Physiol. Res. 41: 147-150, 1992

Acute Pneumonia Reversibly Inhibits Hypoxic Vasoconstriction in Isolated Rat Lungs

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Received August 19, 1991
Accepted November 21, 1991

Summary

Pneumonia was induced in rats by instillation of carrageenin (0.5 ml of 0.7 % solution) into the trachea. Three or four days after instillation, the lungs were isolated, perfused with blood of healthy rat blood donors, and ventilated with air + 5 % CO_2 or with various hypoxic gas mixtures. Pulmonary vascular reactivity to acute hypoxic challenges was significantly lower in lungs of rats with pneumonia than in lungs of controls. The relationship between O_2 concentration in the inspired gas and Po_2 in the blood effluent from the preparation was shifted significantly to lower Po_2 in lungs with pneumonia compared to control ones. These changes were not present in rats allowed to recover for 2-3 weeks after carrageenin instillation. We suppose that blunted hypoxic pulmonary vasoconstriction may contribute to hypoxaemia during acute pulmonary inflammation. Decreased Po_2 in the blood effluent from the isolated lungs with pneumonia implies significant increase of oxygen consumption by the cells involved in the inflammatory process.

Key words

Hypoxic pulmonary vasoconstriction – Inflammation – Lung oedema – Pneumonia – Carrageenin – Isolated lungs

Introduction

Hypoxic pulmonary vasoconstriction is an important mechanism for matching lung blood flow to alveolar ventilation and thereby for preventing arterial hypoxaemia (Orchard *et al.* 1983). It has been suggested that hypoxaemia in individuals with pneumonia may be partly due to blunting of hypoxic pulmonary vasoconstriction in hypoventilated parts of lungs (Light *et al.* 1981, Hanly and Light 1987). Therefore, we have investigated the effect of lung inflammation on pulmonary vasoconstriction induced by acute hypoxic stimuli in the isolated rat lungs.

In isolated lung preparations, where the metabolic activity of the periphery is excluded and the perfusate before entering the preparation is exposed to ambient air, Po_2 of perfusing blood should not be less then Po_2 in the ventilation gas mixture. During ventilation hypoxia the direction of oxygen movement may even be reversed from blood to alveolar gas. If the diffusion of oxygen is impaired, Po_2 at the "sensor of hypoxia", situated most probably in the wall of small pulmonary arteries (Marshall and Marshall 1983), may not reach equally low values as in the healthy lungs at a given level of ventilation hypoxia. This may be a speculative explanation for smaller responses to alveolar hypoxia in lungs with inflammation and diffusion impairment. To explore this possibility we measured Po_2 in the blood effluent from the isolated lung preparation.

Methods

The carrageenin suspension (0.7 % carrageenin in saline, 0.5 ml) was instilled immediately before inspirium into the trachea of Wistar rats anesthetized with ether. This dose of carrageenin is known to produce lung inflammation with signs of suppurative aspiration bronchopneumonia which culminates 2 or 3 days after the instillation (Wachtlová *et al.* 1975). The isolated lungs of 7 male rats (BW 202.9 ± 25.5 g) were prepared 3–4 days after carrageenin instillation. The presence of lung inflammation was macroscopically evident on the preparation of isolated lungs. Another seven male rats (BW 198.6 ± 13.31 g), who received no treatment was the control group. In addition, to find whether carrageenin-induced changes of hypoxic pulmonary vasoconstriction were reversible, we prepared isolated lungs from another 4 male rats (BW 261.2 ± 13.9 g,

none of the differences between the groups in BW was significant) 13–20 days after carrageenin instillation. Resorption phase of carrageenin-induced pneumonia is known to occur by the eighth day after the carrageenin instillation (Wachtlová *et al.* 1975).

The isolated lungs (Hampl and Herget 1990) were prepared from rats of all three groups, anaesthetized with thiopental (100 mg.kg^{-1}BW, i.p.) and heparinized (150 – 250 IU, i.v.). The lungs were ventilated with a normoxic gas mixture (all gas mixtures in this study contained 5 % CO_2 and were balanced with N_2) at 65 breaths.min^{-1}. Maximal inspiratory and expiratory pressures were 9 and 2 cm H_2O, respectively. Pulmonary artery and left ventricle were cannulated and the lungs were removed from the thorax, placed in a thermostated chamber (38 °C) and perfused with homologous blood obtained from 2–3 donor rats by cardiac puncture. The flow rate and outflow pressure were adjusted at 0.06 ml.min^{-1} per gram of BW and -2 cm H_2O, respectively. Lungs were allowed to stabilize 15 minutes and then challenged with ventilation hypoxia (3 % O_2, 10 min) 2 times with a normoxic interval of 10 min to establish the reaction to hypoxia (Hauge 1968). After another 10 min of normoxic ventilation, the dose-response of perfusion pressure to acute hypoxic challenges was measured. The amount of oxygen in the ventilation mixture was decreased in 10-min lasting steps to 10, 5, 3, and 0 %. Finally, normoxic ventilation was restored. As the flow rate was constant, the increases in perfusion pressure reflected pulmonary vasoconstriction. The effluent blood P_{O_2} was measured with an O_2 electrode at the end of each hypoxic stimulus.

The results (presented as means ± S.E.M.) were evaluated using 1-way ANOVA with the Scheffé test (baseline values) and 2-way ANOVA with the Student-Newman-Keuls test for simultaneous multiple comparisons (vasoconstrictor reactivity to hypoxia, effluent blood P_{O_2} at different levels of hypoxia) (Steel and Torrie 1960). $P<0.05$ was considered significant.

Results

Fig. 1 shows that, while the baseline perfusion pressure did not differ between the groups, the vasoconstrictor reactivity to hypoxic stimuli was significantly smaller in lungs with pneumonia than in control ones. After 13–20 days of recovery from pneumonia (recovery group), the vascular reactivity to hypoxia did not differ significantly from that of the control group and was significantly higher than the reactivity of the lungs with acute inflammation.

The relationship between oxygen content in the ventilation gas mixture and the effluent blood P_{O_2} was shifted significantly downwards in lungs with pneumonia compared to lungs of controls and of the recovery group, while there was no difference between the latter two groups (Fig. 2).

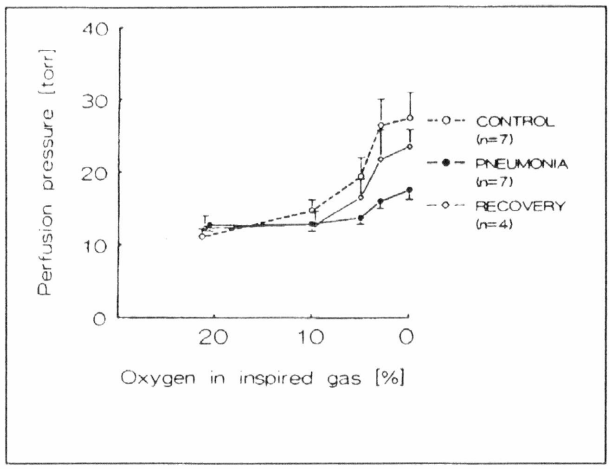

Fig. 1
Dose-response of perfusion pressure to ventilation hypoxia in blood-perfused lungs isolated from control rats (not treated with carrageenin), rats with acute carrageenin pneumonia, and rats recovering from carrageenin pneumonia. 2-way ANOVA indicates that perfusion pressure depends significantly on the amount of O_2 in the inspired gas ($P<0.01$ in all groups) and that the reactivity is lower in lungs of rats with acute pneumonia than in lungs of control rats ($P<0.01$) and than after 2–3 weeks recovery ($P<0.05$). Reactivity does not differ significantly between control and recovery groups.

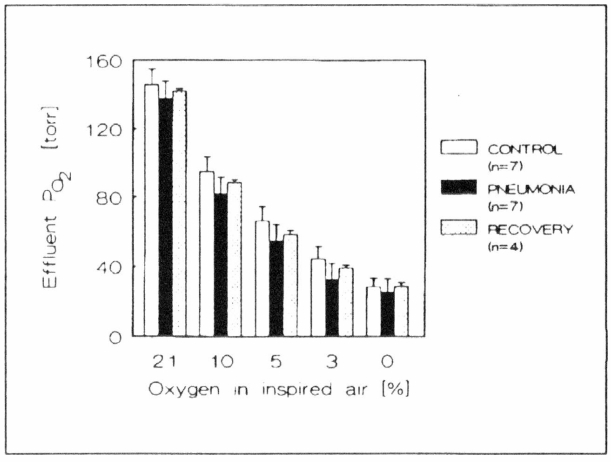

Fig. 2
Effect of ventilation hypoxia on P_{O_2} in blood effluent from the isolated lungs of control rats, rats with acute carrageenin pneumonia, and rats recovering from carrageenin pneumonia. 2-way ANOVA shows significant dependence of effluent blood P_{O_2} on the amount of oxygen in the inspired gas ($P<0.01$ in all groups) and significant difference in the relationship between the pneumonia and control groups ($P<0.01$) and between pneumonia and recovery groups ($P<0.01$). Control and recovery groups do not differ.

Effluent blood P_{O_2} after the dose-response measurement was lower in the pneumonia group (120±3 torr) than before the measurement of dose-

response and than in the control (145±2 torr) and recovery (137±5 torr) groups, where the values did not differ from those before the dose-response measurement.

Discussion

The increased venous admixture in dogs with acute lung inflammation (Light *et al.* 1981, Hanly and Light 1987, Light 1988) was attributed by the authors to blunted hypoxic pulmonary vasoconstriction. Attenuated pulmonary vasopressor responses to breathing 8 % O_2 were demonstrated in awake rats with chronic Pseudomonas pneumonia (Graham *et al.* 1990). The present results show reversible reduction of hypoxic pulmonary vasoconstriction over a wide range of levels of hypoxia in isolated lung preparation from rats with acute pneumonia.

Pneumonia causes pulmonary oedema (Light 1988). Lung oedema itself has been reported to blunt vasocontrictions in response to various degrees of ventilation hypoxia in isolated lungs (Newman *et al.* 1981, Burghuber *et al.* 1984). However, it is possible that in these studies magnitude of the stimulus (P_{O_2} in the wall of small arteries) rather than vascular reactivity was affected because of diffusion impairment (effluent P_{O_2} was not measured). In our preparations from rats with pneumonia the P_{O_2} in the blood effluent from the lungs was significantly lower than in controls. Therefore, it is likely that blunted hypoxic pulmonary vasoconstriction was a result of lower reactivity of pulmonary blood vessels. One wonders, however, why P_{O_2} in effluent blood from the lungs damaged by carrageenin is lower than in controls at equal levels of hypoxia in the inspired gas. In contrast to the situation occurring *in vivo*, the blood flowing from a reservoir into the isolated lungs ventilated with hypoxic gas mixtures will not have lower P_{O_2} than alveolar gas even in gross disturbances of lung ventilation because there is no oxygen consumption in the periphery. In addition, in a reservoir the perfusate comes into contact with ambient air. As a result, the blood perfusing the lung areas with low lung ventilation to perfusion ratio ($\dot{V}/\dot{Q}$) will not decrease the P_{O_2} in the effluent (arterial) blood.

The possible explanation for lower effluent P_{O_2} in the pneumonia group is a significant increase of oxygen consumption in the lungs affected by inflammation. This is not an unlikely interpretation as considerable enhancement of oxygen consumption by the lungs was shown in dogs with acute pneumonia (Light 1988) and in dogs and humans with granulomatous lung disease (Caldwell *et al.* 1970, Fritts *et al.* 1961). It was attributed to metabolic activity of the cells involved in the inflammatory process. Our study was not designed to measure the oxygen consumption in the lungs. Even a rough estimate cannot be calculated because blood in the reservoir and the lung surface was exposed to ambient air. P_{O_2} more than 25 torr in the blood effluent from lungs ventilated with nitrogen + 5 % CO_2 supports the possibility of significant diffusion of ambient air into the preparation. There is no reason, however, to expect that the rate of this diffusion will differ between lungs with pneumonia and the controls.

What are the mechanisms decreasing pulmonary vascular responses to hypoxia in acute lung inflammation? The inflammatory cells release several substances (such as prostacyclin and oxygen radicals) with an inhibitory effect on pulmonary vascular smooth muscle (for recent review see Herget and Ježek 1989). Another explanation may be based on the known inhibitory effect of chronic lung hypoxia on acute hypoxic pulmonary vasoconstriction (McMurtry *et al.* 1980). Such an inhibitory reaction, which starts within a few hours of hypoxic exposure (Greenlees and Tucker 1984) might occur in hypoventilated parts of lungs in rats with carrageenin pneumonia. Furthermore, the injured parts of the lung vascular bed may be partly occluded. Then flow through healthy regions would thus be enhanced. Tucker and Rodeghero (1981) have shown that hypoxic pulmonary vasoconstriction in isolated rat lungs is blunted when flow rate is increased.

Our present results show that in acute pneumonia the lung venous admixture from areas with a low V/Q ratio may be insufficiently prevented by hypoxic pulmonary vasoconstriction because of low vascular reactivity. In addition, the increased lung oxygen utilization due to the inflammatory reaction might contribute to arterial hypoxaemia. We have shown that it is unlikely that the blunting of hypoxic pulmonary vasoconstriction in acute pneumonia is a result of the attenuation of hypoxic stimulus due to diffusion impairment.

Acknowledgements

We thank Mrs. R. Tichá for technical assistance and Dr. M. Vízek for helpful comments. The LKB Multiperspex pump used for perfusion of the isolated lungs was a gift from Hugo Sachs Electronics, March-Hugstetten, F.R.G.

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