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Hyperoxia Prevents Carrageenan-Induced Enlargement of Functional Residual Lung Capacity in Rats

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Summary

Experimental pneumonia induced by intratracheal application of carrageenan or paraquat increases the functional residual lung capacity (FRC) in rats. The mechanism of this increase is not clear, but a decrease in PO_2 may be involved. To test this possibility, we attempted to eliminate the PO_2 decrease in carrageenan-treated rats by exposing them to hyperoxia. Animals of the first group were exposed to 7 days of hyperoxia (F_IO_2 0.78-0.84, *group Car+O_2*) after intratracheal application of carrageenan (0.5 ml of 0.7 % carageenan in saline), whereas animals of the second group were given the same dose of carrageenan but breathed air (*group Car+A*). The third group of rats was kept for seven days in hyperoxia (*group O_2*) and the fourth group served as controls (*C*). The animals were then anesthetized and intubated and their ventilatory parameters and FRC were measured during air breathing. Carrageenan application induced a FRC increase (*Car+A* 2.0±0.2 ml, *C* 1.6±0.1 ml), which was not seen in carrageenan-treated rats exposed to hyperoxia (*Car+O_2* 1.6±0.1 ml). Hyperoxia alone did not affect the value of FRC (*O_2* 1.5±0.1 ml). These results support the hypothesis that a decrease in PO_2 plays an important role in the carrageenan-induced increase of FRC in rats.

Key words
Functional residual capacity • Experimental pneumonia • Carrageenan • Chronic hyperoxia • Control of breathing

Introduction

The functional residual capacity of the lung (FRC) is defined as the thoracic gas volume at the end of expiration (Agostoni and Mead 1964). At this volume, elastic recoils of the lungs and the thorax are balanced. Surprisingly, the FRC was found to be increased in a model of lung pneumonia (Wachtlová *et al.* 1975, Vízek et al. 1983). The stimulus for this increase is not clear, but since hypoxia is known to increase the FRC (Bouverot and Fitzgerald 1969, Bonora and Vízek 1995), we speculated that a decrease in PO_2 could play a certain role. To test whether hypoxia is involved in the FRC increase in model lung diseases, we attempted to prevent a possible decrease in PO_2 by exposing the rats with carrageenan-induced experimental pneumonia to hyperoxia.

Methods

Studies were performed on 29 adult male Wistar rats with an initial body weight of 228±3 g. The techniques used were compatible with the ILAR Guidelines (1996). Experimental pneumonia was induced by an intratracheal

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application of carrageenan (Wachtlová et al. 1975). Two experimental groups (8 animals each) were given 0.5 ml of 0.7 % solution of carrageenan (Sigma) intratracheally; one of the groups was then exposed for 7 days to hyperoxia (group Car+O_2, F_IO_2 0.78-0.84) in a normobaric chamber (Herget and Kuklík 1995) and the other breathed air (group Car+A). Control groups were kept for 7 days either in air (group C) or in hyperoxia (group O_2, F_IO_2 0.78-0.84).

The animals were anesthetized with thiopental (40 mg/kg, i.p.), intubated, and placed in a plethysmograph (Maxová and Vízek 2001). The tracheal cannula (ID 1.7 mm, OD 2.3 mm) was connected to an outer circuit ventilated with room air. Pressure changes in the plethysmograph and tracheal pressure were measured by pressure transducers Elema-Schonander EMT 32 and EMT 34. The FRC was calculated using Boyle's law from the changes in tracheal pressure and lung volume induced by three consecutive efforts after occlusion of the tracheal tube at the end of expiration. A specific computer program (Maxová and Vízek 2002) was used for calculating ventilatory parameters and FRC.

Each ventilatory variable was averaged over six consecutive respiratory cycles. FRC values are the means of three measurements with a time interval of 10 s. The results are presented as means ± S.E.M. ANOVA and Fisher´s PLSD test were used for statistical evaluation of the data. $P<0.05$ was considered significant.

Table 1. Minute ventilation (V'_E), breathing frequency (f_R), tidal volume (V_T) and duration of expiration (TE) in control group (*C*), group exposed to 7 days of hyperoxia (O_2), group breathing air after carrageenan application (*Car+A*) and group exposed to 7 days of hyperoxia after carrageenan application (*Car+O_2*).

	Control	**O_2**	**Car+Air**	**Car+O_2**
N	8	7	8	6
Body weight (g)	293±5	256±5*	268±8*	240±11*
V'_E (ml/min)	208.2±14.3	172.9±8.7	200.5±13.4	163.9±15.4*
f_R (c/min)	145±8	119±7	175±12$^+$	131±15
V_T (ml)	1.4±0.1	1.5±0.1	1.2±0.1*†	1.3±0.1†
T_E (s)	0.21±0.02	0.27±0.02	0.18±0.01†	0.22±0.03

**p<0.05 from the control group, $^+p<0.05$ from all other groups, $^\dagger p<0.05$ from O_2 group*

Results

Ventilatory parameters of all groups are summarized in Table 1. Minute ventilation (V'_E) of both groups of rats exposed to hyperoxia was somewhat lower than in the controls, the decrease being significant in the *Car+O_2* group. This difference was mostly due to lower tidal volume in rats of the *Car+O_2* group.

The rats of the *Car+A* group had a lower tidal volume and a higher rate of breathing than the controls. They also had the shortest duration of expiration (T_E), but their T_E differed significantly only from that of the O_2 group. Both "hyperoxic" groups also had lower rates of breathing than the corresponding "normoxic" rats, although these differences were not significant.

The values of functional residual capacity are shown in Figure 1. As expected, FRC of the rats that breathed air after carrageenan administration was significantly higher than that of the controls. This increase of the FRC was not seen in any group of rats exposed to hyperoxia. It means that hyperoxia blocked the FRC increase resulting from carrageenan application.

Discussion

In this experiment, we tested whether hypoxia could prevent the FRC increase developing during the acute phase of carrageenan-induced pneumonia. The desired level of hyperoxia should therefore ensure higher PaO_2 in the *Car+O_2* than in the *Car+A* group throughout the exposure and to affect the inflammatory process as little as possible. We believe that F_IO_2 around 0.8 also fulfilled the latter condition because it was previously used to induce oxygen tolerance in rats (Coursin *et al.* 1987).

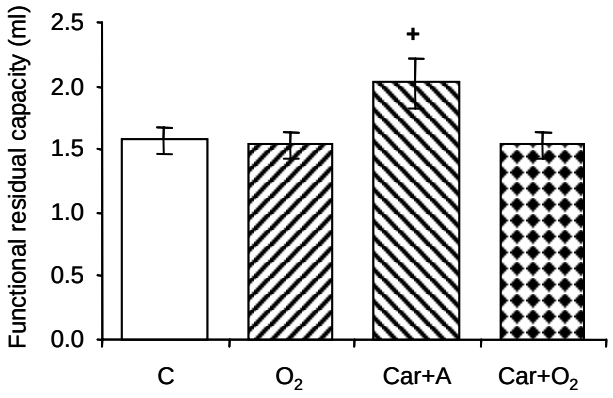

Fig. 1. *Functional residual capacity (FRC) in control group (C), group exposed to 7 days of hyperoxia (O_2), group breathing after carrageenan application air (Car+A) and group exposed after carrageenan application for 7 days to hyperoxia (Car+O_2).* $^{+}p<0.05$ *from all other groups.*

The control rats gained more weight during the experiment than any other group. Nevertheless, we did not express the FRC values in relation to body weight because Sekhon *et al.* (1995) showed that the FRC is related to the age rather than to body weight of rats.

As expected, the application of carrageenan induced an increase of the FRC in the rats breathing air, the relative value of which was comparable to that found by Wachtlová *et al.* (1975). In theory, the FRC increase (hyperinflation) could result from the imbalance of static forces and/or dynamic components (Paleček 2001). Increased lung compliance or decreased thoracic compliance are possible causes of static hyperinflation while shortening of the expiration or increased airway resistance can produce dynamic hyperinflation. Prevention of FRC enlargement in our *Car+O_2* rats could result from interference of hyperoxia with any of the above mentioned mechanisms. However, Wachtlová *et al*. (1975) concluded from their morphological and functional findings that an increased airway resistance is not a likely cause of FRC enlargement during carrageenan-induced pneumonia. Similarly the mean expiratory flow of our groups *C* and *Car* was the same, suggesting the same airway resistance in both groups. It is therefore also unlikely that hyperoxia blocked the FRC enlargement by its effect on airway resistance.

The effect of hyperoxia on the duration of expiration in carrageenan-treated rats cannot be excluded because of the slower rate of breathing in carrageenan-treated rats exposed to hyperoxia. However, the shortened expiration is not a likely cause of the increase in FRC in carageenan-treated rats kept in air, since the shorter duration of the breathing cycle was proportional to a decrease in tidal volume (by 17 % and 15 %, respectively).

We are not aware of any information on the possible effects of hyperoxia on carrageenan-induced pneumonia. Furthermore, data on the interaction of hyperoxia and other types of lung inflammation provide no clue for interpretation of the mechanism preventing the FRC enlargement by hyperoxia. Because we used a well tolerated level of hyperoxia, we believe that it did not substantially change the course of the inflammatory process, however, such a possibility cannot be excluded.

Carrageenan administration has no effect on the lung compliance (Wachtlová *et al.* 1975) so that a change in the compliance of the thorax remains the most likely cause of the FRC increase in our rats. An interesting possibility is that such a change results from the post-inspiratory activity of inspiratory muscles. Inspiratory muscle activity normally ceases shortly after the end of inspiration but, if it persists throughout expiration, it prevents the thorax from collapsing to its relaxed position and increases the FRC. Increased post-inspiratory activity of inspiratory muscles has been reported during hypoxia (Smith *et al.* 1989, Bonora and Boulé 1994) and it was suggested that this plays an important role in the mechanism increasing the FRC during acute hypoxia (Bonora and Vízek 1995) and in the early phase of chronic hypoxia (Bonora and Vízek 2001). Because hyperoxia prevented a carrageenan-induced increase of the FRC, we assume that carrageenan-induced pneumonia resulted in a decrease of PO_2, which was responsible for prolongation of the activity of inspiratory muscles and therefore for the FRC increase.

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