TITLE: HYPOXIC PULMONARY VASOCONSTRICTION INHIBITED BY LUNG MANIPULATION IN RABBITS

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Introduction: It has been hypothesized that the trauma of a thoracotomy and/or the manipulation of the lung reduces the constrictor response of the pulmonary circulation to hypoxia[1]. The present study was undertaken to test this hypothesis and to identify the time course and influencing factors.

Methods: For this study, a new in vivo/in vitro animal model was developed[2]. Adult female New Zealand white rabbits were anesthetized and ventilated with 100% oxygen. After heparinization, an arterio-venous bypass was established. Blood from the right carotid artery passed to a water heated reservoir and was pumped at a constant rate (16 ml/min) back to the femoral vein. An isolated lung was obtained from another rabbit. This lung was suspended in a heated chamber, ventilated with 21% O_2, 5% CO_2, balance N_2 and perfused with blood from the reservoir at a constant rate. The blood passed back to the reservoir and was pumped to the whole rabbit, in this way blood perfusing the isolated lung was continuously metabolized by the intact animal. Finally, the left lung was tied at the hilum, in order to reduce the amount of lung being perfused. Respiratory rate, tidal volume and perfusion rates were set at 50 bpm, 7 ml and 32 ml/min, respectively. Airway and pulmonary artery pressure in the whole rabbit were continuously measured using a Gould transducer and recorded on a Grass recorder. The study protocol was as follows: after a 30 min stabilization period, the isolated lung was intermittently exposed to 5 minutes normoxia and 5 minutes hypoxia (3% O_2, 5% CO_2, balance N_2) for a 90 min period. The studies were divided into seven groups, each containing six preparations (whole rabbit plus isolated lung). In three groups, 30 minutes prior to the surgery, saline (Group 1) or drug-free solvent (Group 2) or ibuprofen 12.5 mg/kg (Group 3) was injected into the ear vein of the whole animal and an additional dose of saline, solvent or ibuprofen was added to the perfusate. In these three groups, repeated hypoxic pressor responses to the isolated lung were measured for 90 min without any surgical procedure. In Group 4, treated with solvent, and Group 5, treated with ibuprofen, a right 4th intercostal thoracotomy was performed; after the first hypoxic challenge, the hypoxic challenges were then continued. This procedure took approximately 7 min. In Group 6, treated with saline, and Group 7, treated with ibuprofen, following the thoracotomy, the right lung of the whole animal was collapsed and compressed with a moist gauze for 5 min and re-expanded by inflating with a PEEP of 20 cm H_2O. These lung manipulations were sequentially repeated three times and took approximately 30 min. ANOVA (one way and two way) and Neuman-Keuls multiple comparison test were used to identify significant ($p<0.05$) differences.

Results: The HPV response of the isolated lung, perfused with blood circulating continuously through the whole animal, decreased with time in linear manner (Groups 1 and 2). However, when ibuprofen was injected before the study (Group 3), the initial response was smaller than that of the control, but it was sustained throughout the experiment. Thoracotomy to the whole animal did not change the HPV response, both in the absence (Group 4) and presence (Group 5) of ibuprofen. To evaluate the net effect of lung manipulation, the data in each of the control groups (Groups 1 and 2) were subtracted from the data of Groups 6 and 7, respectively, and the differences are shown in the figure. Lung manipulation inhibited the HPV response regardless of the presence of ibuprofen, but the responses returned to exceed the control level after lung manipulation only in the absence of ibuprofen. In contrast, the HPV response was restored only partially after lung manipulation in the presence of ibuprofen.

Discussion: These results suggest that: (1) thoracotomy has no effect on HPV, but lung manipulation inhibits the HPV response both in the presence and absence of cyclooxygenase inhibitor and the rapidity of onset and offset suggests the production of a substance such as endothelial derived relaxing factor as the inhibitor; (2) the enhanced HPV response after cessation of the lung manipulation is due to vasoconstrictor prostaglandin production since it does not occur in the presence of ibuprofen; (3) ibuprofen reduces the HPV response probably as a consequence of blocking thromboxane A_2 which is the dominant arachidonic acid product released in response to an hypoxic stimulus in rabbits[3].

References: 1. Grover RF: Anesthesiology 63:580-582, 1984. 2. Marshall C, Ishibe Y, Marshall BE: Meth and Find Exptl Clin Pharmacol 10:5-11, 1988. 3. Westcott JY, McDonne TJ, Chang S, Bostwick P, Voekel NF: Fed Proc 49:1109, 1987.

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FIGURE 1