

The role of pulmonary stretch receptor activation during cough in dogs

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Abstract. The role of pulmonary stretch receptors in the modulation of expiratory muscle activity during cough is controversial. To evaluate their potential influence on expiratory effort during cough, we compared expiratory muscle activity during unobstructed cough to that during obstructed cough in which the trachea was occluded at the end-inspiration and maintained throughout the subsequent expiration. Cough was evoked by mechanical stimulation of the intrathoracic trachea in 9 anesthetized, tracheotomized dogs. Peak triangularis sterni (TS), internal intercostal (IIC) and transversus abdominis (TA) muscle EMG were monitored to assess both rib cage and abdominal muscle activation during expiration. During cough, expiratory activity increased and peak activity shifted from Stage II to Stage I expiration. Peak expiratory muscle activation during unobstructed and occluded coughs were not significantly different: during unobstructed coughs, peak EMG's (mean \pm SE as percent of resting breathing) were TS, 212 ± 18 ; IIC, 425 ± 72 ; TA, 406 ± 66 ; and during obstructed cough: TS, 188 ± 24 ; IIC, 365 ± 44 ; TA, 387 ± 77 ($n = 9$). These data indicate that enhanced vagal stimulation resulting from airway occlusion does not affect expiratory activity during cough. We suggest that during cough, the expiratory muscles are activated in a stereotypical pattern by the neural network generating the cough and this pattern of activation is not affected by phasic vagal input.

Key words: vagal reflex, expiratory muscles, cough

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INTRODUCTION

Cough is a defensive reflex which protects the respiratory tract by expelling mucous and foreign material. This reflex is vagally mediated and depends on afferent information from both slowly (SAR) and rapidly (RAR) adapting pulmonary stretch receptors (Karlsson et al. 1988). However, the specific role of the SAR and RAR in eliciting a cough reflex is unclear. Cough can be evoked by mechanical stimulation of the trachea (Tomori and Widdicombe 1969) which activates RAR not SAR (Karlsson et al. 1988, Matsumoto 1988). On the other hand, inhalation of SO₂ which blocks SAR activity (Davies et al. 1978) prevents cough elicited reflexively (Hanacek et al. 1984, 1991, Sant'Ambrogio et al. 1984). On the basis of these results, it has been postulated that RAR activity triggers the onset of cough whereas SAR activity permits the cough to develop (Hanacek et al. 1984, Sant'Ambrogio et al. 1984, Tatar et al. 1994). Since SAR are not stimulated by mechanical probing of the trachea, the role of SAR during cough may be related to its continuous facilitation of expiratory muscle activity (Sant'Ambrogio et al. 1984, Karlsson et al. 1988). However, phasic activation of the SAR inhibits rather than facilitates expiratory muscle activity (Arita and Bishop, 1983, Cohen et al. 1985, Fregosi et al. 1990). For example, pulsatile lung inflation during expiration inhibits expiratory muscle activity (Romaniuk et al. 1991, 1996). Intrapulmonary pressure increases abruptly stimulating SARs during cough, both its compressive and expulsive phases. The effect of SAR excitation on expiratory muscle activity during cough has not been studied. Thus we compared expiratory muscle activity during unobstructed cough to that during cough with end-inspiratory tracheal occlusion.

METHODS

Experiments were performed on 9 adult mongrel dogs (16–21 kg) in the supine posture. Animals were anesthetized with pentobarbital sodium at an initial dose of 25 mg/kg i.v. Anesthetic level was monitored by the corneal reflex, which was left intact, and maintained by supplemental doses of 2–3 mg/kg of pentobarbital, as needed. Prior to each surgical procedure, a local anesthetic 1% lidocaine was injected subcutaneously in the surgical field. All animals received a cervical tracheostomy and an endotracheal tube (10 mm ID). Blood pressure was monitored by a cannula placed in the femoral

artery and a separate cannula in the femoral vein was used to administer intravenous fluids and anesthetic. Body temperature was kept at $38 \pm 0.5^\circ\text{C}$ with homeothermic blanket (Harvard Apparatus). End-tidal pCO₂ was monitored at the tracheal opening *via* a CO₂ analyzer (HP-47210A Capnometer). Airway pressure and flow signal from pneumotachograph (Fleisch #1) were monitored by a pressure transducer (MP-45; Validyne Co., Northridge, CA) connected to the airway opening. A portion of the superficial muscles of the rib cage, including the pectoralis and transversus costarum, were sectioned unilaterally to expose the parasternal muscle (3rd and 4th space). The parasternal muscle of the 4th intercostal space was sectioned to allow access to the triangularis sterni (TS) muscle. The external oblique and external intercostal muscles were separated over the 9th and 10th space in the mid-axillary line to allow access to the internal intercostal (IIC) muscle. Also, in the abdominal wall, portions of external and internal oblique were isolated to allow access to transversus abdominis (TA) muscle. Bipolar stainless steel electrodes were implanted into TS, IIC and TA muscles to record expiratory EMG activities. Electrodes were placed in the parasternal muscle to record inspiratory activity. From this recording, the duration of inspiratory (T_I) and expiratory (T_E) phases were determined. In three animals, electrodes were placed in thyrohyoid (TH) muscle (extrinsic muscle of upper airway) whose activity is isolated to Stage-I of expiration. Therefore, expiration could be subdivided definitively into Stage-I and II by the activities of TH and TS which is active only in Stage-II expiration (St. John and Zhou 1989, Dick et al. 1993) (see also Fig. 7). Mass efferent activities of each muscle were amplified, rectified and processed by RC circuits with third-order low-pass filters having a time constant of 100 msec (CWE, MA-821) to provide moving averages of EMG activity. Signals were recorded on a 12-channel oscilloscopic recorder (Electronics for Medicine).

Experimental protocol

Coughs were evoked by mechanical stimulation of the intrathoracic trachea with a thin elastic wire in a polyethylene catheter. For the period of 5–10 s, the wire was introduced to trachea and moved with frequency about 1–2 Hz. When the series of coughs was evoked, the wire was retracted and the tracheal tube was connected to a pneumotachograph and a pressure transducer. In our

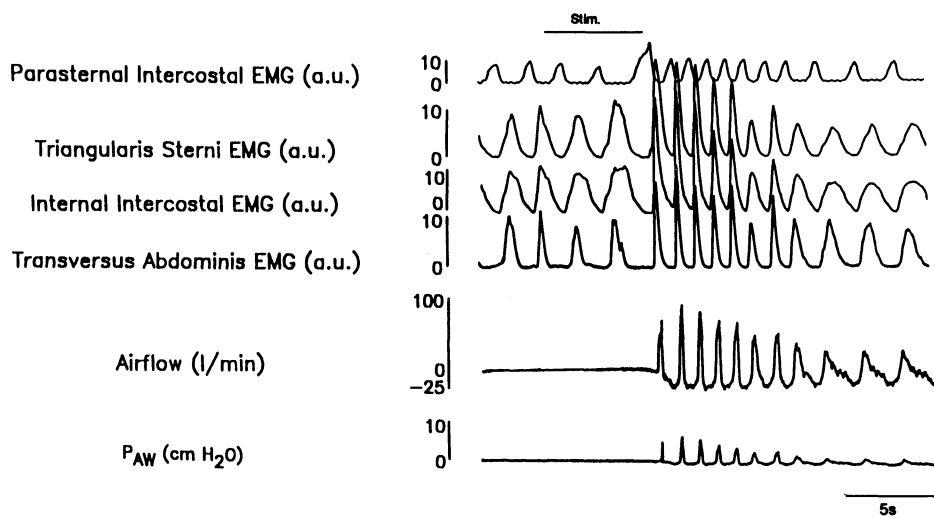


Fig. 1. Representative tracing demonstrating the series of coughs evoked by mechanical stimulation of trachea. At the beginning of cough, there was an increase of integrated inspiratory parasternal EMG activity and then large increase of expiratory activity. Recordings from top to bottom: integrated EMG activities of parasternal, triangularis sterni (TS), internal intercostal (IIC), transversus abdominis (TA) muscles in arbitrary units (a.u.). Airflow in l/min. and airway pressure (P_{AW}) in cm H_2O . During tracheal stimulation, before first cough, flow and pressure measurements were discontinued.

experiments, the compressive phase of cough was eliminated by the tracheostomy. However, in each series of evoked cough we mimicked the compressive phase by occluding the trachea at the end of inspiration for a period of 1-2 s. On average, 8 ± 1 pairs (range: 6-14) of unobstructed and obstructed coughs were compared in each animal. Changes in peak EMG activity were expressed as a percentage of baseline which was taken as the average of three breaths before coughs. To assess the afferent vagal signal during tracheal occlusion, a unilateral vagotomy was performed and the peripheral end of the vagus nerve was dissected and recorded (number of animals; $n = 3$) (Romaniuk et al. 1976). At the end of experiments, bilateral vagotomy was performed. After vagotomy, coughs were evoked by mechanical stimulation of the larynx.

Statistical analysis were made using one-way ANOVA and Neuman-Keuls post-hoc test. A P value of

<0.05 was considered significant, (tolerance for type-1 error, $\alpha = 0.05$, $df = 8$).

RESULTS

During these experiments under baseline conditions, the animals had a mean breathing frequency of 16 ± 5 breaths/min. and an end-tidal CO_2 between 34-40 mmHg. Mechanical stimulation of the intrathoracic trachea evoked a series of cough efforts characterized by a sudden increase of expiratory muscle activity and marked increase in expiratory airflow (Fig. 1). Comparable series of cough efforts were evoked several times during each experiment (range: 6-14). At the beginning of a series of coughs, inspiratory activity as represented by parasternal EMG was augmented. Within a series of coughs each effort can be identified by marked increases in TS, IIC and TA activities. A series of coughs ended

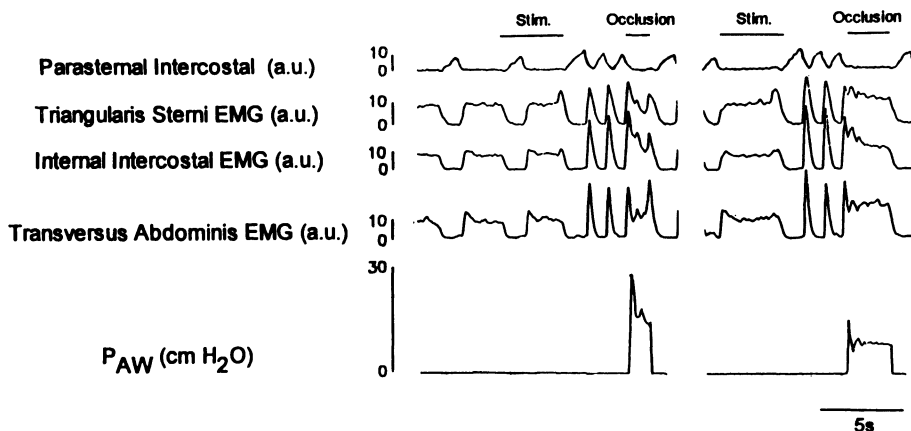


Fig. 2. Effect of tracheal occlusion performed at the end of inspiratory phase on expiratory EMG activities of triangularis sterni, internal intercostal and transversus abdominis muscles. Airway pressure measurements were discontinued before cough.

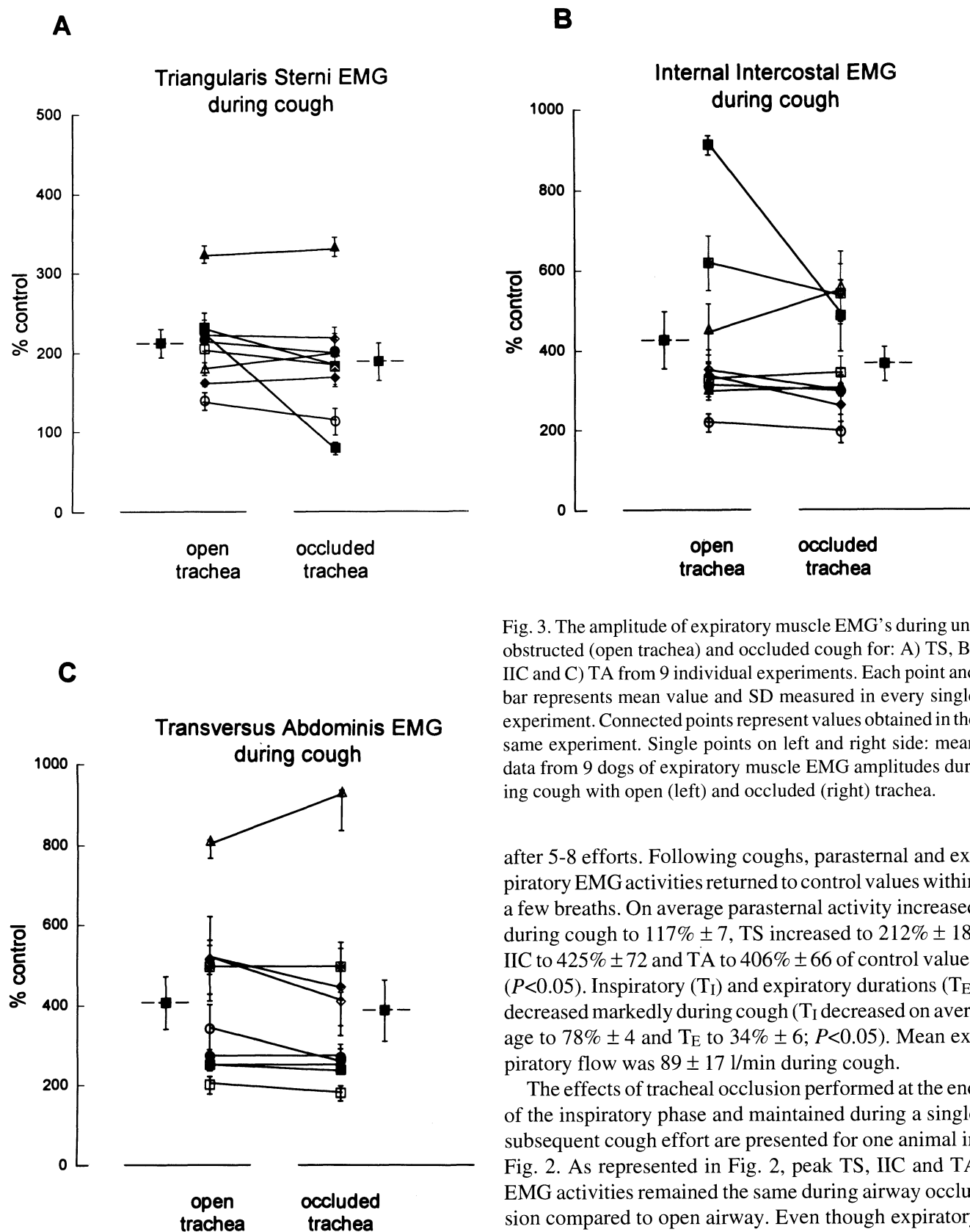


Fig. 3. The amplitude of expiratory muscle EMG's during unobstructed (open trachea) and occluded cough for: A) TS, B) IIC and C) TA from 9 individual experiments. Each point and bar represents mean value and SD measured in every single experiment. Connected points represent values obtained in the same experiment. Single points on left and right side: mean data from 9 dogs of expiratory muscle EMG amplitudes during cough with open (left) and occluded (right) trachea.

after 5-8 efforts. Following coughs, parasternal and expiratory EMG activities returned to control values within a few breaths. On average parasternal activity increased during cough to $117\% \pm 7$, TS increased to $212\% \pm 18$; IIC to $425\% \pm 72$ and TA to $406\% \pm 66$ of control values ($P < 0.05$). Inspiratory (T_I) and expiratory durations (T_E) decreased markedly during cough (T_I decreased on average to $78\% \pm 4$ and T_E to $34\% \pm 6$; $P < 0.05$). Mean expiratory flow was 89 ± 17 l/min during cough.

The effects of tracheal occlusion performed at the end of the inspiratory phase and maintained during a single subsequent cough effort are presented for one animal in Fig. 2. As represented in Fig. 2, peak TS, IIC and TA EMG activities remained the same during airway occlusion compared to open airway. Even though expiratory EMG activity decreased following its peak, it remained

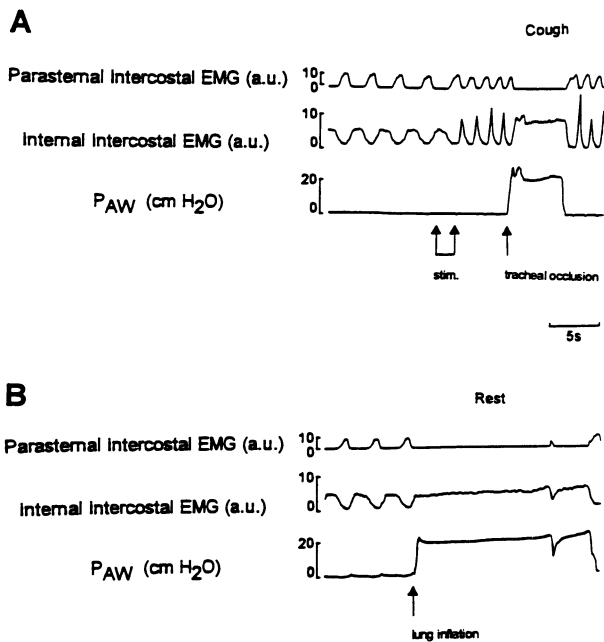


Fig. 4. Prolongation of T_E during tracheal occlusion maintained throughout the entire expiratory period during cough (A) and resting breathing (B). During cough tracheal occlusion had the same P_{AW} value as lung inflation on panel B during rest. Note larger prolongation of T_E during rest (B) compared to cough (A).

elevated, distinctly greater than during control breath. The mean effects of tracheal occlusion on peak expiratory EMGs for each animal are shown in Figure 3 for TS (Fig. 3A), IIC (Fig. 3B) and TA (Fig. 3C). There was no statistical difference between peak amplitudes of expiratory EMGs during obstructed and unobstructed cough

($P > 0.1$). During occluded coughs peak EMGs as percent of preceding breaths for TS increased to 186 ± 24 (Fig. 3A), IIC to 365 ± 44 (Fig. 3B) and TA to 387 ± 77 (Fig. 3C) ($P < 0.05$). EMG values for plateau following peak expiratory activity during airway occlusion were TS = $119\% \pm 14$ (NS), IIC = $254\% \pm 53$ and for TA = $258\% \pm 67$ of the preceding breaths ($P < 0.05$). The mean value of P_{AW} during tracheal occlusion for all animals was $P_{AW} = 20 \pm 3$ cm H₂O.

Although not studied rigorously it was apparent that tracheal occlusion during cough prolonged T_E (Fig. 4). Tracheal occlusion was performed at the same level of lung expansion during cough (A) and under resting conditions (B). Airway occlusion prolonged T_E during coughing. However, the prolongation of T_E during coughing was less than that during resting breathing.

To assess the effects of tracheal occlusion on vagal activity, the presumed afferent pathways of the observed reflex effects, we recorded multifiber afferent activity of the vagus nerve (Fig. 5). As expected, the vagus was phasically active during inspiration. At the onset of the expiration vagal afferent activity decreased and expiratory motor activity (triangularis sterni EMG) increased. Tracheal occlusion was maintained for a short (1 s) time period to simulate the compressive phase of cough and for a long (5 s) period to assess the rate of adaptation of vagal signal. As shown in Fig. 5, phasic vagal afferent activity was maintained at an elevated level during both short (Fig. 5 left panel) and long periods (Fig. 5 right panel) of tracheal occlusion. Since the contralateral vagus nerve remained intact, TS EMG was inhibited by tracheal occlusion. Expiratory EMG inhibition was eliminated after subsequent bilateral vagotomy.

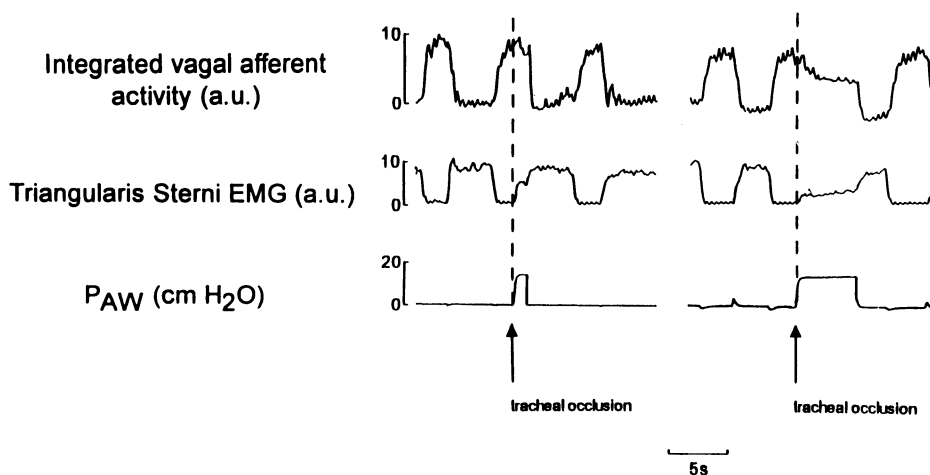


Fig. 5. Effect of tracheal occlusion performed at the end of inspiration on integrated afferent activity of multifiber bundle dissected from the vagus nerve. During tracheal occlusion, triangularis sterni EMG was inhibited. Recordings from top to bottom: integrated vagal afferent activity, TS EMG and airway pressure (P_{AW}).

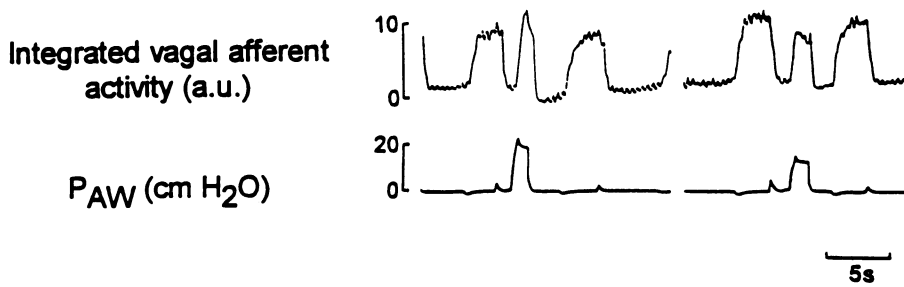


Fig. 6. Effect of pulse lung inflation of different sizes on integrated afferent activity of multifiber bundle dissected from the vagus nerve. Larger inflation evokes stronger excitation of afferent vagal activity.

The effect of tracheal occlusion performed at different levels of lung volume on the amplitude of integrated vagal activity was studied in three animals. The amplitude of the vagal signal varied directly with the magnitude of the airway pressure (Fig. 6). Assuming the amplitude of integrated vagal activity during control inspiration as 100%, the average value of peak vagal activity for $P_{AW} = 10$ and 20 cm H₂O was $59\% \pm 16$ and $108\% \pm 24$ respectively. Thus, recorded activity increased with applied pressure (Fig. 6) and was maintained during prolonged occlusion (Fig. 5). These results suggest that the integrated vagal signal is representative of SAR activity because the amplitude of the signal is maintained throughout the inflation, i.e., an absence of adaptation. If RAR activity had been recorded, then the

amplitude of the integrated vagal afferent activity would decay quickly during tracheal occlusion.

After vagotomy, cough could be evoked only by mechanical stimulation of the larynx.

DISCUSSION

The results of our study demonstrate that dynamic changes of pulmonary stretch receptor activation did not affect the peak amplitude of expiratory muscle activity during cough. Tracheal occlusion performed at the end of inspiration did not influence rib cage and abdominal peak expiratory muscle activities but did affect expiratory timing.

Coughing has a stereotypical sequence of thoracic, abdominal and upper airway activity consisting of the following four phases: inspiration, compression, expulsion and termination. During the expulsive phase, both thoracic and abdominal muscle activity increases to provide the driving force to increase expiratory airflow. In this and other (van Lunteren et al. 1988, 1991) studies, the increase activity was comparable for both thoracic and abdominal expiratory muscles.

Mechanical stimulation of the intrathoracic trachea, evokes a cough *via* RARs, whereas SARs have permissive role in the production of cough (Karlsson et al. 1988). Cough is abolished by blockade of myelinated vagal fibers by cooling (Tatar et al. 1994) or in the conditions of acrylamide neuropathy (see Karlsson et al. 1988). Blockade of SAR by SO₂ inhalation not only abolished the cough triggered by RAR stimulation but also weakened the cough as well as increased the threshold of cough produced by laryngeal stimulation (Hanacek et al. 1984, 1991, Sant'Ambrogio et al. 1984).

One of the most potent vagal reflexes is inspiratory inhibition caused by lung inflation. Lung inflation performed during expiratory phase produces both inhibitory and facilitatory effects on expiratory motor output (Arita

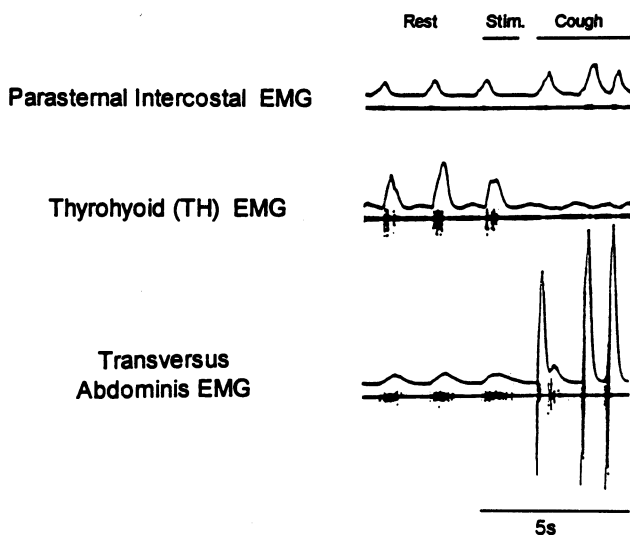


Fig. 7. Patterns of EMG activity of parasternal IC (inspiration), thyrohyoid (expiratory phase I) and transversus abdominis (expiratory phase II) muscles during rest and cough. During cough, peak expiratory activity of TA shifts from phase II to phase I of expiration.

and Bishop 1983, Cohen et al. 1985, Romaniuk et al. 1991). Further, vagal input is inhibitory for rib cage expiratory muscles and facilitatory for abdominal expiratory muscles (Smith et al. 1990, Romaniuk et al. 1996). In our study (Romaniuk et al. 1996), elevation of end-expiratory volume during resting breathing produced inhibition with following facilitation of expiratory muscle activity. In agreement with Smith et al. (1990) data of, the strongest inhibition was manifested on thoracic (TS EMG) whereas facilitation on abdominal (TA EMG) expiratory activities.

The Hering-Breuer inflation reflex does not operate during resting ventilation in conscious humans (Gautier et al. 1981). In contrast to the regulation of inspiratory phase, vagal afferents may be important in humans in control of expiratory phase (Gautier et al. 1981). Further, data obtained from heart-lung transplantation patients (Higenbottam et al. 1987) indicate that vagal afferents are essential for cough to be evoked from lungs. Also, Higenbottam et al. (1987) suggested that SAR modulate cough reflex in man. Banner (1988) suggested that human subjects with weak vagal feedback have low susceptibility to cough. On the other hand, Nishino et al. (1989) suggested that pulmonary stretch receptors do not play an important role in cough, even though cough is stronger during continuous positive airway pressure breathing (CPAP) than during rest. This effect may be a result from stronger activation of expiratory muscles during CPAP. Sant'Ambrogio et al. (1984) suggested that SAR are important for expiratory muscle facilitation. We have shown recently that continuous electrical stimulation of thick myelinated vagal fibers produces a breath-by-breath increase in expiratory motor output independent of chemical drive (Romaniuk et al. 1992). These results support the suggestion that continuous SAR stimulation enhances expiratory activity (Arita and Bishop 1983). Consequently, higher expiratory activity may lower the threshold for cough. In the case when expiratory muscles cannot be excited reflexively, cough is ineffective (Estenne and Gorini 1992).

The effect of changes of phasic vagal activation in cough has not been studied. The results of the present study suggest that phasic excitation of SAR, during either compressive or expulsive phases, do not affect peak expiratory activity during developed cough. This last conclusion is also supported by the studies of Tomori and Widdicombe (1969), Bolser (1991) and Grelot and Milano (1991) which were performed on paralyzed and artificially ventilated animals. In these studies, it was

shown that fictive cough can be produced in the absence of phasic afferent feedback associated with active expiration. These results do not support Bucher (1958) suggestion, that intensity of cough depends on phasic SAR stimulation during preceding inspiratory effort. On the other hand, the fact that during maintained tracheal occlusion during cough expiratory activities following peak were still higher than at rest (Fig. 2) indicates that stimulatory effect of cough supersedes any inhibitory effects of lung inflation on expiratory motor output.

We conclude that phasic vagal input does not play an important role in development of cough. During cough the activity of expiratory muscles is augmented by central mechanism which depends on tonic vagal input.

We also observed that the effect of lung inflation on the duration of T_E is much less during coughing than resting breathing. This is consistent with other data. In particular, when respiration is entrained with other behavioral tasks, such as locomotion, the effect of lung inflation on T_E decreases (Romaniuk et al. 1986).

The mechanism of central blockade of phasic afferent vagal inflow during developed cough is obscure. The obtained results indicate that expiratory activities during cough when once generated cannot be modulated by vagal input (see also Anderson et al. 1996). It was postulated that cough and respiration are generated by two independent brainstem sites (Bucher 1958). However, Shannon et al. (1993) recently postulated that expiratory neurons of Boetinger complex and ventral respiratory group are important for the generation of both eupnoea and cough. Therefore, it is not known if respiratory and cough generators can be separated by means of their localization.

The respiratory cycle can be divided on three separate respiratory phases: inspiration, expiratory phase I (post-inspiration, maximum expiratory airflow) and expiratory phase II (Richter et al. 1986, St. John and Zhou 1989, Dick et al. 1993). We have concluded (Romaniuk et al. 1991, 1996) that Stage-I expiration during spontaneous breathing can be represented by TH motor activity. On the other hand, rib cage and abdominal muscle activities (Fig. 7) reach their maximum during Stage-II expiration. Interactions between central pattern generators (CPGs) for breathing and swallowing (Dick et al. 1993) and for breathing and locomotion (Romaniuk et al. 1994) occurred at phase transitions. During cough, however, peak expiratory activity shifts from Stage-II expiration into Stage-I (Fig. 7). Lawson et al. (1991) and Remmers et al. (1986) showed that stimuli, which trigger

cough, arrest respiration in Stage-I of expiration. On the basis of these results, we suggest that interaction between respiration and cough take place in Stage-I of expiration when the expiratory muscles are driven by cough CPG. It is interesting that, on the basis of experiments performed on fish, Ballintijn and Jüch (1984) also hypothesized that cough and respiration are generated separately and they demonstrated that cough was elicited at the beginning of expiratory (contraction) phase.

Suzuki et al. (1991) demonstrated central blockade of vagal input in experiments in which cough was evoked during apnea produced by Hering-Breuer reflex. In their experiments, respiration was arrested by lung inflation and this inhibition persisted after episode of cough. During cough, vagal inhibition was transiently removed (Suzuki et al. 1991). However, we have also observed that vagal input affects expiratory time during cough. The different effect of vagal input on amplitude and timing is one of general properties of respiratory CPG (Cohen et al. 1985, Fregosi et al. 1990) and it persists during cough.

In conclusion, we suggest that during cough, expiratory motor output is under control of CPG specific for cough. This control takes place during phase I of expiration. Peak expiratory activity is insensitive to phasic vagal input during cough, whereas expiratory time is affected by changes in expiratory lung volume.

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