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Time to peak tidal expiratory flow and the neuromuscular control of expiration

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ABSTRACT: The ratio of the time needed to reach peak tidal expiratory flow (t_{PTEF}) and the duration of expiration (t_E) is used to detect airflow obstruction in young children. t_{PTEF} is decreased in patients with asthma, but knowledge about the physiological determinants of this parameter is scarce. This study examined the relationship between t_{PTEF} and postinspiratory activities of inspiratory muscles and evaluated the effects of changing sensory information from the lung.

Airflow patterns and electromyographic (EMG) activity of inspiratory muscles were recorded in seven spontaneously breathing, anaesthetized cats. The trachea was cannulated and, as a result, the larynx and upper airways were bypassed. Changes in postinspiratory muscle activity were induced by changing afferent sensory nerve information (by cooling the vagus nerves, by administration of histamine and by additional application of continuous positive airway pressure (CPAP)).

Durations of postinspiratory activities of the diaphragm and intercostal muscles (characterized by their time constants τ_{diaphr} and τ_{interc}) correlated strongly with t_{PTEF} ($r=0.85$ and 0.77, respectively). τ_{diaphr}, τ_{interc} and t_{PTEF} were significantly increased during cooling of the vagus nerves (4–8°C) compared with values at 22 and 37°C ($p<0.05$). Conversely, administration of histamine and CPAP caused significant decreases in τ_{diaphr}, τ_{interc} and t_{PTEF}, which were absent during cooling of the vagus nerves.

In conclusion, the time needed to reach peak tidal expiratory flow is highly influenced by the activities of inspiratory muscles during the early phase of expiration which, in turn, depend on the activities of vagal receptors in the lung.

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Tidal breathing analysis is used as a tool to quantify airway obstruction in infants and children. The ratio of the time needed to reach peak tidal expiratory flow (t_{PTEF}) and the duration of expiration (t_E) are decreased in patients with asthma and cystic fibrosis [1–3]. t_{PTEF} is the most important determinant of changes in this ratio in children with asthma [4]. t_{PTEF} increases after the inhalation of a bronchodilator in asthmatics [1, 2] and decreases after bronchial challenge with methacholine [1, 5]. Several authors have shown that the parameter t_E is relatively stable in these patients [6, 7].

Until now, the relationship between the ratio t_{PTEF}/t_E and airway diameter is unclear. It has been suggested that t_{PTEF}/t_E reflects primarily neuromuscular control of expiration, which can be further influenced by changing pulmonary mechanics such as changing airflow resistance or lung compliance [8]. MORRIS *et al.* [8] observed that postinspiratory activity of inspiratory muscles was decreased in patients with airflow obstruction. Activity of inspiratory muscles during the early phase of expiration causes braking of the expiratory airflow. A change in the postinspiratory activity of inspiratory muscles may, therefore, influence t_{PTEF}. In an editorial, MIKKILINENI and ENGLAND [9] stressed the need for studies into the relationship between tidal breathing parameters and control of breathing.

This study was performed to elucidate the relationship between t_{PTEF} and the neuromuscular control of expiration. In an animal model investigations were made into: 1) the relationship between the parameter t_{PTEF} and postinspiratory activity of inspiratory muscles, and 2) the influence of afferent sensory vagus nerve information from the lung on t_{PTEF}. The results for t_{PTEF} were compared with those predicted by a model of the respiratory system.

Methods

Study animals

For this study experimental data were used that had been previously gathered by MEESSEN *et al.* [10] for a study into the effects of histamine and continuous positive airway pressure (CPAP) on end-tidal inspiratory muscle activity. The experimental procedures were described extensively in their study and will be summarized here.

The study was performed on seven adult cats (body weight 5.1±0.3 kg), which were anaesthetized with ketamine-hydrochloride (10 mg·kg^{-1} *i.m.*) and a chloralose-urethane mixture (12.5 and 62.5 mg·kg^{-1} *i.v.*, respectively).

To maintain surgical anaesthesia, supplemental doses of chloralose-urethane (5% of initial dose) were given if needed. Body temperature was maintained between 36 and 38°C. Both cervical vagus nerves were exposed in the mid-neck, freed from the carotid sheaths and cooled with the use of a Peltier element (range 37–4°C±0.2°C).

Airflow recording

The cats breathed spontaneously and were placed in the supine position on an operating table. The trachea was cannulated and connected to a pneumotachometer (Fleisch 0 Gould, Bilthoven, the Netherlands) to measure airflow. The other side of the Fleisch head was connected to a main tube in which a constant bias flow of ~18 L·min^{-1} was maintained, to prevent rebreathing of expired air. With the help of an adjustable flow resistance in the bias flow a CPAP could be set.

From the flow recordings, tE, tPTEF and the ratio tPTEF/tE were determined.

Electromyographic recording

A pair of hooked needle electromyographic (EMG) electrodes was inserted into the costal part of the diaphragm and a second pair of electrodes into a parasternal intercostal muscle in the third or fourth intercostal space. The electrical activities of the diaphragm and intercostal muscles were amplified, filtered (150–3,000 Hz), rectified and fed into leaky integrators with a time constant of 50 ms (Neurolog, Digitimer, Welwyn Garden City, UK).

Signals representing integrated EMG activity of the diaphragm and intercostal muscles, airflow and temperature of the vagus nerves were monitored continuously and were sampled (50 Hz) with a computer (Compaq 386, Houston, TX, USA) and stored on the hard disk for offline analysis.

The measured EMG activities during the expiration were evaluated by fitting the integrated signals with the function $Ae^{-t/\tau}+B$, where t is time, A and B are amplitudes and τ the time constant of the decay of inspiratory muscle activity (τ_{diaphr} for the diaphragm and τ_{interc} for the intercostal muscles). A representative recording is presented in figure 1.

Experimental protocol and background

Changes in τ_{diaphr} and τ_{interc} were induced by changing afferent sensory nerve information from the lung. Vagal nerve receptors in the lung can be stimulated by the administration of histamine or CPAP. Intravenous histamine strongly stimulates rapidly adapting receptors (RAR) by a direct chemical effect [11–13], but also indirectly by mechanical stimulation when bronchoconstriction is induced. CPAP stimulates predominantly slowly adapting receptors (SAR) and, to a lesser extent RAR [14]. Conductance of vagal afferent activity can be inhibited and finally blocked by cooling both cervical vagus nerves. Accordingly, the following experimental protocol was used. After recording at least 10 baseline breathing cycles, 300 µg histamine-diphosphate was administered intravenously. After the change in breathing pattern in response to histamine was apparent for about 20–30 s, CPAP of 0.9 kPa was applied during 6–10 breathing cycles. A high level of CPAP was used to stimulate SAR forcefully. In this way,

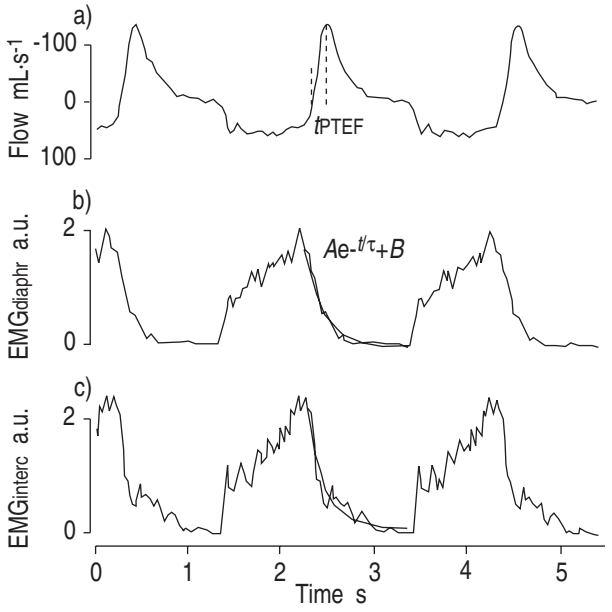

Fig. 1. – Representative recording of a) tidal breathing airflow with concomitant recordings of integrated electromyographic (EMG) activity of b) the diaphragm (diaphr) and c) the intercostal muscles (interc). Postinspiratory EMG activity was fitted with the function $Ae^{-t/\tau}+B$, as shown in the second breathing cycle. tPTEF: time needed to reach peak tidal expiratory flow.

three runs of breathing cycles were recorded subsequently: 1) breathing cycles during control conditions; 2) breathing cycles after the administration of histamine, just before the application of CPAP; and 3) breathing cycles during histamine plus CPAP. All parameters were expressed as a mean value of six regular sequential breathing cycles. The protocol was carried out at the following temperatures of the vagus nerves: 37, 22, 14, 12, 10, 8, 6 and 4°C. Between two consecutive protocols a recovery period was allowed, until the breathing pattern had returned to the pattern prior to the administration of histamine. This protocol provided a wide range of τ values. After preparation of the cat, a typical experiment lasted for about 4 h.

A simplified mechanical model of the respiratory system was adopted to compute tPTEF as a function of τ. This model consists of a single respiratory resistance (R_{rs}) and a single respiratory elastance (E_{rs}) in series (for details see Appendix).

Statistical analysis

All data are presented as mean±SEM. Because of the relatively small sample sizes and because data did not show normal distributions, a Wilcoxon test for paired observations was used to compare differences between baseline, histamine and histamine plus CPAP values and differences between values obtained at different temperatures. A p-value <0.05 was considered significant.

The relationships between tPTEF and τ_{diaphr} and between tPTEF and τ_{interc} were studied with a quadratic random coefficients model, based on the concave curvilinear appearance. In this model the dependent variable tPTEF was related to the independent variables τ_{diaphr} or τ_{interc} as follows:

$$tPTEF = b0 + b1\tau + b2\tau^2 + \varepsilon. \quad (1)$$

In this model the three coefficients $b0$, $b1$ and $b2$ have a three-dimensional normal distribution across the cats with means $\beta 0$, $\beta 1$, and $\beta 2$ and a 3×3 covariance matrix. The variance of the residuals ($\sigma^2\varepsilon$) was supposed to be equal in all cats. Subsequently, the multiple correlation coefficient r between *t*PTEF and τ can be defined as follows:

$$r = 1 - (\sigma^2\varepsilon/\sigma^2tot) \quad (2)$$

where σ^2tot is the variance of all *t*PTEF values.

Results

Relationship between t*PTEF and muscular activity*

Figure 2 shows a positive correlation between *t*PTEF and τdiaphr. This relationship flattens off at higher values of τdiaphr. Therefore, a quadratic term ($b2\tau^2$) was added to the linear equation $tPTEF = b0 + b1\tau$, as described in the Methods section. This equation was fitted for each cat individually. The estimated mean coefficients $\beta 0$, $\beta 1$ and $\beta 2$ are shown in table 1. The estimated mean regression curve is shown in figure 3. The correlation between *t*PTEF and τdiaphr was significant (multiple correlation coefficient r=0.85).

The parameter *t*PTEF also correlated significantly with τinterc (r=0.77). The estimated mean coefficients $\beta 0$, $\beta 1$, and $\beta 2$ are shown in table 1. The estimated mean regression curve for *t*PTEF as a function of τinterc is shown in figure 3.

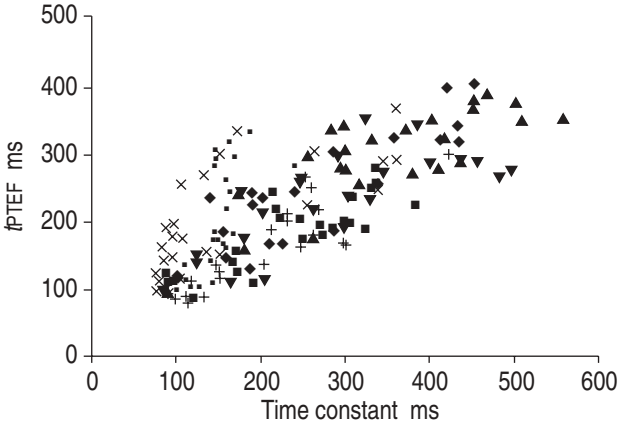

Fig. 2. – Relationship between decay of postinspiratory activity of the diaphragm (expressed as a time constant of the electromyographic signal decay, τdiaphr) and the time needed to reach peak tidal expiratory flow (*t*PTEF) in seven cats under different experimental conditions. The different symbols represent different animals.

Table 1. – Estimated coefficients of the equation $tPTEF = b0 + b1\tau + b2\tau^2 + \varepsilon$ for τdiaphr and τinterc in seven cats

	τdiaphr	τinterc
$\beta 0$ ms^{-1}	25.7 (28.9)	40.3 (22.3)
$\beta 1$	1.2214 (0.3226)	0.9788 (0.1217)
$\beta 2$ ms^{-1}	-1.2630×10^{-3} (0.6518×10^{-3})	-0.9006×10^{-3} (0.1607×10^{-3})

Values are shown as mean±SEM. *t*PTEF: time needed to reach peak tidal expiratory flow; τdiaphr: time constant of the decay of postinspiratory electromyographic (EMG) activity of the diaphragm; τinterc: time constant of the decay of postinspiratory EMG activity of the intercostal muscles. $\beta 0$, $\beta 1$, $\beta 2$: means of the three coefficients $b0$, $b1$ and $b2$.

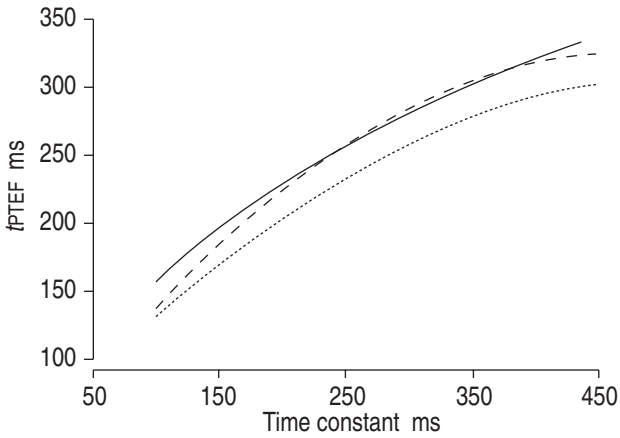

Fig. 3. – Estimated mean regression curves of the relationship between the time needed to reach peak tidal expiratory flow (*t*PTEF) and the time constant of the decay of postinspiratory electromyographic (EMG) activity of the diaphragm τdiaphr (- - -) or the intercostal muscles τinterc (·····) in seven anaesthetized cats.—— : represents the relationship between *t*PTEF and τ according to the mechanical model, with τrs = 0.253 (see Equation A8 of the Appendix).

The model (see Appendix) was used to calculate *t*PTEF as a function of τ. For this calculation a time constant of the respiratory system ($\tau rs = Rrs/Ers$) of 0.253 s was used. This value has been reported as the mean value of six anaesthetized cats in a study of Z$_{IN}$ *et al.* [15]. The calculated *t*PTEF as a function of τ is also shown in figure 3.

Influence of histamine

At temperatures of the vagus nerves >8°C τdiaphr, τinterc and *t*PTEF decreased significantly after *i.v.* administration of histamine (table 2, figs. 4 and 5). At vagal temperatures of 4, 6 and 8°C no significant decreases, or even small increases in these parameters were observed. The parameter *t*E did not change significantly after the administration of histamine at vagal temperatures of 4 and 6°C. At the higher temperatures, *t*E decreased significantly after histamine. The concordant changes in *t*PTEF and *t*E resulted in stable ratios for *t*PTEF/*t*E, without significant influence of the administration of histamine (table 2).

Influence of histamine plus CPAP

Application of CPAP caused a significant further decrease in τdiaphr compared with histamine without CPAP at vagal temperatures <10°C. At lower temperatures no significant changes were observed (fig. 4, table 2). CPAP caused a further decrease of τinterc at vagal temperatures of 22 and 37°C. At temperatures of 4 and 6°C there was a nonsignificant decrease, while at temperatures of 8–14°C there was a nonsignificant increase in τinterc (table 2). The parameter *t*PTEF decreased at all vagal temperatures. This decrease was significant except at 12 and 14°C (fig. 5, table 2). *t*E was not influenced by the application of CPAP at 4 and 6°C. At 8–14°C, *t*E increased significantly compared with the histamine values and was comparable to the baseline values. At temperatures of 22 and 37°, *t*E increased considerably to levels above the baseline values (table 2).

Table 2. – Tidal breathing and inspiratory muscle electromyographic (EMG) parameters in seven cats under different experimental conditions (*i.v.* histamine and continuous positive airway pressure (CPAP) at different temperatures of the cervical vagus nerves)

	Temperature of vagus nerves (°C)							
	37	22	14	12	10	8	6	4
Baseline								
t_E s	0.93	0.93	0.92	0.97	1.03	1.09	1.16	1.27
	0.11	0.10	0.10	0.12	0.12	0.13	0.14	0.13
t_{PTEF} ms	192	191	231	251	291	309	298	287
	16	22	26	33	18	19	16	16
t_{PTEF}/t_E	0.21	0.21	0.26	0.28	0.31	0.31	0.28	0.24
	0.01	0.01	0.04	0.04	0.04	0.04	0.03	0.03
τ_{diaphr} ms	168	185	273	266	302	299	332	287
	24	34	58	59	54	56	56	42
τ_{interc} ms	258	184	242	267	415	395	310	351
	50	29	39	42	71	57	34	66
Histamine								
t_E s	0.69	0.79	0.63	0.69	0.79	0.83	1.00	1.12
	0.11	0.13	0.10	0.09	0.10	0.12	0.11	0.15
t_{PTEF} ms	125	143	175	201	231	269	306	285
	12	24	27	29	25	30	29	28
t_{PTEF}/t_E	0.20	0.20	0.29	0.30	0.32	0.35	0.31	0.27
	0.02	0.03	0.04	0.03	0.04	0.05	0.03	0.03
τ_{diaphr} ms	156	175	188	203	239	271	344	272
	26	42	42	37	28	40	44	32
τ_{interc} ms	159	149	176	207	221	276	342	312
	27	15	19	24	35	41	40	31
Histamine + CPAP								
t_E s	1.64	1.47	0.96	1.18	1.00	1.08	1.03	1.14
	0.42	0.23	0.15	0.24	0.07	0.11	0.12	0.11
t_{PTEF} ms	101	112	161	181	204	235	263	233
	4	10	27	25	26	22	27	15
t_{PTEF}/t_E	0.08	0.09	0.19	0.18	0.21	0.23	0.26	0.21
	0.02	0.01	0.03	0.03	0.03	0.03	0.02	0.01
τ_{diaphr} ms	99	105	171	168	211	259	303	276
	6	13	35	24	38	27	33	16
τ_{interc} ms	116	124	221	215	264	305	284	256
	18	24	42	32	18	54	28	35

t_E: duration of expiration; t_{PTEF}: time needed to reach peak tidal expiratory flow; τ_{diaphr}: time constant of the decay of postinspiratory EMG activity of the diaphragm; τ_{interc}: time constant of the decay of postinspiratory EMG activity of the intercostal muscles.

Because of these changes the ratio t_{PTEF}/t_E was significantly decreased during histamine plus CPAP at vagal temperatures above 8°C. At lower temperatures no changes were observed (table 2).

Influence of cooling of vagus nerves

In all experimental conditions τ_{diaphr}, τ_{interc}, t_{PTEF} and the ratio t_{PTEF}/t_E were significantly lower at vagal temperatures of 22 and 37°C compared with their values at 4, 6 and 8°C (table 2, figs. 4 and 5). No significant changes in baseline t_E values were observed at different vagal temperatures. The changes in t_E induced by administration of histamine and CPAP were not observed at 4 and 6°C.

Discussion

Relationship between t_{PTEF} *and inspiratory muscle activity*

This study shows that t_{PTEF} correlated strongly with τ_{diaphr} and τ_{interc}. A rapid decay in the activities of the diaphragm and intercostal muscles during the first part of expiration correlates with low t_{PTEF} values (fig. 2). Changes in τ_{diaphr} and τ_{interc} were induced by changing the afferent sensory nerve information from the lung. The considerable changes induced in τ_{diaphr} and τ_{interc} were followed closely followed by similar changes in t_{PTEF} (figs. 2 and 3). This suggests that the parameter t_{PTEF} depends strongly on the neuromuscular control of expiration.

The most important driving force of expiratory airflow is the elastic recoil of the respiratory system [16]. In paralysed subjects, after release of artificial inflation of the lungs, the expiratory airflow reaches a peak value almost immediately and is followed by an exponential decay [17, 18]. This decay can be described by τ_{rs}. Thus, in paralysed subjects t_{PTEF} is almost zero. In nonparalysed subjects, expiratory airflow is decreased by the counteracting activity of inspiratory muscles [8]. Therefore, inspiratory muscle activity during the first part of expiration can increase t_{PTEF}.

As shown in figure 1, the decay of inspiratory muscle activity during expiration can be described by a monoexponential function ($Ae^{-t/\tau}+B$). Therefore, the equation of motion of the respiratory system can be solved analytically (Appendix). A simple expression is obtained for t_{PTEF} as function of τ and τ_{rs} (Equation A8 in the Appendix). This

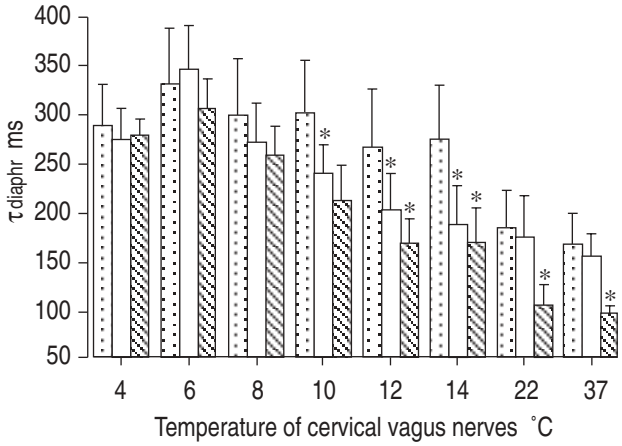

Fig. 4. – Velocity of decay of postinspiratory electromyographic (EMG) activity of the diaphragm (expressed as τ_{diaphr}) in seven cats under different experimental conditions. The bars represent mean τ_{diaphr} values (±SEM) at baseline ( ), after *i.v.* histamine ( ) and after histamine plus continuous positive airway pressure ( ) at different temperatures of the cervical vagus nerves. *: $p<0.05$, significant difference from the previous condition at that temperature.

model shows that τ and τ_{rs} are equally important determinants of *t*PTEF. The computed relationship between *t*PTEF and τ (with τ_{rs}=0.253 s, the average value obtained in anaesthetized cats by ZIN *et al.* [15]) corresponds well with the experimentally observed relationships (fig. 3), with the best relationship for τ_{diaphr}. This is in line with the fact that in the present experimental conditions the diaphragm is the most important inspiratory muscle.

In the model computations, a single value for τ_{rs} (0.253 s) was used for all cats and all experimental conditions. Studies in other mammalian species showed small changes in τ_{rs} after vagotomy and suggested a major influence of vagotomy on the neuromuscular control of breathing [19, 20]. Despite the use of a single τ_{rs} value, a good correlation was observed between experimental data and the model results. In future studies, simultaneous measurements of τ_{rs} may improve the validation of the model.

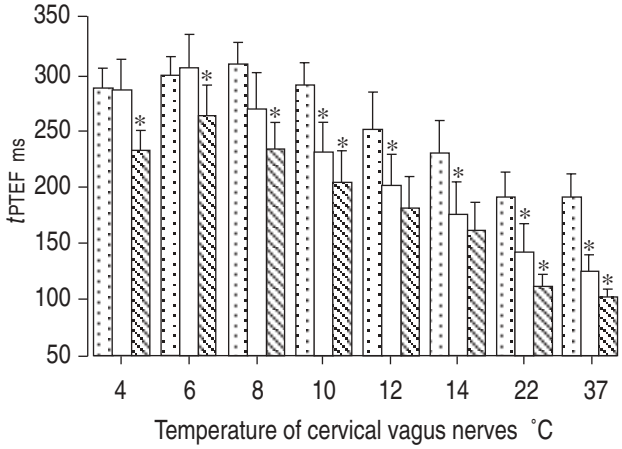

Fig. 5. – Time needed to reach peak tidal expiratory flow (*t*PTEF) in seven cats under different experimental conditions. The bars represent mean *t*PTEF values (±SEM) at baseline (, after *i.v.* histamine ( ) and after histamine plus continuous positive airway pressure ( ) at different temperatures of the cervical vagus nerves. *: $p<0.05$, significant difference from the previous condition at that temperature.

Many studies have shown that *t*PTEF decreases in patients with airflow obstruction [1–5]. With regard to the present findings, this decrease in *t*PTEF may be caused by a decrease in τ_{diaphr} and τ_{interc} in these patients. Several studies have shown a more rapid decay of inspiratory muscle activity in patients with airway obstruction [8, 21].

In the present animal study, the main interest concerned the influence of postinspiratory activity of inspiratory muscles on *t*PTEF. In human subjects expiratory muscles probably do not play an important role during quiet breathing. MORRIS *et al.* [8] found EMG silence over expiratory abdominal muscles in adults with moderate to severe airflow obstruction. In children with asthma it may be supposed that intrinsic muscles of the larynx which control upper airway resistance will also influence expiratory airflow and *t*PTEF. In the present study all animals were intubated to bypass the laryngeal mechanisms. According to the model, changes in upper airway resistance will result in changes in τ_{rs} and will, consequently, influence *t*PTEF. Therefore, further studies into the role of the larynx and the interplay between the activities of laryngeal, inspiratory and expiratory muscles during early expiration in healthy and diseased subjects are needed.

Influence of afferent vagus nerve information on t*PTEF*

This study showed that sensory information from the vagus nerves plays an important role in influencing τ_{diaphr} and τ_{interc} and, consequently, in influencing *t*PTEF. Afferent sensory vagus nerve information can be modulated by cooling the nerves or by stimulation of vagus nerves receptors. It has been shown that at vagal temperatures below 14°C conduction in myelinated fibres is progressively reduced and virtually absent at 4 and 6°C [22, 23]. These myelinated vagus nerve fibres transmit signals from rapidly and slowly adapting stretch receptors (RAR and SAR) in the lung [24].

In this study, changes in afferent vagus nerve activity were induced by administration of histamine and by additionally applied CPAP. Intravenous administration of histamine caused a significant decrease in τ_{diaphr}, τ_{interc} and *t*PTEF at vagal temperatures above 10°C. At lower vagal temperatures no histamine-induced decrease in *t*PTEF was observed (table 2). The application of CPAP after histamine induced a further decrease in τ_{diaphr}, τ_{interc} and *t*PTEF. Similarly, this decrease was not observed at the lowest temperatures of the vagus nerves (table 2). These data show that both the histamine and CPAP-induced changes depend on intact nerve conduction.

Cooling of the vagus nerves resulted in a significant increase of τ_{diaphr} and τ_{interc} (fig. 4). Baseline values of τ_{diaphr}, τ_{interc}, and *t*PTEF were significantly lower at temperatures of 22 and 37°C than at 4, 6 and 8°C. These data show that an increase in stimuli from the vagus nerves resulted in a decrease in the postinspiratory activity of inspiratory muscles.

Although one should be cautious in applying these findings in cats to children, vagal influence on expiratory braking mechanisms is also presumed to occur in the developing human [25]. Therefore, it might be speculated that differences in *t*PTEF between healthy children and asthmatic children with normal lung function [1] are caused by differences in afferent sensory nerve information from the lung.

In conclusion, this study shows that the time needed to reach peak tidal expiratory flow is highly influenced by the activities of inspiratory muscles during the early phase of expiration which, in turn, depend partly on the activities of vagal receptors in the lung. In addition, the good agreement between experimental data and the model res-ults supports the view that the time needed to reach peak tidal expiratory flow is largely determined by the mechanical properties of the respiratory system in combination with the behaviour of inspiratory muscle activity during ex-piration.

Appendix

Model and model equations

Using a simplified mechanical model of the respiratory system the equation of motion can be written

$$P(t) = R_{rs}V'(t) + E_{rs}V(t) \quad \text{(A1)}$$

where P(t) is the driving pressure at time t, $V(t)$ is the lung volume relative to relaxed lung volume, $V'(t)$ represents the flow at time t, and R_{rs} and E_{rs} are the resistance and elastance of the respiratory system, respectively [26]. In the case of passive expiration $P(t) = 0$, where the solution of Equation (A1) yields an exponential decrease in V with time with a time constant equal to that of the respiratory system (τ_{rs}). In the absence of expiratory muscle activity $P(t)$ is solely the result of inspiratory muscle activity. For that case SIAFAKAS *et al.* [27] have shown in anaesthetized cats that $P(t)$ is nearly proportional to inspiratory muscle activity. This implies that if inspiratory muscle activity during expiration can be described by the function $Ae^{-t/\tau}+B$ (see Methods) the corresponding driving pressure will obey the relationship

$$P(t) = P_1e^{-t/\tau} + P_2 \quad \text{(A2)}$$

where P_1 and P_2 are amplitudes and t=0 corresponds to the beginning of expiration. Substitution of Equation A2 into A1 results in

$$P_1e^{-t/\tau} + P_2 = R_{rs}V'(t) + E_{rs}V(t) \quad \text{(A3)}$$

The general solution of this first-order differential equation can be written as:

$$V(t) = E^{-1}_{rs}\{P_1(1-\tau_{rs}/\tau)^{-1}e^{-t/\tau} + P_2\} + Ce^{-t/\tau_{rs}} \quad \text{(A4)}$$

where $\tau_{rs}=R_{rs}/E_{rs}$, and C is a constant, the value of which is determined by the further boundary conditions. At the transition from inspiration to expiration the flow is zero, *i.e.* $V'(t=0) = 0$. According to Equations A2–A4 this results in

$$P(t=0) = P_1 + P_2 = E_{rs}V(t=0) = (1 - \tau_{rs}/\tau)^{-1}$$
$$P_1 + P_2 + CE_{rs} \quad \text{(A5)}$$

from which follows

$$C = P_1\{1 + (\tau_{rs}/\tau - 1)^{-1}\}E^{-1}_{rs} \quad \text{(A6)}$$

In this manuscript, the time that corresponds to peak tidal expiratory flow is denoted as tPTEF. According to this model tPTEF corresponds to the value of t for which

$$V''(t) = 0 \quad \text{(A7)}$$

where $V''(t)$ represents the second derivative of $V(t)$. After substitution of equation A6 into A4, $V''(t)$ can be calculated. Application of the condition $V''(t) = 0$ for $t = t$PTEF results (after some mathematical manipulations) in the following relationship for tPTEF:

$$t\text{PTEF} = (1/\tau - 1/\tau_{rs})^{-1}\ln(\tau_{rs}/\tau). \quad \text{(A8)}$$

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