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DEFENSIVE REFLEXES OF THE RESPIRATORY SYSTEM IN ANAESTHETIZED RABBITS DURING HIGH FREQUENCY JET VENTILATION

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SUMMARY

The defensive airway reflexes during high frequency jet ventilation (HFJV) were studied in anaesthetized, non-vagotomized ($n = 16$) and vagotomized ($n = 11$) rabbits. The animals were ventilated by a high frequency jet ventilator. Sneezing and coughing were evoked by mechanical stimulation of the airways. During HFJV spontaneous breathing was inhibited only in the non-vagotomized rabbits. Mechanical stimulation of the airways during HFJV evoked sneezing and coughing, in which the inspiratory component was inhibited. This inhibition occurred not only in defensive reflexes evoked from the regions with increased pressure (trachea, bronchi), but also from the nose. Vagotomy diminished but did not fully eliminate the changes in sneezing accompanying HFJV. The intensity of maximum expiratory efforts was not significantly affected by HFJV in both subgroups.

INTRODUCTION

High frequency jet ventilation (HFJV) maintains adequate gas exchange with high frequencies (2–10 Hz) and small tidal volumes applied to the airways. An important advantage of this method is the low peak intrapulmonary pressure produced. However, HFJV with a short expiratory time causes an elevation of end-expiratory lung volume and airway pressure (dynamic, or inadvertent positive end-expiratory pressure (PEEP)). Changes in afferent inputs from receptors of the airways, lungs and chest wall evoked by HFJV may change the output from respiratory centres, the spontaneous respiratory activity and the defensive airway reflexes.

Spontaneous breathing activity during HFJV was studied by van Vught, Versprille & Jansen (1987), but no information is available about the interactions of HFJV with sneezing and coughing either in animals or humans.

The aim of this study was to find out if mechanical stimulation of the airways can elicit defensive airway reflexes during HFJV in anaesthetized, non-paralysed rabbits and to determine if the vagal nerves are involved in any potential reflex effects.

METHODS

Experiments were carried out on twenty-seven rabbits, mean weight $3{\cdot}25 \pm 0{\cdot}10$ kg, under general anaesthesia induced and maintained by sodium pentobarbitone (Pentobarbital, Spofa, Praha, Czecho-Slovakia; induction, 40 mg/kg^{-1} I.V. and maintenance, 15 mg kg^{-1} h^{-1}). The animals were tracheotomized and ventilated via a tracheal cannula.

Interpleural pressure was recorded from the 7th or 8th right intercostal space with an LDP 165 electromanometer (Tesla, Valašské Meziříčí, Czecho-Slovakia) and interpleural cannula. Intratracheal pressure was measured via a catheter (0·7 mm i.d., 1·1 mm o.d.) attached to an electromanometer (LDP 165, Tesla). The distal end of the catheter was situated near the carina. The frequency response of the system was flat up to 60 Hz. The catheter was flushed with air on alternate

Table 1. *Parameters characterizing sneezing during spontaneous breathing at the beginning of the experiment (C1), in the 15th and 30th minute of HFJV, and after a further 30 min of spontaneous breathing at the end of the experiment (C2)*

	C1	15th minute	30th minute	C2
MNE (number/attack)	7·7±0·9	5·9±0·8*	4·2±0·5**	7·0±2·7
f (min^{-1})	60·0±3·9	47·7±4·9*	33·1±4·9**	60·0±2·0
MIA_i (kPa)	1·46±0·09	0·67±0·10**	0·49±0·10**	1·68±0·15
MIA_e (kPa)	1·57±0·15	1·51±0·15	1·50±0·15	2·00±0·20

MNE, mean number of efforts per sneezing attack; f, frequency of efforts; MIA_i, mean inspiratory intensity of the attack; MIA_e, mean expiratory intensity of the attack. Significant difference from control (C1): * $P < 0·05$; ** $P < 0·001$. Means±S.E.M.

ventilation cycles. Blood pressure in the femoral artery was recorded with an electromanometer (LDP 102, Tesla). Arterial blood gases were evaluated using a blood gas analyser (BMS-3, Radiometer, Copenhagen, Denmark).

In non-vagotomized rabbits, sneezing, laryngopharyngeal and tracheobronchial stimulation-induced coughing reflexes were elicited by rhythmic repetitive mechanical stimulation of nasal, laryngeal and tracheobronchial regions with a nylon fibre (0·2 mm diameter). Defensive airway reflexes were elicited during spontaneous breathing (control 1, C1) in the 15th and 30th minute of HFJV with a jet ventilator (Beat-2, Konštrukta and Chirana, Trenčín, Stará Turá, Czecho-Slovakia) at a frequency of 5 Hz with an insufflation pressure of 150 kPa and inspiratory time:expiratory time ratio of 1·0, and after 30 min of spontaneous breathing following HFJV (control 2, C2).

Bilateral cervical vagotomy was performed in eleven rabbits. In these animals, we studied only changes in sneezing characteristics during HFJV, since defensive reflexes from the lower airways could not be elicited after vagotomy. We evoked sneezing during spontaneous breathing at the beginning (C1), 5 min after vagotomy, in the 15th and 30th minute of HFJV with the same ventilatory parameters as in non-vagotomized rabbits, or with addition of CO_2 to inspired gas mixture to maintain normocapnia, and after 30 min of spontaneous breathing after HFJV (C2).

From pleural pressure recordings we evaluated the following parameters during sneezing or coughing: the mean number of efforts per attack (MNE); the frequency of efforts in each attack (f); the intensity of the maximum inspiratory and expiratory efforts (IME_i and IME_e, respectively, as changes in intrapleural pressure); the total inspiratory and expiratory intensity of the attack (TIA_i and TIA_e, respectively; the sum of all individual inspiratory and expiratory efforts in each attack); and the mean intensity of the attack (intensity of the attack divided by the number of efforts). The body temperature was kept constant by a heated table. The rabbits were killed by overdosing with the anaesthetic drug (sodium pentobarbitone) at the end of the experiments.

Results are expressed as means±S.E.M. Student's t test was used to determine the significance or difference of means.

RESULTS

During HFJV spontaneous breathing was inhibited in non-vagotomized rabbits. The arterial partial pressure of O_2 (P_{a,O_2}) rose from 9·7±0·6 to 11·0±0·05 kPa ($P < 0·001$) and the arterial partial pressure of CO_2 (P_{a,CO_2}) fell from 3·6±0·2 to 2·5±0·3 kPa ($P < 0·01$). Peak intratracheal pressure during HFJV was 0·82±0·09 kPa in the 15th minute of HFJV and 0·81±0·09 kPa in the 30th minute of HFJV. The dynamic PEEP was 0·42±0·04 and 0·43±0·04 kPa in the 15th and 30th minute, respectively.

In vagotomized animals, HFJV did not inhibit spontaneous breathing. P_{a,O_2} increased from 7·5±0·33 to 11·4±0·05 kPa ($P < 0·001$) and P_{a,CO_2} was maintained near to the initial values (3·2±0·2 *versus* 3·5±0·3 kPa, $P > 0·05$). Peak intratracheal pressure was 0·86±0·04 kPa in the 15th minute and 0·88±0·06 kPa in the 30th minute of HFJV. The

Table 2. *Parameters characterizing laryngopharyngeal stimulation-induced coughing during spontaneous breathing and HFJV*

	C1	15th minute	30th minute	C2
MNE (number/attack)	4·7 ± 0·6	3·5 ± 0·4	3·4 ± 0·6	4·0 ± 0·6
f (min^{-1})	55·5 ± 3·9	40·3 ± 5·3*	36·3 ± 6·8*	50·0 ± 10·0
MIA_i (kPa)	1·01 ± 0·14	0·09 ± 0·05**	0·08 ± 0·05**	0·94 ± 0·14
MIA_e (kPa)	1·64 ± 0·12	1·34 ± 0·15	1·55 ± 0·23	1·58 ± 0·25

For explanation, see legend to Table 1.

Table 3. *Parameters characterizing tracheobronchial stimulation-induced coughing during spontaneous breathing, C1, C2 and in the 15th and 30th minute of HFJV*

	C1	15th minute	30th minute	C2
MNE (number/attack)	6·7 ± 1·8	3·2 ± 0·5*	3·1 ± 0·8*	4·3 ± 1·2
f (min^{-1})	57·3 ± 4·5	29·5 ± 6·5**	22·9 ± 5·9**	60·0 ± 1·8
MIA_i (kPa)	1·11 ± 0·13	0·28 ± 0·09**	0·13 ± 0·08**	1·18 ± 0·29
MIA_e (kPa)	1·69 ± 0·15	1·62 ± 0·15	1·45 ± 0·20	1·80 ± 0·25

For explanation, see legend to Table 1.

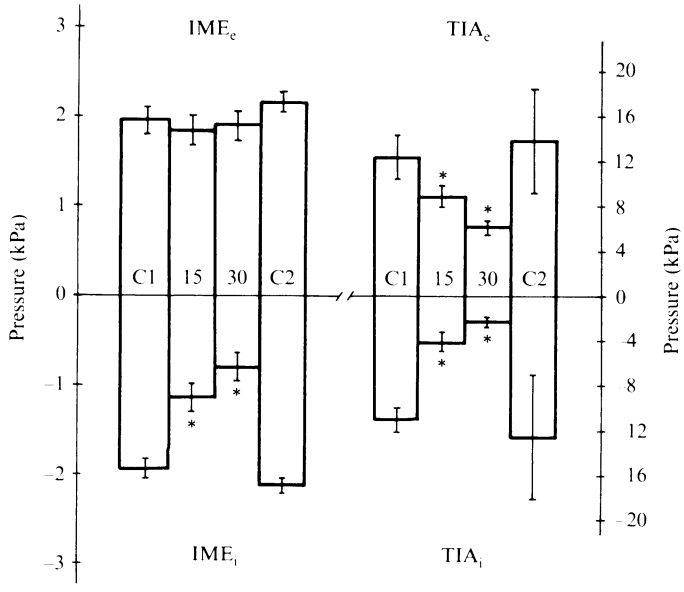

Fig. 1. Intensity of maximum expiratory effort (IME_e) and inspiratory effort (IME_i) and total expiratory and inspiratory intensity (TIA_e and TIA_i, respectively) of sneezing attacks at the beginning of the experiment (C1), in the 15th and 30th minute of the HFJV and after another 30 min of spontaneous breathing in non-vagotomized rabbits (C2). * Significantly different from control (C1). Values are given as means ± S.E.M.

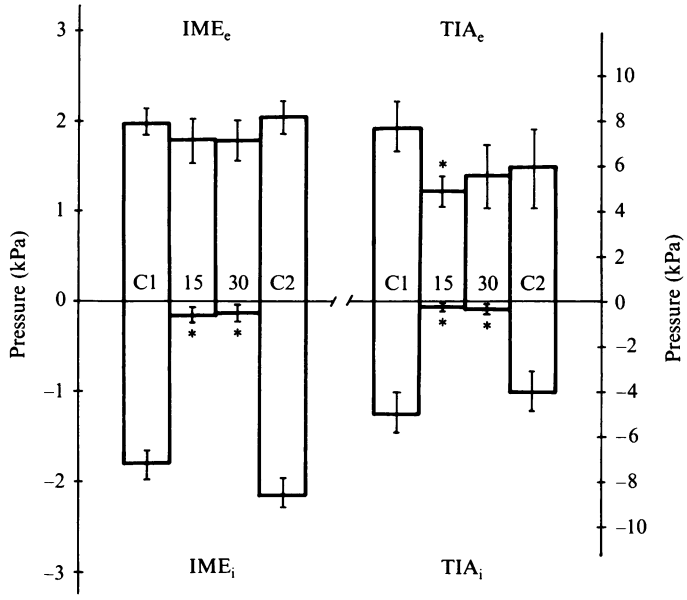

Fig. 2. The same parameters as in Fig. 1, recorded during laryngopharyngeal stimulation-induced coughing. Abbreviations as in Fig. 1.

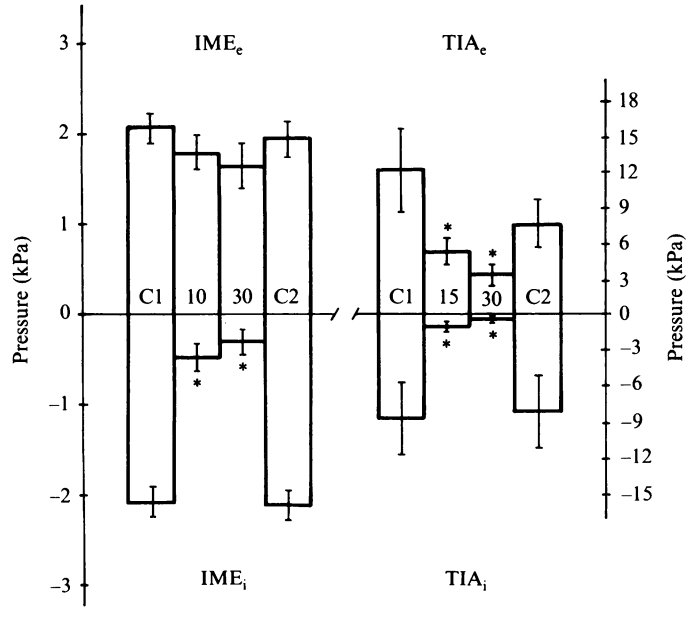

Fig. 3. The same parameters as in Fig. 1, recorded during tracheobronchial stimulation-induced coughing before, during and after HFJV. Abbreviations as in Fig. 1.

dynamic PEEP was $0{\cdot}38 \pm 0{\cdot}05$ kPa in the 15th minute and $0{\cdot}39 \pm 0{\cdot}03$ kPa in the 30th minute. Intratracheal pressures during HFJV did not differ significantly between the subgroups ($P > 0{\cdot}05$).

In non-vagotomized animals mechanical stimulation of the upper airways and trachea

Table 4. *Parameters of sneezing during spontaneous breathing at the beginning of the experiment (C1), 5 min after vagotomy (V), in the 15th and 30th minute of HFJV and after another 30 min of spontaneous breathing in vagotomized rabbits at the end of the experiment (C2)*

	C1	V	15th minute	30th minute	C2
MNE (number/attack)	8·5±0·6	6·7±0·5*	6·2±0·4	5·7±0·4	6·3±0·3
f (min^{-1})	65·7±3·8	47·7±2·4***	47·3±2·7	48·5±2·5	56·5±3·1*
MIA_i (kPa)	1·35±0·12	1·15±0·12	0·7±0·05**	0·7±0·12**	1·05±0·1*
MIA_e (kPa)	1·9±0·15	1·45±0·17	1·32±0·15	1·38±0·12	1·5±0·17

For explanation, see legend to Table 1. Probability levels after vagotomy (V) are given in relation to control (C1); during HFJV (15th, 30th minute) they are given in relation to previous values (V); and at the end of the experiment (C2) they are given in relation to values in the 30th minute of HFJV. Significant difference: * $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

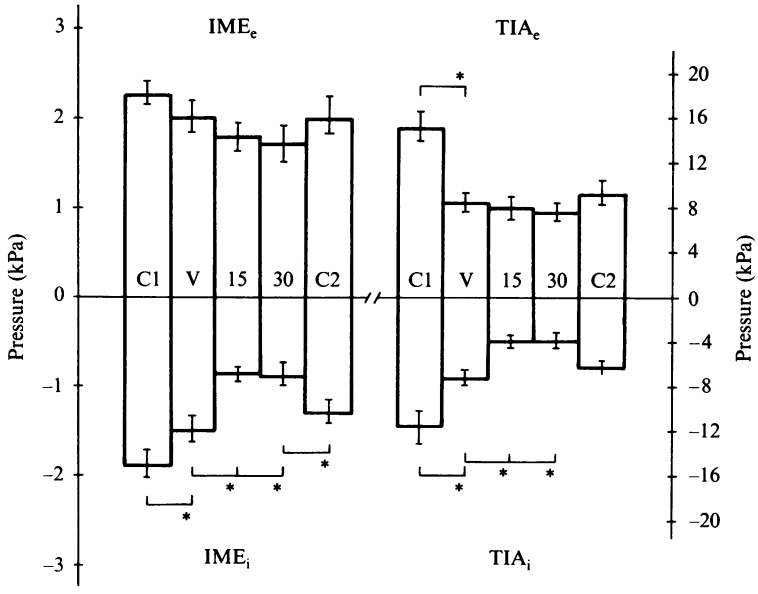

Fig. 4. The same parameters as in Fig. 1, recorded during sneezing in vagotomized rabbits at the beginning of the experiment (C1), 5 min after bilateral cervical vagotomy (V), in 15th and 30th min of HFJV and after another 30 min of spontaneous breathing (C2).

was still able to elicit sneezing and coughing during HFJV. However, all inspiratory components were inhibited. The intensities of the maximum and mean expiratory efforts of these defensive reflexes evoked during spontaneous breathing and HFJV did not differ significantly. The total expiratory intensity of the attacks was decreased during HFJV owing to reduction of the number of efforts. Parameters of defensive reflexes during HFJV in non-vagotomized rabbits are given in Tables 1–3 and Figs 1–3.

Vagotomy reduced the number and frequency of efforts as well as the inspiratory and expiratory parameters of sneezing. HFJV in vagotomized animals further inhibited the inspiratory components of sneezing (Table 4, Fig. 4). Changes of the sneezing parameters in the vagotomized animals were similar to control animals, but the inhibition after

vagotomy was smaller (e.g. IME_i was decreased in HFJV in animals without vagotomy by 58·2% of the initial value, after vagotomy by 41·3%; TIA_i in the non-vagotomized animals was decreased by 79·7% and in the vagotomized animals by 46·3%; and MIA_i was reduced by 66·4% *versus* 39·0%, respectively.

DISCUSSION

High frequency jet ventilation (HFJV) applies pulses of air to the lungs and increases lung volume, both of which affect structures of the airways and lungs and their receptors. It is known that HFJV in piglets (van Vught *et al.* 1987) and high frequency oscillation ventilation (HFOV) in dogs (Davenport & Dalziel, 1989) and rabbits (Kohl, Freund & Koller, 1991) evoke suppression of spontaneous breathing. These results demonstrated that the major factor suppressing central respiratory activity is the effect of the lung volume increase caused by dynamic PEEP.

One type of pulmonary receptor activated during high frequency ventilation is the slowly adapting stretch receptor (SASR) (Sant Ambrogio & Davenport, 1986). This was investigated in more detail by Kohl & Koller (1988) and Kohl *et al.* (1991). Their findings suggested that the apnoea during HFOV in rabbits is mediated mainly by stimulation of SASR and other vagal pulmonary receptors. The irritant and/or C fibre receptors, might exert some influence on the mechanisms regulating respiration during HFJV and HFOV.

In the present experiments HFJV was accompanied by the suppression of spontaneous breathing in anaesthetized rabbits. This suppression was eliminated by bilateral cervical vagotomy, supporting its reflex vagal origin.

During HFJV we were able to provoke coughing and sneezing in spite of the inhibition of spontaneous breathing. However, the inspiratory components of the reflexes, including those from the nose and larynx, were inhibited. Total expiratory intensity of the attacks was decreased owing to reduction in the number of efforts, but the intensity of individual efforts was not reduced.

These results are in agreement with our previous findings (Javorka, Michalík, Čakloš & Bevilaqua, 1982) in anaesthetized cats, that increased intrapulmonary pressure during continuous positive airway pressure (CPAP) breathing caused weakening mainly of the inspiratory components of sneezing, coughing and especially of the aspiration reflex. This reflex is characterized by deep inspiratory efforts without forced expiration. After vagotomy, the increased intrapulmonary pressure still diminished the intensity of the aspiration reflex (Javorka, Pakosová, Tojčíková, Hrušovská & Tomori, 1983).

In the present study, in vagotomized animals only changes in sneezing characteristics were examined during HFJV, since after vagotomy it is not possible to elicit defensive lower airway reflexes, and the aspiration reflex is not present in rabbits (Korpáš & Kaloczayová, 1974). Bilateral vagotomy itself reduced sneezing activity, both in number and frequency of the efforts and in total intensity of the episodes, in accordance with Burkart & Bucher (1960). The HFJV inhibition of the deep preparatory inspirations of sneezing persisted after vagotomy, but was less pronounced. These findings indicate that, as well as vagal receptors some other mechanisms regulating defensive airway reflexes might be involved in these artificial conditions.

Receptors of the chest wall and diaphragm are stimulated by dynamic PEEP and by the modulation of the intrapulmonary pressure occurring during HFJV. This may exert an inhibitory effect on inspiratory efforts, because intercostal muscle spindle afferent activity is known to have a potent inhibitory effect on inspiration (Remmers, 1970; Shannon, 1980).

Chest wall vibration inhibits inspiratory diaphragmatic activity (Homma, 1980). England, Onayemi & Bryan (1984) found that apnoea during HFV in cats results from inspiratory inhibition mediated by both vagal afferent and chest wall mechanisms. These mechanisms may also be involved in the inhibition of inspiratory efforts in sneezing and coughing during HFJV.

During PEEP (or CPAP), the lung volume increase forces the chest to an inspiratory position. This alters the potential for both inspiration and expiration, by changing the initial length of the respiratory muscles, which influences the force of contraction (Hanáček & Korpáš, 1982).

Our results show that the defensive airways reflexes are active during HFJV in anaesthetized non-paralysed rabbits. At least three factors, probably in combination, could be involved in the inhibition of the inspiratory components of these reflexes: vagal pulmonary receptors; receptors of the chest wall and diaphragm; and the mechanophysical properties of the respiratory system.

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