NTG and SNP did not affect CO. NIF and HYD demonstrated the least pulmonary specificity. NIF resulted in the smallest decrease in PAP; HYD resulted in a large decrease in SVR with only a moderate decrease in PVR. The drug hemodynamic profiles in this study are consistent with the limited data on human pulmonary hypertension.[1] The description of unique hemodynamic profiles indicates that rational selection of pulmonary vasodilators will depend upon baseline HR, rhythm, PAP, SAP, and CO.

Reference. 1. Packer M. Vasodilator therapy for primary pulmonary hypertension. Ann Intern Med 103:258-270, 1985