Title: EFFECTS OF PHORBOL MYRISTATE ACETATE ON THE LONGITUDINAL DISTRIBUTION OF PULMONARY VASCULAR RESISTANCE IN SHEEP

Authors: E. R. Baer, M.D., R. G. Pearl, M.D., and L. C. Siegel, M.D.

Affiliation: Department of Anesthesia, Stanford University Medical Center, Stanford, California 94305

Introduction. Pulmonary hypertension is an important prognostic variable in acute respiratory failure. Increases in pulmonary capillary pressure (PCP) can produce hydrostatic pulmonary edema and exacerbate permeability pulmonary edema. Activation of neutrophils has been suggested as a mechanism of acute lung injury during acute respiratory failure.[1] Phorbol myristate acetate (PMA) activates neutrophils and produces acute respiratory failure with pulmonary hypertension and pulmonary edema.[2] The pulmonary edema may be a result of increased PCP, increased pulmonary capillary permeability, or both.[3] This study examines changes in PCP, pulmonary arterial resistance (Ra), and pulmonary venous resistance (Rv) during PMA-induced respiratory failure and pulmonary hypertension.

Methods. Six male sheep weighing 20-30 kg were anesthetized with thiopental (20 mg/kg iv followed by a continuous infusion of 5-20 mg/kg/h). Animals were mechanically ventilated with oxygen to maintain arterial pCO_2 at 35-40 mmHg. Femoral arterial, femoral venous, and pulmonary arterial catheters were inserted. Hemodynamic measurements included heart rate, mean systemic arterial pressure, mean pulmonary arterial pressure (PAP), pulmonary artery occlusion pressure (PAOP), central venous pressure and cardiac output (CO; by thermodilution). Saline was infused as necessary to maintain PAOP constant. With each set of measurements, 6 pulmonary artery occlusion profiles were acquired at 200 Hz with an analog-to-digital converter. During the acquisition of each profile, ventilation was interrupted in order to eliminate respiratory variation. Following one hour of stable baseline hemodynamic measurements, PMA (5.0 ug/kg, n=2 and 2.5 ug/kg, n=4) was injected over one minute and measurements were obtained after 0.25, 0.5, 0.75, 1, 1.5, 2,3,4, and 5 h. For each PAOP profile, a least squares fit to a biexponential decay was obtained and used to calculate PCP.[4] Ra was calculated as (PAP-PCP)/CO and Rv as (PCP-PAOP)/CO. Statistical analysis used repeated measures analysis of variance and the Newman-Keuls' multiple range test.

Table	PAP mmHg	PCP mmHg	PAOP mmHg
Baseline	10.3±0.6	5.34±0.64	2.30±0.26
0.25 h	30.4±3.6*	14.9±2.18*	5.45±0.62*
0.50 h	19.9±1.5*	7.55±1.42	3.63±0.59*
0.75 h	17.8±1.1*	6.75±0.68	2.94±0.28
1.0 h	17.3±1.7*	6.45±0.40	3.36±0.19
1.5 h	16.4±1.8*	7.51±0.88	3.21±0.12
2.0 h	15.4±1.4	5.78±0.52	2.92±0.11
3.0 h	14.6±1.7	5.49±0.74	2.89±0.05
4.0 h	15.3±2.0	5.10±0.73	3.05±0.26
5.0 h	13.6±1.4	5.25±0.62	2.74±0.09

*P<0.05 compared to baseline

Results. Pulmonary hypertension occurred within 2-5 min of PMA administration. In the 4 sheep receiving 2.5 ug/kg PMA, PAP, PVR, Ra, Rv, and PCP increased to maximal values at 0.25 h (Table) and then rapidly decreased. Rv and PCP returned to baseline values at 0.5 h, a time when PAP, PVR, and Ra were still significantly elevated. PVR and Ra returned to baseline values at 0.75 h and PAP at 2 h. Two animals received PMA 5.0 ug/kg, a dose previously described in a model of pulmonary hypertension in awake sheep.[3] Both animals developed pulmonary hypertension, severe hypoxemia, electrocardiographic changes, and biventricular failure, and died 15-30 min later. This higher dose of PMA resulted in marked increases in PCP (from 8.6±3.4 to 24.7±4.9 mmHg) and Rv (from 0.9±0.4 to 9.6±1.6 mmHg/l/min) at 0.25 h.

Discussion. Pulmonary edema in acute respiratory failure may be due to increases in PCP or capillary permeability. In a similar model of PMA-induced acute respiratory failure,[3] analyses of changes in lung lymph flow and protein concentration suggested that both mechanisms were present. Pulmonary edema immediately after PMA was related to increased PCP. Subsequently, pulmonary edema was sustained by increased permeability. In the present study, PCP and Rv increased shortly after 2.5 ug/kg PMA and then rapidly returned to baseline. Pulmonary edema and pulmonary dysfunction subsequently occurred with normal PCP, consistent with increased capillary permeability. In this model of acute respiratory failure, PCP and the longitudinal distribution of pulmonary vascular resistance varied over time, suggesting that pulmonary vasodilator therapy to decrease PCP may be indicated in some but not all situations of acute respiratory failure.

References.

1. Turino GM, Rodriguez JR, et al. Amer J Med 57:493-505, 1974
2. O'Flaherty JT, Consart S, et al. Amer J Path 101:79-92, 1980
3. Loyd JE, Newman JH, et al. J Appl Physiol 54:267-276, 1983
4. Siegel LC, Pearl RG. Anesthesiology 68:305-307, 1988

Ra mmHg/l/min	Rv mmHg/l/min	PVR mmHg/l/min	CO l/min
1.78±0.19	1.12±0.25	2.91±0.37	2.85±0.24
8.12±2.50*	4.87±1.30*	13.0±2.93*	2.16±0.42*
5.49±1.41*	1.68±0.44	7.19±1.71*	2.57±0.42
4.41±0.57	1.60±0.47	6.00±0.10	2.61±0.27
4.10±0.86	1.17±0.28	5.27±1.12	2.77±0.21
2.92±0.64	1.38±0.30	4.30±0.76	3.16±0.18
3.21±0.60	0.95±0.20	4.16±0.75	3.12±0.24
3.07±0.64	1.62±1.00	3.94±0.74	3.07±0.16
3.22±0.68	0.65±0.17	3.87±0.80	3.33±0.26
2.53±0.41	0.79±0.22	3.23±0.54	3.38±0.23