

Title: ATP INHIBITS HYPOXIC PULMONARY VASOCONSTRICTION

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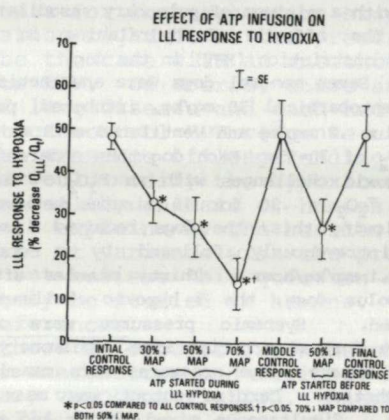
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INTRODUCTION: Adenosine triphosphate (ATP) appears to be an ideal vasodilating and hypotension producing drug because it creates a very favorable myocardial oxygen consumption/supply ratio. ATP reduces myocardial oxygen consumption by decreasing systemic vascular resistance, arterial pressure, developed left ventricular pressure (afterload), heart rate, and increases myocardial oxygen supply by greatly increasing myocardial blood flow. In addition, ATP has none of the drawbacks of sodium nitroprusside in that it does not cause tachyphylaxis, rebound hypertension, or metabolic toxicity. The mechanism of action of ATP seems to be via increased cellular cAMP. Since all other potent vasodilators, especially the B_2 -agonists (whose actions are mediated by increased cAMP), inhibit hypoxic pulmonary vasoconstriction (HPV), it is reasonable to hypothesize that ATP also reverses or inhibits HPV. The purpose of this investigation was to test this hypothesis by examining dose (ATP induced systemic hypotension) - response (magnitude of lobar HPV) relationships.

METHODS: Four 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_{CO_2} was 38 ± 1 torr. Blood pressure in the femoral and pulmonary arteries and left atrium were measured directly (MAP, P_{pa} , and 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. We express blood flow to the LLL 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); randomized reduction in MAP by ATP infusion to 30% ($29 \pm 2\%$), 50% ($48 \pm 1\%$), and 70% ($68 \pm 3\%$) of control value (ATP started during LLL - N_2); return to LLL - O_2 and then re-establishment of LLL - N_2 (middle control LLL - HPV response); return to LLL - O_2 and then reduction in MAP by ATP infusion to 50% ($53 \pm 5\%$) of control value (ATP started before LLL - N_2); and then induction of LLL - N_2 ; return to LLL - O_2 and re-establishment of LLL - N_2 (final control LLL - HPV response).

RESULTS: Reduction in MAP to $50 \pm 3\%$ (pooled data) of control (from 115 ± 9 to 57 ± 5 torr) caused a

61 + 3% increase in cardiac output (from 1.79 ± 0.2 to 2.89 ± 0.6 L/min, $p < 0.025$) and a 67 + 5% decrease in systemic vascular resistance (from 5571 ± 1158 to 1773 ± 366 d.sec.cm⁻⁵, $p < 0.005$). Pulmonary vascular resistance was decreased by 19 + 3% (from 377 ± 93 to 315 ± 53 , NS). Hemodynamic changes caused by 30 and 70% ATP-induced reductions in MAP were, respectively, less than and greater than those caused by a 50% ATP-induced reduction in MAP. The figure shows the



whether the ATP infusion was started during or before the establishment of LLL hypoxia, the ATP infusion caused a dose related decrease in the LLL HPV response. There were no significant differences between the three control (initial, middle, final) hypoxic responses and there were no significant differences between the hypoxic responses performed during 50% decrease in MAP whether the ATP infusion was started during or before the LLL hypoxia.

DISCUSSION: Our results show conclusively that ATP dose - dependently inhibits hypoxic pulmonary vasoconstriction. This result is not unexpected since all B_2 -agonists tested so far (isoproterenol, ritodrine, salbutamol, and orciprenaline) also dose dependently inhibit HPV and the effect of both B_2 -agonists and ATP are mediated by increasing cellular cAMP. Thus, although ATP may be an ideal vasodilator and hypotensive drug in patients with normal lungs, these results emphasize that caution must be exercised when ATP is infused in patients with abnormal lungs. Under these circumstances a decrease in oxygenation may occur due to reversal of pre-existing hypoxic pulmonary vasoconstriction and close monitoring of arterial oxygenation is indicated. These results suggest a central role for cAMP in mediating pulmonary vascular responsiveness to hypoxia.