HIGHLIGHTED TOPIC | Reflexes from the Lungs and Airways

Effects of pulse lung inflation on chest wall expiratory motor activity

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1Departments of Physiology and Biophysics, Case Western Reserve University, MetroHealth Medical Center, Cleveland; 2Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Brecksville; and 3Division of Pulmonary and Critical Care Medicine, Department of Medicine, Case Western Reserve University, Cleveland, Ohio

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Romaniuk JR, Dick TE, Kowalski KE, and DiMarco AF. Effects of pulse lung inflation on chest wall expiratory motor activity. *J Appl Physiol* 102: 485–491, 2007. First published September 7, 2006; doi:10.1152/japplphysiol.00130.2006.—The effects of pulse lung inflation (LI) on expiratory muscle activity and phase duration (Te) were determined in anesthetized, spontaneously breathing dogs (n = 20). A volume syringe was used to inflate the lungs at various times during the expiratory phase. The magnitude of lung volume was assessed by the corresponding change in airway pressure (Paw; range 2–20 cmH2O). Electromyographic (EMG) activities were recorded from both thoracic and abdominal muscles. Parasternal muscle EMG was used to record inspiratory activity. Expiratory activity was assessed from the triangularis sterni (TS), internal intercostal (IIC), and transversus abdominis (TA) muscles. Lung inflations <7 cmH2O consistently inhibited TS activity but had variable effects on TA and IIC activity and expiratory duration. Lung inflations resulting in Paw values >7 cmH2O, however, inhibited expiratory EMG activity of each of the expiratory muscles and lengthened Te in all animals. The responses of expiratory EMG and Te were directly related to the magnitude of the lung inflation. The inhibition of expiratory motor activity was independent of the timing of pulse lung inflation during the expiratory phase. The inhibitory effects of lung inflation were eliminated by bilateral vagotomy and could be reproduced by electrical stimulation of the vagus nerve. We conclude that pulse lung inflation resulting in Paw between 7 and 20 cmH2O produces a vagally mediated inhibition of expiratory muscle activity that is directly related to the magnitude of the inflation. Lower inflation pressures produce variable effects that are muscle specific.

respiration; control of expiration; vagal reflexes

The respiratory responses to increases in lung volume applied during expiration are generally considered to be purely facilitatory in nature (26). This concept is rooted in the classic experiments of Breuer and Hering (8), in which it was demonstrated that sustained lung inflation caused by airway occlusion at end inspiration increased the duration of the subsequent expiratory phase. Other studies (7, 32, 37) have also shown that increases in lung volume produced by positive-pressure breathing or by threshold loading facilitate expiratory muscle activation.

These prior studies, however, generally evaluated the effects of sustained lung inflation [i.e., applied for a time equal to or greater than expiratory duration (Te)]. Pulse lung inflation (i.e., applied for a time less than Te), however, may have quite different effects. More recent studies, in fact, have demonstrated that lung inflations are not entirely facilitatory but that they may also have inhibitory effects (4, 9, 12, 21). For example, although small to moderate lung inflations facilitate, larger lung inflations depress internal intercostal nerve and medullary expiratory neuronal activities (12). These studies suggest that the control of expiratory muscle activation is more complex than originally proposed.

A systematic evaluation of the effects of lung inflation (over a wide range of inflation pressures) on both rib cage and abdominal muscle activation has not been performed. Furthermore, the effects of lung inflation on triangularis sterni activation, a muscle that has been shown to have an important expiratory action (15) are also unknown. It was our hypothesis that pulse lung inflation applied during the expiratory phase generally exerts inhibitory influences on expiratory motor output through vagally mediated reflex effects. Such reflex effects may provide a means of modulating expiratory braking in newborns, allowing maintenance of elevated lung volumes (20).

The purpose of the present study, therefore, was to more closely examine and further characterize the effects of lung inflation applied during the expiratory phase on both thoracic and abdominal expiratory motor activities. This was accomplished by assessing the stimulus response relationship between the magnitude of lung inflations applied during the expiratory phase and expiratory chest wall muscle activity. Tests were performed with two types of anesthesia and at various anesthetic levels to differentiate reflex effects, which may be sensitive to anesthesia (17, 31).

### METHODS

Studies were performed on 20 adult dogs (mongrel, weight 15–20 kg). Animals were divided into three different groups on the basis of anesthetic protocol. *Group 1* (n = 6) received an initial dose of 25 mg/kg iv of pentobarbital sodium. *Group 2* (n = 11) 30 mg/kg iv of pentobarbital, and *group 3* (n = 3) were anesthetized with α-chloralose (70 mg/kg) and urethane (0.6 mg/kg). Supplemental doses of anesthetic (pentobarbital 1–2 mg/kg iv in *group 1* and 2 or α-chloralose 20 mg/kg and urethane 0.2 mg/kg iv in *group 3*) were administered as needed to maintain absent withdrawal reflexes but intact corneal reflexes. All studies were performed in the supine posture. 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). Tidal volume was recorded by integrating electro-
cally the flow signal from a pneumotachograph (Fleisch #1). Airway pressure (Paw) at the endotracheal tube 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 (0.05 in. diameter) were placed directly into exposed muscles to record their electromyographic (EMG) activities. EMG activity was recorded from the following muscles: triangularis sterni (TS; fourth space), internal intercostal (IIC; ninth or tenth space), and transversus abdominis (TA). Parasternal intercostal EMG (third space) was also recorded to determine the onset and offset of the inspiratory phase. 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 integrated parasternal, TS, IIC, and TA EMG activities were recorded on ultraviolet-sensitive paper (Electronics for Medicine, Honeywell, Pleasantville, NY) for subsequent analysis.

Experimental protocol. The effects of pulse lung inflation (duration 1.0–1.5 s) on TS, IIC, and TA EMG were examined by varying the magnitude and timing of lung inflation and flow rate independently. Although lung inflations were applied manually with a large-volume syringe, the magnitude of inflation was assessed by the corresponding change in airway pressure. Airflow during lung inflation ranged between 1.5 and 3 l/s unless the effects of airflow were being evaluated. Multiple lung inflations were administered (mean: 30/animal) and a recovery period of 5–10 breaths elapsed between inflations. Lung inflations of various magnitudes were applied during the plateau of expiratory EMG activity. 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 integrated parasternal, TS, IIC, and TA EMG activities were recorded on ultraviolet-sensitive paper (Electronics for Medicine, Honeywell, Pleasantville, NY) for subsequent analysis.

Table 1. Mean values

<table>
<thead>
<tr>
<th>Group</th>
<th>Anesthesia</th>
<th>Breathing Frequency, breaths/min</th>
<th>Te, s</th>
<th>End-Tidal PO2, Torr</th>
<th>Tidal Volume, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Pentobarbital (25 mg/kg)</td>
<td>18.5 ± 0.6</td>
<td>2.5 ± 0.3</td>
<td>37 ± 0.5</td>
<td>315 ± 17</td>
</tr>
<tr>
<td>Group 2</td>
<td>Pentobarbital (30 mg/kg)</td>
<td>14.8 ± 1.1</td>
<td>3.7 ± 0.3</td>
<td>40.5 ± 1.0</td>
<td>319 ± 21</td>
</tr>
<tr>
<td>Group 3</td>
<td>α-Chloralose + urethane</td>
<td>12.2 ± 5.2</td>
<td>4.3 ± 0.8</td>
<td>41 ± 2.0</td>
<td>321 ± 34</td>
</tr>
</tbody>
</table>

Values are mean ± SE. Te, expiratory time.
between groups 1 and 2 ($P > 0.01$). The results from both groups therefore are presented together. Over a wide range of inflation pressures, the magnitude of the inhibitory responses of expiratory muscle activities was directly related to the magnitude of lung inflations.

The inhibition of expiratory muscle activity in response to lung inflation was statistically greater for TS ($P \leq 0.05$) compared with IIC and TA for inflation sizes in the range 5 to 12.5 cmH$_2$O (Fig. 2). For inflation of 5 cmH$_2$O, inhibition of TS was statistically significant ($P < 0.05$) but changes in IIC and TA were not. These results indicated that TS had the lowest threshold and the most sensitive reflex response to lung inflation. Facilitation of TA in response to small lung inflations was not statistically significant.

The inhibitory response to lung inflation was independent of the rate of inflation. However, inflations with high flow rates (2.5–5 l/s) occasionally resulted in a short-lasting excitation of IIC just prior to the inhibitory response during $\alpha$-chloralose-urethane anesthesia.

**Effect of timing of lung inflation on expiratory motor activity.** Because TS EMG responded to lung inflation with the lowest threshold and the greatest consistency, this muscle was used to evaluate the effect of timing of lung inflation on expiratory motor activity. For lung inflations of approximately the same size (250–300 ml, that which resulted in $\sim 50\%$ inhibition of integrated TS EMG activity), the degree of inhibition was unrelated to the time in expiration during which the lung inflation was applied (Fig. 3). Results for an individual animal are shown in Fig. 3A and for the entire group in Fig. 3B.

**Effect of lung inflation on $T_e$.** Lung inflations resulting in Paw > 7 cmH$_2$O prolonged $T_e$ and the magnitude of this prolongation was linearly related to the magnitude of the inflation (Fig. 4). There was no significant difference between $\alpha$-chloralose-urethane and pentobarbital studies. For small lung inflations in six of nine animals, lung inflation shortened $T_e$ in pentobarbital- but not in $\alpha$-chloralose-urethane-anesthetized animals, resulting in the single data point below control values in Fig. 4. Both relationships showed a good fit to linearity ($r > 0.9$ for both); intercepts with axis at 100% had positive values for both: 6.5 cmH$_2$O for group 2 and 2.5 cmH$_2$O for group 3.

**Effects of lung inflation postvagotomy.** Following bilateral transection of the vagi, pulse lung inflation did not produce any inhibition of expiratory muscle activity nor prolong the expiratory phase. In fact, large lung inflations (Paw > 15 cmH$_2$O) resulted in excitation of IIC and shortening of $T_e$. This excitation was more pronounced in $\alpha$-chloralose-urethane-anesthetized animals.

**Effects of vagal stimulation.** Because high-intensity electrical stimulation of the vagus nerve increases the probability of stimulation of afferents other than from pulmonary stretch receptors (20), the effects of vagal stimulation were evaluated only for TS EMG because the threshold for evoking inhibition of TS EMG was much lower than that of IIC. The threshold for IIC EMG inhibition was $\sim 1.5$ T for TS EMG. Stimulation of the central end of the transected vagus nerve inhibited the magnitude of TS activity in each animal. Increasing intensity of electrical stimulation resulted in progressively greater degrees of inhibition (Fig. 5B). In response to 1.5-T intensity of stimulation (39), the average TS EMG inhibition was 29.67 $\pm$ 6.95% of control values ($P < 0.0001$). The relationship between the intensity of vagal stimulation and the degree of TS inhibition was qualitatively similar to that between lung inflation.

![Fig. 1. Effects of lung inflation (LI) of varying size on triangularis sterni (TS), internal intercostal (IIC), and transversus abdominis (TA) electromyographic (EMG) activities in a single animal anesthetized with pentobarbital sodium (Group 2). Small LI facilitated TA activity (first 2 inflations), whereas larger LI decreased EMG activities of each of the expiratory muscles. See Effects of the magnitude of lung inflation on expiratory muscle activity for further explanation. Recordings from top to bottom: integrated EMG activities of parasternal intercostal, TS, IIC, and TA muscles. Paw, airway pressure.](http://jap.physiology.org/)

![Fig. 2. Relationships between magnitude of LI (expressed as the corresponding change in Paw) and changes of expiratory motor activities. Mean results are presented for animals anesthetized with pentobarbital (●; $n = 17$) and $\alpha$-chloralose-urethane (○; $n = 3$). With increasing LI, integrated expiratory EMG activities of each muscle was progressively inhibited. For small LI (<7 cmH$_2$O) there was a small degree of facilitation of TA EMG. The error bars represent SE. Arrows indicate statistically significant differences in TS response compared with both IIC and TA responses at different lung inflations ($P < 0.01$).](http://jap.physiology.org/)
Effects of lung inflation on expiration. Small to moderate pulse lung inflations result in increases in expiratory premotor output from the caudal medulla (11, 28). In contrast, caudal (29) and rostral medullary expiratory neurons (4, 19) appear to be inhibited in response to lung inflation applied during the expiratory phase.

The differences in response to lung inflation observed in these previous studies are most likely attributable to variations in duration and inflation magnitude. These previous investigations are consistent with the notions that a continuous increase in vagal stimulation enhances expiratory motor output (6, 35), whereas phasic input decreases expiratory activity depending on the size of stimulus (36). Cohen et al. (12) found that small to moderate inflations facilitated medullary expiratory neuronal and IIC motor activity, but larger inflations depressed activity in unanesthetized decerebrate cats. They compared the effects of inflation magnitude near control inspiration with inflations one-third this size (both of 700-ms duration). In general, large inflations depressed activity, whereas the small inflations facilitated activity. Bajic et al. (4) found similar results in anesthetized dogs and demonstrated a direct relationship between the magnitude of inflation pressure and degree of IIC inhibition. Cohen et al. (12) also showed that an inflation (0.5-s duration) similar in magnitude to that of spontaneous breathing resulted in an initial depression of activity followed by a rebound increase in caudal medullary expiratory neuronal and IIC nerve activity to greater than control levels. Arita and Bishop (2) found that maintained lung inflation evoked an initial silent phase in 6 of 10 animals followed by a prolonged burst of IIC motor unit potentials. The results of Arita and Bishop can be explained by a transient inhibitory effect of lung inflation followed by excitation due to continuously enhanced vagal input and chemical drive as well as a habituation of inhibitory effects.

The results of the present investigation are consistent with and extend the results of these previous studies. We also found that small lung inflations (<7 cmH2O) facilitated TA, whereas inflation of different magnitudes and TS inhibition. Results from a single experiment to illustrate this similarity are presented in Fig. 5.

As with pulse lung inflation, the degree of inhibition of expiratory motor activity during stimulation was not dependent on the time during which electrical stimulus was applied during the expiratory phase. This is demonstrated for one animal in Fig. 6, in which the same stimulus was applied multiple times during a single expiration and resulted in similar degrees of inhibition.

**DISCUSSION**

We report that pulse lung inflations (Paw > 7 cmH2O) applied during the expiratory phase provoke vagally mediated inhibition of expiratory motor activity. The degree of this inhibition increases progressively with increasing inflation magnitude. Moreover, the degree of inhibition is independent of the timing of lung inflation during the expiratory phase. In contrast, small lung inflations (Paw < 7 cmH2O) applied during the expiratory phase result in facilitation of TA EMG activity, either facilitation or inhibition of IIC EMG activity, and inhibition of TS EMG activity. Importantly, the observed inhibitory effects were not dependent on the type nor depth of pentobarbital anesthesia. In agreement with the previous studies performed in animals (28) and humans (25), we also observed that expiratory prolongation in response to lung inflation is dependent on the magnitude of lung inflation.

**Effects of pulse inflation on the intensity of expiratory motor activity.** Both facilitatory and inhibitory effects of lung inflations on the intensity of expiratory motor activity have been described previously. Bishop and Bachofen (7) found that the application of constant positive-pressure breathing and of expiratory threshold loading recruited quiescent abdominal muscles. The amount of this activity increased in proportion to the level of pressure applied during the expiratory phase (6). Polacheck et al. (33) demonstrated that an increase in the amplitude of expiratory activity, in response to lung inflation, is the result of a prolongation of T_e rather than increases in the rate of rise or earlier onset of activation. In contrast, other studies have documented inhibition of IIC motor unit potentials (2) and IIC EMG (4) in response to pulse lung inflations.
larger inflations depressed all expiratory motor activity. Furthermore, our results indicate that there is a differential response of abdominal and rib cage expiratory motor output to changes in vagal input. As suggested by Smith et al. (40), only small lung inflations facilitated TA and inhibited TS EMG muscles. Larger inflations, however, uniformly inhibited the activity of each of these expiratory muscles. In addition, our results also indicate that the degree of TS inhibition by lung inflation is qualitatively similar to that of the IIC; the activities of both IIC and TS muscles were inhibited progressively and in graded fashion by pulse inflations between inflation pressures of 5 and 15 cmH₂O. The greater sensitivity of TS EMG to lung inflation, however, suggests that TS activity is more responsive to vagal afferent feedback.

Vagally mediated facilitation and inhibition of expiratory motor activity that is dependent on the magnitude of lung inflation resembles the facilitation and graded inhibition of inspiratory activity that can be recorded prior to the inspiratory off switch (5, 10, 13, 16, 42). In contrast to inspiratory graded inhibition (18), however, expiratory inhibition is not dependent on the timing of vagal stimulation during the expiratory phase.

Effect of anesthesia. Pentobarbital anesthesia was used for purposes of consistency with previously performed studies evaluating the neural control of expiratory muscle activation (see above and also Refs. 15, 41). Inhibition of expiratory motor activity, however, cannot be attributed to pentobarbital anesthesia because inhibition of thoracic expiratory activities has also been observed in decerebrate (12) and awake (1, 40) animals as well.

The transient excitation of IIC muscle activation by inflation with high flow rates was observed only in α-chloralose-urethane- but not in pentobarbital-anesthetized dogs. This transient excitatory reflex may be related to extravagal stretch reflexes (3, 38) because some excitation of IIC EMG was preserved after vagotomy.

Neural pathways involved in the alterations of expiratory motor activation. Although the observed reflex effects are clearly vagally mediated, we can only speculate as to the specific vagal receptors involved in mediating the inhibitory effects on expiratory motor activity. For several reasons, however, our results suggest that pulmonary stretch receptors (PSR) are primarily responsible. First, both the excitatory (on TA with small inflations) and inhibitory effects occurred with the application of modest lung inflations within the physiological operating range of changes in airway pressure. Second, thoracic expiratory inhibition could be reproduced by threshold electrical vagal stimulation that has been shown to selectively activate reflexes from pulmonary stretch receptors (22, 27). Although activation of pulmonary C-fiber receptors has been shown to inhibit expiratory muscle activity (23, 24), the threshold for their activation is higher by one order of magnitude. Third, other studies (4) have demonstrated that the neural responses to step inflations have a relatively slow adaptation rate consistent with pulmonary stretch receptor activation.

Low-intensity electrical vagal stimulation showed no “conditioning” or time relationship between the application of repeated stimuli and the observed response (see Fig. 6). Lack of any potentiation suggests (27, 39) that the inhibitory effect was transmitted by PSR fibers. Studies with the application of SO₂ block (14) would be useful to confirm the role of PSR in mediating this reflex.

While previous investigators (4) did find a small degree of time dependency for expiratory bulbospinal neurons in response to step and ramp inflations, the lung inflation stimulus was maintained throughout the expiratory phase in...
those studies and, therefore, did not allow complete discrimination between timing effects of the stimulus and central motor output. In the present investigations, the same stimulus of short duration was applied at different times within the expiratory phase, allowing its effect on the amplitude of expiratory motor output to be differentiated from mechanisms controlling Te.

Postvagotomy, the enhancement of IIC in response to large inflation (15 cmH2O < Paw < 20 cmH2O) is most likely secondary to activation of spinal mediated stretch reflexes (3, 34). This reflex may decrease the inhibitory effect of large inflation on IIC observed before vagotomy in α-chloralose-urethane-anesthetized animals (Fig. 2).

**Functional implications.** The potential significance of a reflex inhibition of expiratory motor activity in response to increases in lung volume is unclear. However, it is possible that these responses may defend the respiratory system against rapid increments in airway pressure and changes in functional residual capacity (FRC).

Inhibition of expiratory muscle activity and prolongation of Te in response to large lung expansions may play a role in the mechanism of expiratory braking in infants (30) and serve to optimize expiratory flow patterns. It is well established that newborns require a reflex mechanism that allows them to maintain an elevated FRC. It has been suggested that this mechanism may be consequent to postinspiratory activation (20, 30). Vagally mediated inhibition of expiratory activity would support the dynamic elevation of FRC in infants, in whom vagal reflexes are stronger compared with adults. With prolonged increases in lung volume such as that induced by positive end-expiratory pressure, expiratory activity is eventually facilitated to overcome the load and to preserve ventilation.

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**REFERENCES**


