Title: Amrinone Reduces Elevated Pulmonary Vascular Resistance in Isolated, Perfused Rabbit Lungs

Authors: Jeffrey P. Morray, M.D., Karen Powers, B.S.,William R. Clarke, M.D.

Affiliation: Departments of Anesthesiology and Pediatrics, University of Washington School of Medicine, Children's Hospital and Medical Center, Seattle, WA 98105.

Introduction: The purpose of our study was to quantitate amrinone's pulmonary vasodilating effect under conditions of both normal and increased pulmonary vascular pressure (PPA) and resistance (PVR) in an isolated perfused lung model in which all other determinants of PVR were controlled.

Methods and Materials: The heart-lung block from 16 anesthetized New Zealand white rabbits was removed and placed in a temperature controlled chamber. The lungs were ventilated with FIO_2=0.21, at 25 breaths/min, PIP10-15 cm H_2O, and PEEP 1 cm H_2O. The pulmonary artery was perfused with Krebs-Ringers I solution with 3% Dextran-70 and 1% albumin in which pH (7.40-7.45), PCO_2 (35-40 mm Hg), PO_2 (127-130 mm Hg) and temperature (36-37°C) were controlled. Pulmonary flow (Q) was adjusted with a roller pump and measured as left atrial outflow via an electromagnetic flow probe. Pulmonary artery (PPA) and venous (PV) pressures were measured in inflow and outflow cannulae, respectively. Venous drainage was collected in a reservoir, the height of which was adjusted to maintain PV at 2-3 cm H_2O at all Q's. After 30 minutes, PPA was measured over a range of Q, and a PPA/Q curve was constructed. The thromboxane mimetic U46,619 (Upjohn Co., Kalamazoo, MI) was given by continuous infusion to achieve a stable increase in PPA of 40-50%; the infusion was maintained at a constant rate for the balance of the study. After 15 minutes, a repeat PPA/Q curve was generated. Amrinone (A) was administered as a bolus to the perfusion reservoir to achieve a final concentration of 4 μg/ml (n=4) or 8 μg/ml (n=4). Controls received either 4 μg/ml (n=4) or 8 μg/ml (n=4) (A) without prior exposure to U46,619. A final PPA/Q curve was generated. PPA at Q=200 ml/min was used to calculate PVR ([PPA-PV]/Q). Data was analyzed with student's t-test for paired data, with significance defined as p<0.05.

Results: See Table. There was no change in PPA or PVR in animals given either 4 or 8 μg/ml (A) without prior U46,619. Eight μg/ml (A) given following U46,619 resulted in significant decreases in PPA and PVR; the decreases in these parameters following 4 μg/ml (A) were not significant.

Discussion: Administration of 8 μg/ml (A) reduced both PPA and PVR, but only when pulmonary vascular tone was elevated. (A) reduced PVR via direct pulmonary vasodilation, since all other PVR determinants were held constant. (A) has potential utility for treatment of mediator-induced pulmonary hypertension.

All values mean ±SD	AMRINONE 4μg/ml			AMRINONE 8μg/ml		
	CONTROL	U46,619	AMRINONE	CONTROL	U46,619	AMRINONE
PPA (cmH2O)	10.2 ±1.6	17.2 ±3.3*	15.4 ±0.8*	10.7 ±1.7	18.1 ±1.4*	13.4 ±1.4*+
PVR (cmH2O/ml/min)	0.051 ±0.008	0.086 ±0.016*	0.077 ±0.004*	0.054 ±0.008	0.091 ±0.007*	0.067 ±0.007*+
Percent of Control PVR	100	169.2 ±30.9*	153.1 ±25.6*	100	170.9 ±23.9*	125.1 ±10.7*+

* p<0.05 compared to control + p<0.05 compared to U46, 619

TITLE: PULMONARY CAPILLARY PRESSURE MEASUREMENT FROM PULMONARY ARTERY OCCLUSION PRESSURE PROFILE ANALYSIS

AUTHORS: G. Wakerlin, M.D., T. Flavin, M.D., L.C. Siegel, M.D., G.V. Benson, B.S., R.G. Pearl, M.D.

AFFILIATION: Depts. of Anesthesia and Cardiovascular Surgery, Stanford University Medical Center, Stanford, CA 94305

Three different methods have been proposed for estimation of pulmonary capillary pressure (Ppc) from pulmonary artery occlusion pressure (PAOP) profiles[1-3]. This study compared the 3 methods for estimating Ppc from PAOP profiles against Ppc estimated by lung lymph flow in sheep.

Methods: Seven male sheep were anesthetized with thiopental (15 mg/kg iv), intubated and ventilated with 1% halothane in 50% O_2. Pulmonary and femoral arterial catheters were inserted. A standard lung lymph fistula was created including a left atrial balloon catheter. Four hours later baseline hemodynamic measurements, including at least 3 PAOP profiles, and lymph flow rate were obtained every 20 min until stable. Left atrial pressure (Pla) was then increased by 7.5 and 15 mmHg by inflation of the left atrial balloon. Following recovery, the thromboxane A_2 analog U46619 was administered to increase pulmonary artery pressure by 10, 20 and 30 mmHg over baseline with measurements (U10, U20, U30) at each level. Ppc at baseline and during left atrial balloon inflation was estimated by the Gaar equation and linear regression was used to determine the relationship between lymph flow and Ppc. This relationship was then used to estimate Ppc during U46619 infusion. In addition, each PAOP profile was fit to a biexponential decay ($ae^{-\alpha t} + be^{-\beta t}$ + Pla) and Ppc was estimated either by the slow exponential (Ppc = b + Pla; method 1)[1] or by a method which corrects for the interaction between the 2 exponentials (method 2)[2]. In addition, a single exponential ($he^{-\gamma t}$ + Pla) was fit to the PAOP profile starting 0.3 sec after occlusion, and Ppc was estimated as h + Pla (method 3)[3]. The Ppc estimates of the 3 methods during U46619 infusion were compared by repeated measures ANOVA and the Newman-Keuls' test.

Results: Ppc estimated by the Gaar equation correlated with lymph flow (r>0.9) prior to U46619 in all sheep. Ppc estimated by all 3 methods of PAOP decay analysis correlated with Ppc estimated from lymph flow in all sheep. However, the estimates of Ppc by the three methods of decay analysis differed. Method 1 produced estimates similar to lymph flow, method 2 underestimated Ppc, and method 3 overestimated Ppc (Table).

Discussion: Although all 3 methods of estimating Ppc correlated with Ppc derived from lymph flow, the values differed. Method 2, which corrects for interactions between exponentials, underestimated Ppc, consistent with recent results comparing the 3 methods in dogs[4]. Method 3 has been validated in dog studies[3,4], but frequently overestimated Ppc in this sheep study. Based on our results, we suggest that the slow exponential technique (method 1) be used for analysis of in vivo PAOP decay profiles.

Table. Difference (mean ± SE) between Ppc measured from PAOP analysis and Ppc measured from lymph flow

	Method 1	Method 2	Method 3
U10	1.0 ± 0.9	-2.0 ± 1.0	6.1 ± 0.8
U20	0.4 ± 3.1	-3.7 ± 3.2	6.8 ± 2.8
U30	-3.8 ± 3.3	-7.0 ± 4.0	3.7 ± 2.3

References: 1) Anesthesiology 66:614, 1987. 2) Anesthesiology 70:527, 1989. 3) Am Rev Respir Dis 140:217, 1989. 4) Am Rev Respir Dis 140:1228, 1989.