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Bifurcation of the Respiratory Response to Lung Inflation in Anesthetized Dogs

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Abstract

Numerous studies have demonstrated the effect of lung volume on prolongation of duration of expiration (TE) with limited understanding of the TE shortening and termination of expiration as observed in newborn. In 14 dogs, the effects of varied onset of lung inflation during expiration on the TE were evaluated. When lung inflation was applied in the first part of expiration (20–60% of TE) TE was lengthened. However, in the second portion (60–80% of TE) of expiration, lung inflation either terminated or prolonged TE; whereas in the last portion of expiration (80–90% of TE), lung inflation tended to terminate expiration prematurely. The effects were abolished after bilateral vagotomy. We postulate that prolongation of TE relates to the Hering-Breuer inflation reflex, which increases the time needed for a passive expiration; whereas the ability to shorten TE could relate to Head's paradoxical reflex acting to initiate inspiration or to activate inspiratory motor activity to brake expiratory flow as occurs in the newborn.

Keywords

Respiration; Expiratory Off-Switch; Vagal Reflexes

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1. Introduction

Elevation of end-expiratory lung volume produces vagally mediated prolongation of expiratory time (TE). Breuer and Hering (1868) originally described the effect of static lung volume on TE, whereas Knox (1973) studied the dynamic characteristics of this reflex. In anesthetized cats, Knox applied pulse lung inflation of the same magnitude at different times during TE and reported that the Breuer Hering reflex, an expiratory-prolonging inflation reflex, was modulated by time, *i.e.*, the later during TE that inflation was applied, the greater TE was prolonged. However, the response to lung inflation applied in the last 30–40% of expiration depended on the level of anesthesia. Pulse lung inflation did not affect TE in lightly anesthetized cats with a breathing frequency (fR) of 24–26 breaths per minute (bpm), but could shorten TE in deeply anesthetized cats, fR 12–15 bpm. Finally, Knox (1973) noted that TE shortening was consistently evoked by electrical stimulation of the central end of the vagus at a stimulus strength just sufficient to inhibit inspiratory activity late in inspiration. He attributed this stimulus strength to the activation of the largest vagal afferent fibers, which innervate pulmonary stretch receptors (PSRs). But he also noted the similarity between TE shortening in response to lung inflation in late expiration in deeply anesthetized cats and TE shortening evoked by lung deflation (Knox, 1973). Thus, TE shortening could be evoked by PSRs or by other receptors such as irritant receptors (Widdicombe, 2006).

The studies of Lewis *et al.* (1990) using superior laryngeal nerve stimulation, and Sammon *et al.* (1993b) using vagal stimulation, suggest that bifurcation of respiratory responses to sensory stimulation may be an expression of a property of the respiratory control network rather than the activation of different types of afferent input. But as such, this property is not incorporated in current models of vagal regulation of expiratory time (Rybak *et al.* 1997). We are also aware, that in 2001, Satoh and his co-workers observed variable effects of single ventilator breaths on TE in dogs studied during non-rapid eye movement sleep. The researchers reported this finding but without further discussion. To study our hypothesis that bifurcation of the TE response to lung inflation occurs consistently at a specific time in the respiratory cycle and with stimulation of presumably slowly adapting pulmonary stretch receptors, we studied the effect of lung inflation on TE in anesthetized dogs. We chose dogs because they have large airways and breathe much more slowly than other commonly used species, so lung inflation can be applied with a low airflow at various times during the breath (Romaniuk *et al.*, 1991). We applied a relatively small lung inflation which was approximately 50% of that used in prior studies (Cross *et al.*, 1960) and delivered it with low airflow rates to avoid eliciting a response from rapidly adapting receptors (Knox 1973, Widdicombe 2006).

2. Methods

2.1 Surgery

Adult dogs (mongrel, weight 15–20 kg, n=14) were anesthetized with pentobarbital (30 mg/kg, *iv*, n=11) or with the mixture of urethane and α -chloralose (600 & 70 mg/kg respectively *ip*, n=3). Anesthesia (2 mg/kg of Nembutal or 200 mg/kg of urethane and 20 mg/kg of α -chloralose) was maintained at a level at which nociceptive withdrawal reflexes were absent but corneal reflexes were intact. Dogs were placed in the supine posture for the

experiments. A cuffed endotracheal tube was sutured into the cervical trachea. End-tidal pCO₂ was monitored at the tracheal-tube opening (CO₂ analyzer, Beckman LB-2). During the experiments, end-tidal pCO₂ was maintained near baseline values (3.6–3.9%). Tidal volume was determined by integrating electrically the flow signal from a pneumotachograph (Fleisch #1). Endotracheal pressure (P_{AW}) was recorded with a pressure transducer (Validyne MP-45) connected to the airway opening. Body temperature was monitored with a rectal probe and maintained with a heating blanket at 38 ± 0.5 °C. Catheters were placed in the femoral vein and artery to administer fluids and monitor blood pressure, respectively.

Bipolar, teflon-coated, stainless steel electrodes (0.005" dia) were placed directly in exposed muscles to record their electromyographic (EMG) activities. We recorded EMG activity from parasternal intercostal (third space) and triangularis sterni (fourth space) muscles. These EMG activities were amplified, rectified and integrated (time constant: 0.1 s) [Charles Ward Enterprises, Ardmore, PA], to obtain moving averages of activity. Airway pressure and both raw and integrated parasternal intercostal and triangularis sterni activities were recorded on UV sensitive paper (Electronics for Medicine, VR-12) for subsequent analysis.

2.2. Experimental Protocol

To assess the effects of lung inflation on TE, an inflation of the same magnitude and duration was applied at various points throughout the expiratory phase with a volume syringe. Inflations were separated by at least five unperturbed cycles and applied after integrated triangularis sterni activity had plateaued (generally within initial 25% of expiration). The magnitude of lung inflation was suprathreshold for inhibition of triangularis sterni EMG (Romaniuk *et al.*, 1996) and was assessed by P_{AW}. Although the administered inflations were comparable in each experiment, across experiments mean lung inflation was 6.5±1.5 cm H₂O or 200±30 ml (75% of average tidal volume) and applied over a range of 1 to 1.5 s. A large number of inflations (mean: 29±2; range: 18–44) were applied in each animal with a recovery period of 5–10 breaths between each inflation. No data were obtainable during the final 10% of expiration due to variability of TE.

2.3. Data Analysis

TE was measured from the rapid decline of parasternal intercostal activity to the onset of the next burst of parasternal activity. Changes in TE of the test breath and the timing of pulse lung inflation applied during the test expiratory phase were expressed as percentages of the average of TE from three preceding 'baseline' cycles (%TE control). The relationship between percent change in TE and timing of lung inflation was determined for each dog. Group mean data were calculated at various levels of lung inflation timing at 5% increments of baseline TE. A single point from each dog at each 5% increment was obtained by averaging the data ± 2.5% around each 5% step. Statistical comparisons were made using paired t tests and linear regression analysis. A p value of < 0.05 was considered significant.

3. Results

In every experiment, lung inflation resulted in prolongation of expiration when it was applied after the plateau in integrated triangularis sterni activity until mid-expiration (approximately 30% – 60% of expiration). During this period, the degree of prolongation of expiration was dependent upon the timing of the lung inflation, *i.e.* the later in expiration that the inflation was applied; the greater, the prolongation of expiration. However, lung inflations applied between 60 and 80% of TE (in pentobarbital anesthetized animals) evoked one of two responses: either prolongation (Figure 1 upper panel) or premature termination (Figure 1 lower panel). In the case of prolonged TE, expiratory muscle activity showed a transient inhibition (graded inhibition) associated with the lung inflation and a rebound to plateau after release of inflation (Figure 1 upper panel). With shortening of TE, expiratory muscle activity ceased before inflation reached its maximum and the next inspiration started while lungs were still inflated (Figure 1 lower panel). Similar results were obtained with the mixture of urethane and α -chloralose anesthesia as shown for a single animal in Figure 2. Results of the TE dependence on the timing of inflation from representative animal anesthetized with pentobarbital are shown in Figure 3A. Mean results are presented in Figure 3B. Lung inflation applied in the range of 20–60% of TE led to prolongation of TE in a linear fashion (upper line). If lung inflation terminated expiration prematurely (Figure 1 lower panel), this followed a line of identity between the timing of inflation and TE (Figure 3, lower line). Thus, from ~60 to ~80% of the expiratory phase, there were two different response characteristics describing the dependence of TE on the time of inflation which paralleled each other (Figure 3).

Beyond 80% of the expiratory phase, lung inflation predominantly resulted in termination of expiration. In the last 10% of TE, the evoked response had the same variability as the control TE.

The TE changes in relation to the timing of lung inflation obtained from the experiments performed on dogs anesthetized with a mixture of urethane and α -chloralose were similar to those observed in pentobarbital anesthetized animals (Figure 4). However, the range of lung inflation timing for which the bifurcated TE response was observed was in the range of 45%–65% of TE. After vagotomy, lung inflation did not produce prolongation of TE.

4. Discussion

We found that the expiratory prolongation produced by pulse lung inflation is time dependent such that within the first 60% of expiration, the later in expiration that lung inflation is applied, the greater the prolongation of expiration. However, between 60 and 80 % of expiration, there was a bifurcation of the response. Expiration either prolonged along the same linear relationship or shortened prematurely below control values along a separate, but also linear, relationship. Both effects were obtained for lung volumes and airflows below or comparable to eupneic values. With these stimuli, low-threshold, slowly adapting pulmonary stretch receptors (PSR) were activated with minimal activation of high-threshold, rapidly adapting receptors (Widdicombe 2006). While the type of anesthesia did not affect the presence of the bifurcation; it appeared to affect the range of TE containing the

bifurcation. With urethane and α -chloralose anesthesia, lung inflation began earlier in expiration than with pentobarbital anesthesia. This result supports the concept that respiratory reflexes are less depressed during urethane and α -chloralose than pentobarbital anesthesia (Taylor, 1960). Vagotomy abolished TE prolongation to lung inflation which consequently eliminated bifurcation of TE responses.

4.1 Effects of Pulse Inflation on Expiratory Time

In the present study in dogs, a bifurcated response was observed consistently and independent of anesthetic. The response was easier to measure when TE was longer and breathing was more regular. This may explain why Knox (1973) concluded that prolongation of TE was a general result (see Figure 7) and the premature termination of TE was an exception attributable to the cat being heavily anesthetized. However, anesthetic level affected TE; TE was < 1.5 s in lightly but > 2.5 s in heavily anesthetized cats. The longer TE allowed the shortening of TE to be apparent. In contrast in our experiments using two types of anesthetic, TE was long (2–4 s) which permitted lower airflows to inflate the lungs and the opportunity to measure consistent effects of the timing of lung inflation on TE in expiration. During our experiments, we did not observe inspiratory augmentation or rapid shallow breathing evoked by lung inflation. These types of responses would be expected to result from activation of rapidly adapting receptors (Widdicombe, 2006). Also, expiratory termination was initiated shortly after the onset of lung inflation and not at its maximum volume. However, we cannot completely dismiss a possibility of irritant receptor activation by small lung inflations, in which the expiratory-prolonging effects of pulmonary stretch receptors might be insufficient to counteract the effects of Head's paradoxical effect (Cross, 1961; Davies and Roumy, 1982). Finally our results are also supported by experiments reported by Satoh et al. (2001) who also performed their experiments on dogs breathing slowly ($f_R < 20$ bpm). Not only did they find TE bifurcation in response to lung inflation but also found that TE bifurcation did not depend on the volume of lung inflation in the range from 50% to 150% of tidal volume. For these reasons, we conclude that the stimulus for the expiratory off-switch is not related to high airway pressure and secondary to a mass activation of most PSRs but a dynamic property of the respiratory pattern generator in response to the initial activation of PSRs (Sammon *et al.* 1993a).

4.2 Vagal Reflex Have an Essential Role in Respiration in Neonates

Our study provides further insight into our understanding of the vagal reflexes observed in newborn humans. Unlike adults, lung inflation in newborns affects TE (Cross *et al.*, 1960; Martin *et al.*, 1978). According to results presented by Cross *et al.* (1960) small lung inflations shorten expiratory time (see Fig. 2 in their work) and larger prolong TE in newborn. We have observed similar effects in experiments performed in anesthetized dogs (Romaniuk *et al.*, 2007). In most explanations of vagal modulation of TE in newborn infants, researchers (Baldwin *et al.*, 2006) cite Knox (1973, compare his Figs. 3&7) but have focus strictly on the TE prolongation observed early in expiration. A general acceptance of lung inflation as only prolonging TE limits the understanding of the interaction among lung volume, phase duration and control of airflow as interdependent variables controlled by the infant (Cross, 1961, Frappell and MacFarlane, 2005, Hassan *et al.*, 2001, McCallion *et al.*, 2005).

The links among these variables are not well described. For instance, expiratory braking could affect expiratory phase due to generation of post-inspiratory activity in upper airway valvular muscles as well as maintenance of inspiratory activity in the diaphragm in early expiration. Consistent with activation of inspiratory and/or post-inspiratory activity, pulse lung inflation during expiration can inhibit expiratory activity (Romaniuk *et al.*, 2007). Thus, activation of post-inspiratory and/or inspiratory motor activity and inhibition of expiratory motor activity may reflect central activity that prolongs the expiratory phase (McCallion *et al.*, 2005). The reflex described here contains a bifurcation late in expiration at which point lung inflation can increase or decrease expiratory time. The shortening of expiratory time would not be predicted by the transient activation of post-inspiratory or inspiratory activity but rather by an activation of pre-inspiratory (Pre-I) activity. Pre-I activity may be related to post-inspiratory activity (Richter *et al.*, 1986). Interestingly, the opposite, activation of expiratory activity during inspiration, has been observed in infants who occasionally opposed inflation by tightening their abdominal muscles (McCallion *et al.*, 2005).

Maturation of respiratory function including braking of expiratory airflow requires vagal activity in the newborn (Lalani *et al.*, 2001, Arsenault *et al.*, 2003). Expiratory braking is mediated by multiple mechanisms including the recruitment of ‘inspiratory’ motor activity during mid- and late- expiration (Noble *et al.*, 1987), which corresponds with the timing of TE bifurcation observed in our experiments.

In newborn animals, not only does lung volume play a critical role in determining TE (Fedorko *et al.*, 1988) but it is also essential for learning to breathe (Dutschmann *et al.*, 2009). While breathing can be generated by brainstem neurons independent of sensory feedback, generally the pattern functions in the context of reflex responses to changes in the external conditions and internal demands. Yet, lung inflation has minimal effects on the breathing pattern in adult humans (Shea *et al.*, 1998). Indeed during relaxed wakefulness and during sleep, breathing patterns were indistinguishable among normals, patients with heart transplants only, and patients with combined heart-lung transplants (Shea *et al.*, 1998). This difference between newborns and adults regarding the effects on vagal input on patterning may be attributable to learning to breathe, in that the Kölliker-Fuse nuclei determine phase duration and maintain the pattern in the absence of vagal input. Following vagotomy in newborn (P1-P6) and adult rats, VT and TI increases similarly, but TE in newborn increases more than 4 fold that of adult rats (Fedorko *et al.*, 1988). Vagal input entrains the rhythm in newborn (P4) and juvenile rats (P28) but juvenile rats ‘learn’ the imposed rhythm and terminate inspiration before the next vagal activation whereas newborn rats do not adjust to the imposed rhythm. Thus, if the TE bifurcation is a property of only the mature respiratory pattern generator, then we speculate that TE bifurcation is executed by the interaction of pontine and vagal inputs on the Bötzing and Pre-Bötzing Complexes in either prolonging or shortening TE.

Recently, pertinent studies have been conducted on respiratory control in neonates during assisted ventilation (Baldwin *et al.*, 2006; Beck *et al.*, 2004; Hassan *et al.*, 2001; McCallion *et al.*, 2005). Lung inflation during expiration produced prolongation of TE (Beck *et al.*, 2004). However, in analyzing their results (presented in their Fig. 5), the question arose, as to whether a single or two separate relationships existed between timing of inflation and the

TE response; in particular, one that started with 200 ms delay and another, with about 400 ms delay after inflation. The latter case could be an example of TE bifurcation.

4.3 Neural Pathways Involved in Alterations of Expiratory Time

An important consideration in the alteration of TE by lung inflation is the time dependence of the response which suggests that it is mediated by neurons involved with pattern generation. The central pattern generator for respiration has three distinct phases two of which occur during the expiratory phase, *i.e.* Stage-I expiration or post-inspiration and Stage-II expiration (Richter *et al.* 1986, St. John and Zhou, 1989 and 1990). Post-inspiratory neurons become progressively more hyperpolarized during Stage-II expiration but are depolarized at the end of Stage-II expiration. These neurons are excited by vagal input and inhibit expiratory neurons of the central pattern generator (Bellingham *et al.*, 1992, Manabe and Ezure, 1988). However, it is unlikely that they alone mediate the prolongation of expiration because their response would decrease rather than increase as Stage-II expiration progressed. One would predict that a cell group that became progressively depolarized during Stage-II expiration such as the Bötzing neurons is mediating this response. Pre-inspiratory neurons have been hypothesized to be a potential off-switch for expiration (Klages *et al.*, 1992). These cells, in conjunction with post-inspiratory neurons, may mediate the elicited phase-switch in late expiration (Klages *et al.*, 1992). But, it is unknown if the same neurons mediate inhibitory effects of lung inflations on expiratory motor output (Arita and Bishop, 1983, Cohen *et al.*, 1985, Bellingham *et al.*, 1992).

The elimination of TE bifurcation after vagotomy does not preclude a role of extra-vagal reflexes in evoking the responses of TE to lung inflation because sensory information from the chest wall receptors may contribute to shortening of expiratory time in vagally intact animals (Bolser *et al.*, 1988). It needs to be noted that long-term effects of vagotomy were not studied in the present work. It would be interesting to observe if short term plasticity of central respiratory pattern regulation can develop expiratory time control similar to those described by Thach *et al.*, (1980) in a newborn infant with complete interruption of intercostal to phrenic neural pathways.

4.4. Bifurcation of TE response as common characteristics of neural control of breathing

Concerning the phenomenon of two different TE responses to the same stimulus in the latter portion of expiration, similar observations have been made in other studies of respiratory control. Lewis *et al.* (1990), for example, observed two different responses to the same superior laryngeal nerve stimulus applied during the inspiratory phase, *i.e.* either transient inhibition with prolongation of cycle time or inspiratory termination with reduction in cycle time. The response depended on the time allowed between stimuli. Various combinations of responses were observed when less than seven respiratory cycles elapsed between applied stimuli, whereas a single consistent response was observed when seven or more cycles elapsed between stimuli. These investigators concluded that stimulus aftereffects were responsible for the unpredictable responses, and that these effects persisted for 7 respiratory cycles or approximately 25s. Similar results were obtained by Sammon *et al.* (1993b) in experiments with electrical vagal stimulation during inspiration and expiration. Marek *et al.* (1983) and Trippenbach and Kelly (1985) also showed that vagal stimulation at the end of

expiration may prolong, shorten, or have no effect on expiratory duration. The reversal of TE responses in the middle of expiratory time in response to afferent stimulation was also described by Remmers *et al.* (1986). They found that this effect depended on stimulus aftereffects. The bifurcated response of TE observed in the present study may also be attributable to stimulus aftereffects of vagal reflexes or described in terms of short-term plasticity of the respiratory network (Karczewski and Romaniuk, 1980, Siniiaia *et al.*, 2000). The model of short-term plasticity in the central processing of the Breuer Hering reflexes (Wang *et al.*, 2005, MacDonald *et al.*, 2009) and the model of chaotic dynamics in the respiratory system (Sammon *et al.*, 1993a,b, Mangin *et al.*, 2009) are recent attempts to describe the time-dependent complexity of the respiratory network.

General description of vagal control of expiratory time needs to include studies performed in neonates. The phenomenon of expiratory braking in infants was explained by such mechanisms as activation and prolongation of post-inspiratory activity, activation of laryngeal adductor muscles, ‘inspiratory’ muscle activation, and expiratory interruption (Zhang and Bruce, 2000, Baldwin, 2006, Kosch *et al.*, 1985, McCallion 2005). They all serve as a control of expiratory volume, especially in situations that require a ‘dynamically’ elevated lung volume (Sammon *et al.*, 1993a, Thach *et al.*, 1980, Thach, 2001). It is not known how these mechanisms are interrelated. However, our present clarification of Knox’s classical result may enlighten other investigators in the breadth of interpretation of their results and assist in the development of a new experimental and modeling approach.

In summary, our results indicate that lung inflation applied in the latter portion of expiratory time may either prolong or terminate expiration. We postulate that bifurcation of the TE response may be the manifestation of respiratory pattern generator and its interaction of pontine and vagal inputs. These reflexes might be significant in understanding respiratory control mechanisms in newborn infants.

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HIGHLIGHTS

- Vagal control of expiratory phase duration (TE) was studied in anesthetized dogs
- Lung inflations during expiration produced bifurcation of TE response
- TE shortening depends on timing rather than type of receptor stimulated
- Presented data offer reflex mechanisms for expiratory time regulation in newborns

FIGURE 1.

Representative tracings recorded from the animal anesthetized with pentobarbital demonstrating the effects of lung inflation applied in the latter portion of expiration on expiratory time.

Upper panel: Lung inflation transiently inhibited triangularis sterni EMG and prolonged expiratory time.

Lower panel: Lung inflation of the same magnitude and applied at the same time in the expiratory phase terminated expiration prematurely, causing a phase transition to inspiration. Recordings from top to bottom: integrated EMG activities of parasternal intercostal and triangularis sterni muscles, and airway pressure.

FIGURE 2.

The same phenomena as presented on Figure 1, but recordings were done during experiments with application of the mixture of urethane and α -chloralose.

FIGURE 3.

Relationship between timing of pulse lung inflation and duration of the expiratory phase (TE). Pulse lung inflations of similar duration and magnitude were delivered at various times throughout the expiratory phase. In the initial 60% of TE, the later the time of application of lung inflation, the greater was the prolongation of TE. Beyond ~60% of TE, lung inflation evoked one of two responses: expiration was either prolonged along the same linear relationship or was terminated prematurely. Results from a single animal are shown in the left panel (A) and mean results are shown on the right panel (B).

FIGURE 4.

The same relationship as presented on Fig. 3, but from experiments performed with application of urethane α -chloralose anesthesia. Results from a single animal are shown in the left panel (A) and mean results are shown on the right panel (B).