Title: RITODRINE INHIBITS HYPOXIC PULMONARY VASOCONSTRICTION

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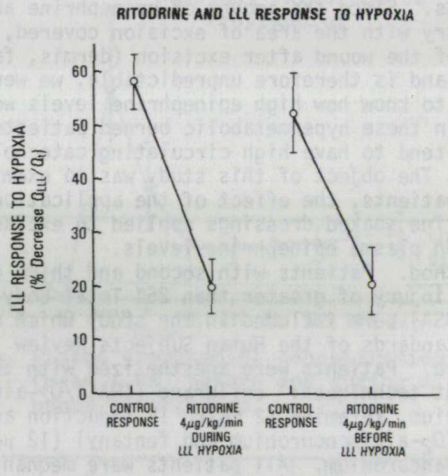
INTRODUCTION: Ritodrine is a new B_2-agonist that inhibits uterine contractions and is used clinically to inhibit preterm labor. However, several occurances of severe acute pulmonary edema and respiratory failure have been described following the use of Ritodrine to impede preterm labor. The etiology of the acute lung disease is presently obscure. However, since all other B_2-agonists drugs, namely isoproteronol, salbutamol, and orciprenaline, dose-dependently inhibit the ventilation/perfusion autoregulatory mechanism of hypoxic pulmonary vasoconstriction (HPV), it is reasonable to hypothesize that an etiologic component of the particularly severe acute respiratory failure following the administration of Ritodrine is failure of the lung to diminish blood flow to damaged areas of the lung. The purpose of this investigation was to test the hypothesis that Ritodrine inhibits HPV in an experimental model that allows direct examination of pharmacological influence on HPV.

METHODS: Six pentobarbital anesthetized dogs were intubated and ventilated with one side of a dual piston Harvard ventilator. Following a left thoracotomy, electromagnetic flow probes were placed around the main and left lower lobe (LLL) pulmonary arteries. The LLL bronchus was intubated distal to a ligature and ventilated independently and synchronously with the rest of the lung (RL) with the second piston of the respirator. Appropriate LLL and RL ventilation was achieved by manipulating the two tidal volumes and external dead spaces. The respiratory rate was adjusted so that P_aCO_2 was 39 $\pm$ 3 torr. Blood pressure in the femoral and pulmonary arteries and left atrium were measured directly (MAP, P_{pa}, P_{la}, respectively). The LLL was ventilated with 100% O_2 or with 95% N_2 and 5% CO_2 to obtain LLL control hyperoxia (LLL - O_2) or LLL hypoxia (LLL - N_2) respectively. The rest of the lung was ventilated with 100% oxygen throughout the experiment. Blood flow to the LLL was expressed as a fraction of the cardiac output (Q_{LLL}/Q_t). The LLL HPV response was computed as the maximum percent decrease in Q_{LLL}/Q_t during LLL - N_2 from the preceding LLL - O_2 value. The experimental sequence (see abscissa of figure) consisted of induction of LLL - N_2 (initial control LLL - HPV response); start infusion of Ritodrine 4 ug/kg/min during LLL - N_2 until all hemodynamic variables (heart rate, MAP, P_{pa}, P_{la} and compartmental blood flows) were stable; discontinuance of Ritodrine infusion and return to LLL - O_2 until all hemodynamic variables were once again stable and within 10% of the initial control values (which took approximately 2 - 3 hours); induction of LLL - N_2 (second control LLL - HPV response); return to LLL - O_2 and then start infusion of Ritodrine 4 ug/kg/min during LLL - O_2 until all hemodynamic variables were stable; and then induction of LLL - N_2 (with continued Ritodrine infusion). The order of Ritodrine infusion before and during LLL - N_2 HPV responses was randomized.

RESULTS: Ritodrine infusion alone caused a significant increase in cardiac output (from 2124 $\pm$ 190 to 2964 $\pm$ 333 ml/min, $p<0.01$), heart rate (from 95 $\pm$ 6 to 177 $\pm$ 13 /min, $p<0.001$), P_{pa} (from 16.4 $\pm$ 1.5 to 19.8 $\pm$ 1.3 torr, $p<0.05$), and a decrease in MAP (from 108 $\pm$ 3 to 80 $\pm$ 7, $p<0.025$), and P_{la} (from 6.2 $\pm$ 1.1 to 5.8 $\pm$ 1.1, NS). The figure shows that



whether the ritodrine infusion was started during or before the establishment of LLL - N_2, the ritodrine infusion caused a 69.8 $\pm$ 4.1 and 63.0 $\pm$ 5.1 percent decrease, respectively, in the LLL HPV response. There were no significant differences between the two control hypoxic responses and their were no significant differences between the hypoxic responses performed during ritodrine infusion whether ritodrine infusion was started during or before the LLL hypoxia.

DISCUSSION: These results show that ritodrine greatly inhibits hypoxic pulmonary vasoconstriction. This result is not unexpected since all other B_2-agonists tested so far also greatly inhibit HPV. Although our results do not clearly indicate a mechanism of acute lung damage by ritodrine, the increase in cardiac output through a dilated relaxed pulmonary vasculature most probably caused the increase in P_{pa} and it may be that part of the pulmonary edema observed clinically is caused by hydrostatic mechanisms. If constant infusions of Ritodrine are employed, the long duration of action may cause accumulation of drug and perhaps result in even greater pulmonary change. Our results indicate that once lung damage is present or induced by Ritodrine, the gas exchange defects are magnified by failure of the lung to autoregulate and utilize hypoxic pulmonary vasoconstriction.