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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 Breuer-Hering 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.

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. (1989) 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

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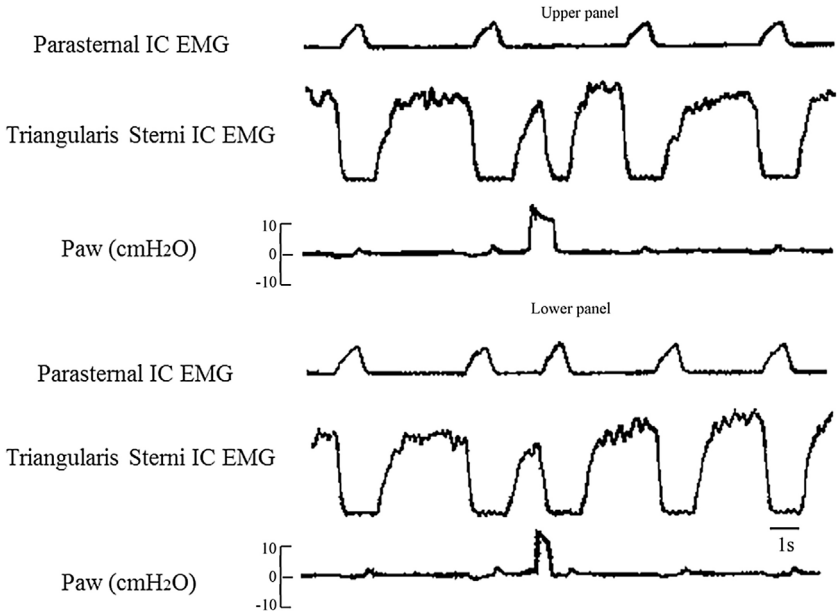

Fig. 1. Representative tracings recorded from the animal anesthetized with pentobarbital demonstrating the effects of lung inflation applied in the latter portion of expiration on expiratory time.
Upper panel: Lung inflation transiently inhibited triangularis sterni EMG and prolonged expiratory time.
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.

(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 pCO_2 was monitored at the tracheal-tube opening (CO_2 analyzer, Beckman LB-2). During the experiments, end-tidal pCO_2 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 H_2O or 200 ± 30 ml (75% of average tidal volume) and applied over a range of 1–1.5 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). However, lung inflations applied between 60 and 80% of TE (in pentobarbital anesthetized animals) evoked one of two responses: either prolongation (Fig. 1, upper panel) or premature termination (Fig. 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 (Fig. 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 (Fig. 1, lower panel). Similar results were obtained with the mixture of urethane and α-

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