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SHORT COMMUNICATION

Hypercapnia Does Not Affect Functional Residual Capacity Enlargement Induced by Chronic Hypoxia

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Summary

To determine whether changes in partial pressure of CO_2 participate in mechanism enlarging the lung functional residual capacity (FRC) during chronic hypoxia, we measured FRC and ventilation in rats exposed either to poikilocapnic (group H, F_IO_2 0.1, F_ICO_2 <0.01) or hypercapnic (group H+CO_2, F_IO_2 0.1, F_ICO_2 0.04-0.05) hypoxia for the three weeks and in the controls (group C) breathing air. At the end of exposure a body plethysmograph was used to measure ventilatory parameters (V'_E, f_R, V_T) and FRC during air breathing and acute hypoxia (10 % O_2 in N_2). The exposure to hypoxia for three weeks increased FRC measured during air breathing in both experimental groups (H: 3.0±0.1 ml, H+CO_2: 3.1±0.2 ml, C: 1.8±0.2 ml). During the following acute hypoxia, we observed a significant increase of FRC in the controls (3.2±0.2 ml) and in both experimental groups (H: 3.5±0.2 ml, H+CO_2: 3.6±0.2 ml). Because chronic hypoxia combined with chronic hypercapnia and chronic poikilocapnic hypoxia induced the same increase of FRC, we conclude that hypercapnia did not participate in the FRC enlargement during chronic hypoxia.

Key words

Functional residual capacity • Chronic hypoxia and hypercapnia • Chronic hypoxia • Rat

Functional residual capacity of the lung (FRC) is defined as the thoracic gas volume at the end of expiration (Agostoni and Mead 1964). Several studies have shown that chronic hypobaric or normobaric hypoxia increases FRC in experimental animals (Harris 1945, Barer *et al.* 1978, Vízek *et al.* 1983) and humans (Hurtado 1964). However, the mechanism responsible for this enlargement is not fully understood (Paleček 2001). Although it has been accepted that hypoxia plays a crucial role in this phenomenon, the possible effect of accompanying hypocapnia has not been clarified. It is important to note that acute hypocapnic hypoxia increased the postinspiratory activity of the diaphragm (PIIA), which brakes expiratory flow and prevents thorax from collapsing to its control volume (Smith *et al.* 1989, Bonora and Vízek 1995), while hypercapnia decreased PIIA (Smith *et al.* 1989).

To elucidate the consequences of P_{CO_2} changes for FRC enlargement during chronic hypoxia we decided to compare ventilatory parameters and FRC in rats exposed to three weeks of poikilocapnic or hypercapnic hypoxia.

Studies were performed in 30 adult male Wistar rats with an initial body weight of 350-400 g. Two

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experimental groups (10 animals each) were exposed either to poikilocapnic (group H, F_IO_2 0.1, F_ICO_2 <0.01) or hypercapnic hypoxia (group H+CO_2, F_IO_2 0.1, F_ICO_2 0.04-0.05) in a normobaric hypoxic chamber (Herget and Kuklík 1995) for 21 days. Ten control rats (group C) breathed air.

For the measurements, the animals from all groups were anesthetized with an intraperitoneal injection of Thiopental (40 mg/kg), intubated and placed in a whole body plethysmograph (Maxová and Vízek 2001a). The tracheal cannula (ID 1.7 mm, OD 2.3 mm) was connected to an outer circuit ventilated either with air, or with a hypoxic mixture (10 % O_2 in N_2). Pressure changes in the body plethysmograph due to breathing were monitored against the atmospheric pressure by a differential pressure transducer (Elema-Schonander EMT 32) and ventilation was ascertained by body plethysmography. Tracheal pressure was measured with a pressure transducer (Elema-Schonander EMT 34). 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 was used to calculate ventilatory parameters and FRC. A computer program was used to define maximal and minimal values of plethysmographic pressure during one cycle. The difference between these two, related to the calibration signal, was used to calculate the tidal volume and together with the time elapsed between two maximal pressures also minute ventilation. Similarly, the difference during occluded breath together with tracheal pressure corresponding to maximal plethysmographic pressure was used for calculating FRC.

The variables were measured during the 5th and 10th minute of air breathing and after that during the 5th and 10th minute of hypoxic mixture breathing.

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

Ventilatory parameters and body weight of experimental and control rats are summarized in Table 1. The body weight was lower in both hypoxic groups than in the controls, the body weight of hypoxic and hypercapnic rats being the lowest.

Minute ventilation (V'_E) during air breathing was lower in both experimental groups than in the controls. In acute hypoxia, V'_E of all groups significantly increased compared to air breathing, its relative change being similar. During the ventilatory response to acute hypoxia, we observed differences in the breathing pattern between experimental and control groups. The increase of ventilation in the controls was due to a proportional increase of breathing rate (f_R) (to 139 %) and tidal

Table 1. Minute ventilation (V'_E), breathing frequency (f_R) and tidal volume (V_T) in control (C), hypoxic-poikilocapnic (H) and hypoxic-hypercapnic (H+CO_2) groups during air and hypoxic mixture (10 % O_2 in N_2) breathing.

		Controls	Hypoxic-poikilocapnic	Hypoxic-hypercapnic
Body weight (g)		414.6 ± 12.6	332.2 ± 5.1 *	288.4 ± 9.7 *#
V'_E *(ml/min)*	*Air*	169.5 ± 13.5	135.4 ± 8.0 *	119.8 ± 7.5 *
	Hypoxia	339.8 ± 15.6	260.5 ± 16.3 *	237.3 ± 14.5 *
f_R *(c/min)*	*Air*	112.7 ± 5.8	70.1 ± 3.4 *	72.2 ± 4.0 *
	Hypoxia	156.3 ± 6.5	144.2 ± 10.0	146.9 ± 11.4
V_T *(ml)*	*Air*	1.50 ± 0.07	1.96 ± 0.12 *	1.68 ± 0.11
	Hypoxia	2.19 ± 0.08	1.84 ± 0.09 *	1.66 ± 0.09 *

**p<0.05 from the control group, # p<0.05 between groups H and H+CO_2.*

volume (V_T) (to 146 %) of the values during air breathing. The increase in ventilation in both chronically hypoxic groups was due to an increase of f_R only (to 206 % and 203 %, respectively), while V_T did not change. The duration of expiration shortened in acute hypoxia in all groups: from 0.28 s to 0.21 s in the controls, from 0.58 s to 0.21 s in the hypoxic poikilocapnic group and from 0.55 s to 0.23 s in the hypoxic hypercapnic group.

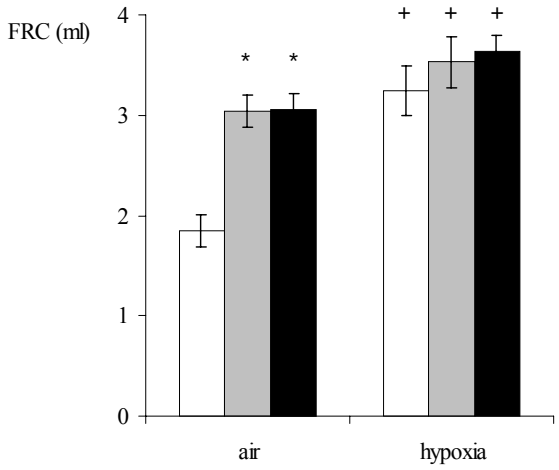

Fig. 1. *Functional residual capacity (FRC) in control (□ C), hypoxic-poikilocapnic (▨ H) and hypoxic-hypercapnic (■ H+CO_2) groups during air breathing and acute hypoxia, (10 % O_2 in N_2), *p<0.05 from the control (C) group, $^+$ p<0.05 between values obtained in the respective groups exposed to air and hypoxia.*

Values of functional residual capacity are shown in Figure 1. The FRC of chronically hypoxic rats was enlarged during air breathing to the same extent in both, poikilocapnic and hypercapnic groups. During acute hypoxia, FRC increased in all groups. The increase was more pronounced in the controls – 175 % of the value during air breathing ($p<0.0001$) than in experimental rats – 116 % ($p=0.004$) and 119 % ($p=0.0002$), respectively. The absolute hypoxic values of FRC did not differ in all three groups.

We designed this experiment to determine the effect of chronic hypercapnia on FRC changes during chronic hypoxia. Although we did not measure the end-tidal or arterial P_{CO_2} in our rats, the CO_2 concentration between 4 and 5 % ensures an end tidal P_{CO_2} above normal. As described by Walker *et al.* (1985), Pa_{CO_2} in rats exposed to 5 % CO_2 reached more than 45 mm Hg. The fact that ventilation of rats in poikilocapnic hypoxia were doubled means that their P_{CO_2} had to decrease. Aaron and Powell (1993) reported that in rats exposed to the same level of poikilocapnic hypoxia Pa_{CO_2} was around 25 mm Hg. We therefore compared the effects of chronic hypo- and hypercapnic hypoxia.

Similarly to previous experiments in rats (Barer *et al.* 1978, Sekhon *et al.* 1995), our chronically hypoxic animals gained less weight than the controls and it might have influenced their ventilation. Ventilation is mainly related to CO_2 production and some effect of the body mass should thus be expected. Indeed, in contrast to absolute values, the ventilation of chronically hypoxic rats expressed per kg of body weight did not differ from that of controls either during air breathing or in acute hypoxia. On the other hand, the tidal volumes per kg of body weight during air breathing were larger in both hypoxic groups than in the controls. This difference disappeared in acute hypoxia. In agreement with our previous finding (Vízek and Bonora 2001) the breathing frequency in rats after chronic hypoxia was slower. Because of the relatively large V_T during air breathing, the ventilatory response of our experimental groups to acute hypoxia was mainly due to the increase in f_R, while increase of both f_R and V_T was found in the controls. The shortening of expiration during acute hypoxia may have participated in the mechanism of FRC enlargement causing dynamic hyperinflation of the lungs (Paleček 2001). However, expiration shortened in the experimental group more than in the controls while FRC increased less than in controls, suggesting a relatively small influence of the shortening of expiration for FRC increase.

We did not see any difference in the absolute values of FRC in rats exposed to chronic poikilocapnic or hypercapnic hypoxia. We therefore concluded that the CO_2 concentration had no influence on FRC enlargement during chronic hypoxia. Nevertheless, if related to body weight FRC in hypercapnic and poikilocapnic rats slightly differed. However, Sekhon *et al.* (1995) reported that control rats and rats of the same age but with lower body weight (due to restriction of food intake) had the same absolute values of FRC, showing that FRC is related rather to the age than to the weight of rats. Recalculation of FRC for body weight in rats of the same age and the same weight at the beginning of the experiment but with a different weight gain during the experiment, would artificially affect the results.

The FRC enlargement due to chronic hypocapnic hypoxia was reported previously (Hurtado 1964, Barer *et al.* 1978, Sekhon *et al.* 1995), however, as far as we know, the present paper is the first report about

the effect of chronic hypoxia combined with hypercapnia. Our finding is a relevant contribution for elucidation the mechanism of FRC increase during chronic hypoxia. The increase in diaphragmatic postinspiratory inspiratory activity (Smith *et al.* 1989) and its prolongation till the end of expiration, which brakes the expiratory flow and prevents thorax from collapsing to its resting volume, seems to be important for FRC enlargement during acute hypoxia (Bonora and Vízek 1995). Because the increase in PIIA also lasts during the first days of chronic hypocapnic hypoxia (Bonora and Vízek 2001), it was suggested that it may also play a certain role in FRC enlargement in chronic hypoxia. However, since acute hypercapnia is known to decrease PIIA (Smith *et al.* 1989), our finding suggests that the PIIA increase is not crucial for FRC enlargement during chronic hypoxia.

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