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INCREMENTAL PULMONARY VASCULAR RESISTANCE INCREASES WITH ELEVATION OF PULMONARY VENOUS PRESSURE

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INDEXING WORDS

pulmonary venous pressure; incremental pulmonary vascular resistance; multipoint pressure-flow plots; isolated lung

SYNOPSIS

The aim of this study was to determine whether elevation of pulmonary venous pressure affects incremental pulmonary vascular resistance. We vascularly isolated the left lower lobe of the lung and perfused with blood using a pulsatile pump. Blood flow to the isolated lobe was decreased in 6 to 7 steps from about 8 to 1 ml/kg/min. Incremental pulmonary vascular resistance was estimated from the slope of the pressure-flow relationship between pulmonary arteriovenous pressure difference and pulmonary blood flow at different pulmonary venous pressures. Incremental pulmonary vascular resistance increased as pulmonary venous pressure was elevated. This result suggests that an increase in cardiac output, i.e., an increase in pulmonary blood flow, results in a larger increase of pulmonary arterial pressure in high pulmonary venous pressure than in low pulmonary venous pressure.

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INTRODUCTION

Borst et al.[1] stated that both pulmonary arterial pressure and left atrial pressure are major determinants of pulmonary vascular resistance. Hyman[5] demonstrated that elevation of pulmonary arterial pressure led to an increase in pulmonary vascular resistance. Pulmonary vascular resistance simply provides a knowledge of hemodynamics at the given operating point. It is the pressure-flow curve that provides a dimensional improvement in understanding of the hemodynamic changes in different conditions.[10] The slope of the pressure-flow curve, which is referred to as the incremental resistance, is the measure of how the pressure changes in response to small changes in flow. Ducas et al.[3] and Shoukas[17] reported that an increase in left atrial pressure caused a decrease in incremental pulmonary vascular resistance. Elevation of pulmonary arterial pressure or left atrial pressure elicits various humoral and neural reflexes, which actively affect incremental pulmonary vascular resistance. Therefore, the experimental results described above may be a sum of the effects of these reflexes.

Atrial natriuretic peptide (ANP) is known to be secreted from the atrial wall in response to an increase in atrial pressure[2,4,8,13,14,15,20] and to dilate the pulmonary vascular beds.[6,19] In order to eliminate the effect of ANP on incremental pulmonary vascular resistance, we perfused the lung through the pulmonary artery to the pulmonary vein without changing atrial pressure. Incremental pulmonary vascular resistance was estimated as a slope of a regression line of the multipoint pulmonary pressure-flow plots. The multipoint pulmonary pressure-flow plots were obtained at fixed pulmonary venous pressure of 0, 5, 10 or 15 mmHg.

METHODS

Materials and General Surgical Preparations

Nine mongrel dogs (5.0-11.7 kg) were anesthetized with an intravenous injection of pentobarbital sodium in a dose of 30 mg/kg. The dogs were intubated and ventilated on room air at a tidal volume of 15 ml/kg (14 breath/min, 4 cmH2O PEEP) with a

respirator.

The chest was opened at the left sixth or seventh intercostal space. A perfusion circuit for the left lower lobe was filled with heparinized blood (about 200 ml) exsanguinated from the dog. A plastic tube of 6-7 mm inside diameter was inserted into the lower branch of the left main pulmonary artery and connected to the outflow side of the perfusion pump. The left lower pulmonary vein was catheterized through an incision in the left atrial appendage, and connected to the inflow of the reservoir (Fig. 1).

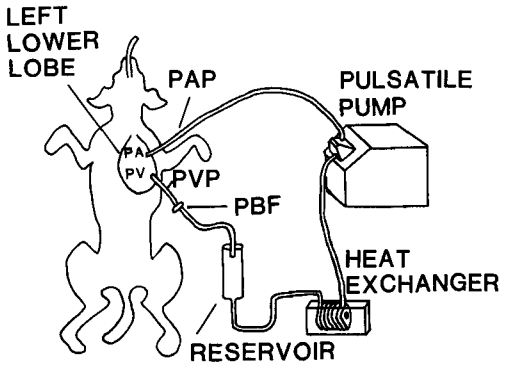

Fig. 1 Schematic illustration of experimental arrangement. PA:pulmonary artery, PV:pulmonary vein, PAP:pulmonary arterial pressure, PVP:pulmonary venous pressure, PBF:pulmonary blood flow. See text for explanation.

Blood in the reservoir was warmed (36-37°C) with a heat exchanger and perfused with a pulsatile pump through the pulmonary arterial catheter. Pulmonary arterial and venous pressures were monitored. The blood which passed through the left lower lobe was drained into the reservoir via the venous catheter inserted into the pulmonary vein. An electromagnetic flow probe for pulmonary blood flow was placed on the venous catheter. Pulmonary arterial pressure, pulmonary venous pressure and pulmonary blood flow were recorded on a strip chart. Pulmonary blood flow data were normalized with respect to the individual dog's body weight to allow comparison among dogs.

Estimation of incremental pulmonary vascular resistance

Pulmonary blood flow was decreased in 6 to 7 steps from about 8 to 1 ml/kg/min. The decrease in each step was approximately 1 ml/kg/min. The differences between pulmonary

arterial pressure and pulmonary venous pressure were plotted against the pulmonary blood flow. This relationship was referred to as multipoint pulmonary pressure-flow plot. Using the method of least squares, we estimated the slopes of the multipoint pulmonary pressure-flow plots, which is regarded as incremental pulmonary vascular resistance.

Protocol

We studied the effects of elevation of pulmonary venous pressure on incremental pulmonary vascular resistance. Decrease in pulmonary venous pressure caused by stepwise decreases in pulmonary blood flow were corrected by elevating an outlet of the pulmonary venous catheter. Thus, pulmonary venous pressure was fixed at 0, 5, 10 or 15 mmHg while changing pulmonary blood flow from approximately 8 to 1 ml/kg/min. We generated multipoint pulmonary pressure-flow plots and estimated the slope. This procedure was repeated at every pulmonary venous pressure. Pulmonary venous pressure was fixed in random order. Hematocrit was measured at the beginning and end of each procedure.

Statistical Analysis

Data are presented as means±SE. The data were statistically evaluated using a two-way analysis of variance. Post hoc analysis was achieved by Dunnett's multiple-sample test. Significance was accepted when $p<0.05$.

RESULTS

Fig. 2 shows a representative record of pulmonary arterial pressure in response to stepwise decreases in pulmonary blood flow. In this case, pulmonary venous pressure was corrected and fixed at 0 mmHg.

The representative multipoint pulmonary pressure-flow plots obtained at fixed pulmonary venous pressures of 0, and 15 mmHg and their regression lines are shown in Fig. 3. The slope of the corresponding regression line increased as pulmonary venous pressure was increased. The summarized data of slope for 9 dogs are shown in Fig. 4. At pulmonary venous pressures of 0, 5, 10

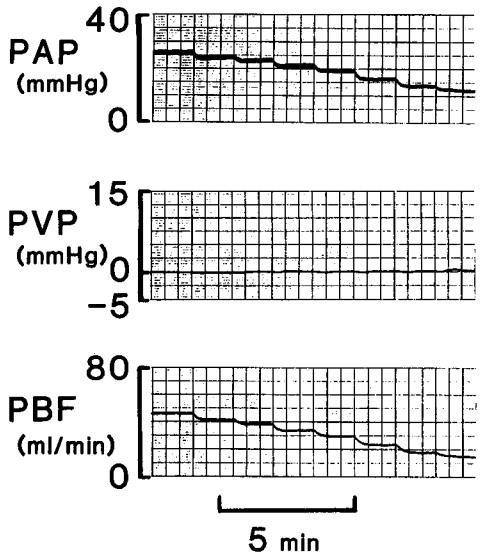

Fig. 2 Example of experimental records. Pulmonary blood flow (PBF) was decreased in steps of 5 to 10 ml/min. Decrease in PBF caused decreases in pulmonary arterial pressure (PAP) and pulmonary venous pressure (PVP). Decreases in PVP were corrected to zero mmHg by elevating an outlet of the pulmonary venous catheter.

and 15 mmHg, incremental pulmonary vascular resistance was 2.2±0.2, 2.2±0.1, 2.4±0.1 and 2.6±0.2 mmHg•min•kg/ml, respectively. Thus, incremental pulmonary vascular resistance increased as pulmonary venous pressure increased. The slope at pulmonary venous pressure of 15 mmHg was significantly larger than these at pulmonary venous pressures of 0 and 5 mmHg.

Fig. 3

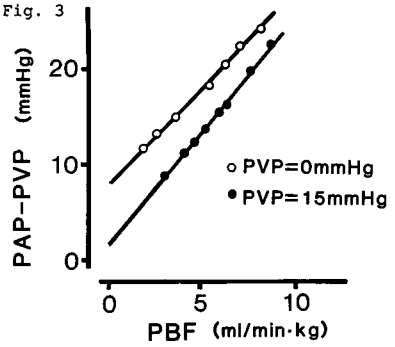

Fig. 4

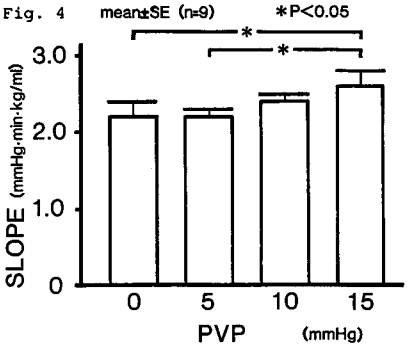

Fig. 3 Examples of the multipoint pulmonary pressure-flow plots at different fixed pulmonary venous pressure in a dog. The ordinate is the difference between pulmonary arterial (PAP) and venous pressures (PVP). The abscissa is pulmonary blood flow (PBF). Coordinates for PVP of 0, and 15 mmHg are indicated by open circle, and closed circle, respectively.

Fig. 4 Comparison of the slopes of the regression line determined by the method of least squares from multipoint pulmonary pressure-flow plots at four levels of pulmonary venous pressure (PVP: 0, 5, 10, 15 mmHg). The bars represent means±SE (n=9). The asterisks indicate significant differences from the response at PVP of 15 mmHg.

DISCUSSION

Our study suggests that elevation of pulmonary venous pressure increases incremental pulmonary vascular resistance which was estimated as the slope of the regression line of the multipoint pulmonary pressure-flow plots. These results appear to be in conflict to the results of Ducas et al.[3] and Shoukas.[17] These investigations also estimated incremental pulmonary vascular resistance as a slope of the regression line of the pulmonary arterial pressure-flow plots which was determined while left atrial pressure was fixed at constant value. They concluded that elevation of left atrial pressure decreased incremental pulmonary vascular resistance. However, elevation of left atrial pressure promotes a release of atrial natriuretic peptide (ANP). ANP relaxes vascular smooth muscle which results in decreases in incremental pulmonary vascular resistance. Therefore, the difference may be due to whether or not incremental pulmonary vascular resistance is modified by ANP.

Pulmonary vascular resistance is classically defined as the ratio of mean pulmonary arteriovenous pressure difference to pulmonary blood flow. This definition assumes that pulmonary pressure-flow relationships are linear over the range of pulmonary blood flow or pulmonary arteriovenous pressure difference and that the pressure difference at zero pulmonary blood flow equals zero. Shoukas[17] and Nakamura et al.[12] clearly showed that the pulmonary arteriovenous pressure difference-flow relationships could be regarded as linear in the physiological range of pulmonary blood flow, but at very low pulmonary blood flow the relationships became nonlinear. Shoukas,[17] Lodato et al.[9] Naeije et al.[11] Nakamura et al.[12] and Tsuchiya et al.[18] showed that the pulmonary arteriovenous pressure difference-flow relationships do not pass through the origin. Therefore, the classically calculated pulmonary vascular resistance does not allow to assess a change in pulmonary arterial pressure in response to a change in pulmonary blood flow.

Hyman[5] distended the pulmonary artery with the lumen fixed and observed significant increases in pulmonary arterial and venous pressures. He concluded that pulmonary arterial distention leads to active constriction of the pulmonary arteries and veins.

Osorio and Russek[16] demonstrated that the pulmonary arterial pressure was increased by stimulation of the baroreceptors in the pulmonary artery. They, however, did not show a change in incremental pulmonary vascular resistance.

The pulmonary artery can also be distended by increases in pulmonary arterial pressure, which is caused by increases in pulmonary venous pressure or left atrial pressure. Shoukas[17] increased left atrial pressure and estimated the resultant change in incremental pulmonary vascular resistance from the slope of the regression line of the multipoint pulmonary pressure-flow plots. He reported that incremental pulmonary vascular resistance decreased with increasing left atrial pressure. Ducas et al.[3] also demonstrated that an increase in left atrial pressure decreased incremental pulmonary vascular resistance. In the present study, however, we found that incremental pulmonary vascular resistance increased with increasing pulmonary venous pressure. This discrepancy may be caused by the difference in the way pulmonary venous pressure was increased.

Recently, atrial natriuretic peptide has been found to be released from the right and left atrial walls in response to right or left atrial wall stretch.[2,4,8,13,14,15,20] Since Shoukas[17] and Ducas et al.[3] increased left atrial pressure, ANP was probably released and may have affected incremental pulmonary vascular resistance. In the present study, however, we changed pulmonary venous pressure and did not change either right or left atrial pressures. Therefore, we were able to exclude an effect of ANP on incremental pulmonary vascular resistance. A large number of high-affinity receptors for ANP were found on the pulmonary artery and vein.[7] ANP released in venous blood via the coronary sinus from the atrial wall passes through the lung. Weselcouch et al.[19] and Ishikawa et al.[6] reported that ANP relaxed the pulmonary artery. Taking these facts into account, the change in incremental pulmonary vascular resistance in response to increased left atrial pressure in the studies of Shoukas[17] and Ducas et al.[3] may be modified by ANP. Therefore, an increase in left atrial pressure is not a suitable way to study an effect of increased pulmonary venous pressure on incremental pulmonary vascular resistance. In this study, we catheterized the pulmonary artery for perfusion and the pulmonary vein for drainage.

Therefore, both right and left atrial pressures were not changed by changing pulmonary venous pressure. This experimental model eliminated the effects of ANP and other humoral factors on incremental pulmonary vascular resistance.

In the present experiment, we studied the effect of an increased pulmonary venous pressure on incremental pulmonary vascular resistance and found that the increase in pulmonary venous pressure increased incremental pulmonary vascular resistance. This result suggests that the change in incremental pulmonary vascular resistance caused by increased left atrial pressure reported by Shoukas[17] and Ducas et al.[3] is the sum of the effects of ANP and the increases in pulmonary venous pressure. In their study, dilation of the pulmonary vascular beds by ANP might overwhelm an increase in incremental pulmonary vascular resistance due to an increase in left atrial pressure. Therefore, we can conclude that the increase in pulmonary venous pressure may increase incremental pulmonary vascular resistance.

The incremental pulmonary vascular resistance and pressure-flow curve may provide an important pathophysiological and clinical information for pulmonary hypertension. Pulmonary hypertension may be theoretically classified into two types, i.e., pulmonary hypertension with and without an increase in incremental pulmonary vascular resistance. In a case of pulmonary hypertension with normal incremental pulmonary vascular resistance, an increase in pulmonary arterial pressure in response to an increase in pulmonary blood flow is same as that in a healthy case. On the other hand, an increase in pulmonary arterial pressure is larger in a case of pulmonary hypertension with an increased incremental pulmonary vascular resistance than in normal. In such case, decrease of pulmonary venous pressure and/or left atrial pressure may effectively suppress an elevated pulmonary arterial pressure.

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