Title: ISOPROTERENOL PROTECTS AGAINST PULMONARY EDEMA IN ENDOTOXIN LUNG INJURY

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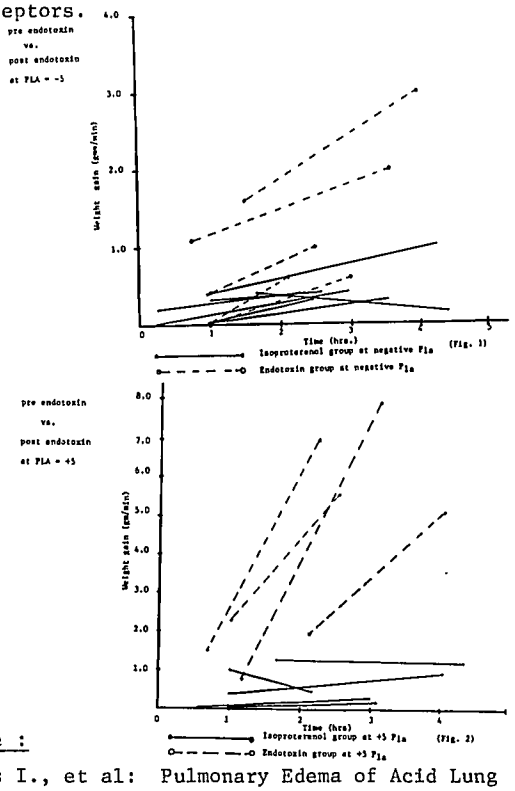
Introduction: It has recently been reported that Isoproterenol strikingly reduces the pulmonary edema following acid lung injury by preventing both the increase in pulmonary vascular pressure and permeability that occurs after acid instillation.[1] We investigated the effects of Isoproterenol in the blood perfused isolated pig lung model exposed to E Coli endotoxin in doses known to cause pulmonary hypertension and increased vascular permeability.

Methods: Twenty-22 kg pigs of both sexes were studied after anesthesia with Ketamine 8mg/kg IM and Pentobarbitol 30mg/kg IV. The animals' tracheas were cannulated and the lungs ventilated with room air at tidal volume of 15cc/kg and rate of 10/min. The heart and lungs were left in situ after median sternotomy, heparinization, and exanguination via aortic cannula over 7-10 minutes. The pulmonary artery and left atrial appendage were entered with stainless steel cannulae and secured with ligatures to isolate the pulmonary circulation. A constant perfusion of autologous whole blood at flows of 20cc/kg/min with a Sarns pump was maintained at 38°C. Five percent CO_2 was added to inspired air to maintain pCO_2 of the perfusate between 35-45 mm Hg and $NaHCO_3$ was added to maintain pH between 7.35-7.45. Hemoglobin saturation remained > 90%. Tracheal, pulmonary artery (Ppa), and left atrial (P_{la}) pressures were measured continuously. Lung weight change was measured continously as the inverse of reservoir weight. P_{la} was maintained negative but was transiently increased to +5 following measurement of lung weight gain, and lung weight gain was again measured at +5 P_{la}. Pulmonary artery pressures were allowed to stabilize and lung weight change was measured. Subsequently, Isoproterenol infusion into the PA was begun at varying rates (0.5 to 60mcg/min) and again lung weight change was measured. Thereafter, E. Coli endotoxin was infused into the PA at the rate of 100mcg./min. until PA pressure reached 2 x control. PA pressure was then allowed to stabilize and lung weight change was measured over time. Group means were compared by the two sample T-test and results considered significant if $p < .05$.

Results: In a control group (n=3) without endotoxin exposure, Ppa and lung weight did not change appreciably over 2-4 hrs. of constant perfusion. In the isolated lung preparations challenged with endotoxin (n=5), Ppa increased markedly as the initial response to endotoxin infusion and was accompanied by an increase in lung weight. After discontinuing endotoxin infusion, Ppa peaked and then slowly returned to near baseline values. However, in this group lung weight gain continues over time (Fig. 1). Each line in the graphs represents a single animal, with weight gain measured before and after endotoxin. In the experimental group (n=7) in which Isoproterenol infusion was begun prior to challenge with endotoxin, Ppa was reduced by 25-50% and lung weight showed no change. In spite of a similar infusion of endotoxin (.65-1.2mg) the experimental group showed significantly less lung weight gain than did the endotoxin alone group ($p < .01$) (Fig. 1). In the Isoproterenol group, increase of P_{la} to +5 produced significantly less weight gain than did a similar increase in P_{la} in the endotoxin alone group ($p < .01$) (Fig. 2). In a single experiment, the nonselective beta blocker propranolol infused in a 20mg bolus was associated with a dramatic increase in lung weight at both positive and negative P_{la} in an animal in the Isoproterenol group.

Discussion: Our results suggest that Isoproterenol pretreatment attenuates the magnitude of pulmonary hypertension following endotoxin infusion. Perhaps more importantly, it strikingly prevents the increased edema formation resulting from lung injury. This effect is particularly evident when the pulmonary vasculature is stressed by increasing P_{la}. These findings strongly suggest that the protection offered by Isoproterenol is related to its effect on pulmonary microvasculature rather than to a simple reduction in Ppa. We were able to show the reversibility of the protective effect of Isoproterenol in one animal, suggesting that the protective effect of Isoproterenol is mediated via beta adrenergic receptors.



Reference :

1. Mizus I., et al: Pulmonary Edema of Acid Lung Injury Is Attenuated by Agents that Elevate cAmP, Circulation 68: III p 234, 1983.