Volume-timing relationships during cough and resistive loading in the cat

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Bolser, Donald C., and Paul W. Davenport. Volume-timing relationships during cough and resistive loading in the cat. J Appl Physiol 89: 785–790, 2000.—The relationship between pulmonary volume-related feedback and inspiratory (CTI) and expiratory (CTE) phase durations during cough was determined. Cough was produced in anesthetized cats by mechanical stimulation of the intrathoracic tracheal lumen. During eupnea, the animals were exposed to single-breath inspiratory and expiratory resistive loads. Cough was associated with large increases in inspiratory volume (VI) and expiratory volume (VE) but no change in phase durations compared with eupnea. There was no relationship between VI and CTI during coughing. A linear relationship with a negative slope existed between VI and eupneic inspiratory time during control and inspiratory resistive loading trials. There was no relationship between VE and CTEs during all coughs. However, when the first cough in a series or a single cough was analyzed, the VE/CTE relationship had a positive slope. A linear relationship with a negative slope existed between VE and eupneic expiratory time during control and expiratory resistive loading trials. These results support separate ventilatory pattern regulation during cough that does not include modulation of phase durations by pulmonary volume-related feedback.

The cough reflex is an important protective reflex that is essential for the maintenance of patent airways in health and disease. This reflex is associated with intense motor activation of inspiratory and expiratory muscles of the chest wall and abdomen, high airflows, and large tidal volumes. Although the pharmacology of the cough reflex has been the subject of extensive study (4), relatively little is known regarding the physiological regulation of ventilatory patternning of this defensive reflex. In particular, only a limited amount of information is available on the role of pulmonary volume-related feedback in the regulation of cough. Although pulmonary volume-related feedback has an important permissive effect on the cough reflex (13, 22), it may have little effect on the magnitude of abdominal motor discharge during cough (20).

During eupnea, there are well-known relationships between inspiratory volume (VI) and inspiratory time (TI) and between expiratory volume (VE) and expiratory time (TE). Lower VI or VE are associated with longer TI or TE (7, 15, 32, 33). These effects of pulmonary volume-related feedback on the timing of the respiratory pattern are due to vagal afferent input from slowly adapting stretch receptors (SARs) (8, 32).

The role of SAR feedback in the modulation of inspiratory and expiratory phase timing during the cough reflex is unknown. According to the predicted relationship between volume and phase timing, respiratory cycles associated with large volumes should have relatively short phase durations (7, 32, 33). In the cat, tidal volumes of ~70 ml elicited by hypercapnia are associated with TI values that are ~70% of those during eupnea (11). However, tidal volumes during cough can exceed 100 ml in the cat (29), and TI values during fictive cough are not different from those during eupnea in this species (3). The purpose of these experiments was to determine the effect of pulmonary volume-related feedback on phase timing during cough. The hypothesis was that the relationship between volume and phase timing normally observed during eupnea and mechanical loading would not be observed during the cough reflex.

METHODS

Five cats (2.5–4.0 kg) were anesthetized with pentobarbital sodium (35 mg/kg iv). End-tidal CO2 (ETCO2) was monitored, and supplemental anesthetic was administered when ETCO2 dropped below 3.9%. Animals with ETCO2 above 5.0% usually did not cough consistently and were excluded from analysis. Catheters were placed in a femoral artery and vein for monitoring blood pressure and administering drugs, respectively. Atropine sulfate (1.0 mg/kg iv) was administered to block reflex tracheal secretions. A three-way tracheal cannula was inserted through an incision at the fourth tracheal segment, and the animals were allowed to breathe spontaneously. Body temperature was maintained at 37 ± 1°C with an electric heating pad. The animals were placed in a supine position.

A pneumotachograph (Fleisch no. 0) was attached to the tracheal cannula. Airflow was recorded with a differential pressure transducer (model DP45, Validyne) attached to the pneumotachograph. Volume was obtained by electrical integration of airflow. Integration of each breath phase (inspiration or expiration) was performed separately, providing a

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continuous individual display of $V_I$ and $V_E$. $V_I$ was obtained by integration of only the inspiratory portion of the airflow signal. Integration was initiated when the airflow signal moved away from zero airflow in the inspiratory direction and was completed when the airflow signal returned to zero. $V_E$ was similarly obtained by integration of only the expiratory portion of the airflow signal. The integrators were programmed to reset the breath-phase volume signal to zero when the airflow signal for that breath phase returned to zero. The $V_I$ and $V_E$ were measured as the peak integrated volume for their respective breath phase.

A balloon-tipped catheter was passed down the esophagus to record esophageal pressure ($P_{es}$). The balloon was inflated with a syringe and was considered properly placed when 1) manual compression of the thorax increased balloon pressure and 2) cough elicited negative pressure changes during inspiration and positive pressure changes during expulsion. $P_{es}$ was recorded with a differential pressure transducer (model P23XL, Ohmeda).

Cough was produced by mechanical stimulation of the lumen of the intrathoracic trachea. A cork with a 20-gauge stub adapter inserted through the middle was inserted into one end of the three-way tracheal cannula. This modified cork allowed the intrathoracic trachea to be mechanically stimulated by a wire placed through the adapter. A 2.5-cm length of PE-50 tubing was attached to the wire to prevent damage to the intrathoracic trachea during stimulation. The wire was completely retracted into the tracheal cannula between stimulus trials. Resistance of the modified cork and wire system was 82 cmH$_2$O · ml$^{-1}$ · s. This system has been used previously to elicit cough (3). Multiple coughs were elicited by repetitive stimulation of the airway at 2 Hz for trials lasting 10–15 s. Single coughs were produced by introducing the wire into the intrathoracic airway until a cough was initiated and then retracting it into the tracheal cannula.

Inspiratory or expiratory resistive loads or tracheal occlusion were applied during eupnea by using a loading manifold and nonrebreathing valve attached to the pneumotachograph. The modified cork, placed in one end of the tracheal cannula, that was used to allow mechanical stimulation of the intrathoracic airway was replaced with a conventional cork for loading trials. Resistive loads of three magnitudes (100, 200, and 400 cmH$_2$O · ml$^{-1}$ · s) and tracheal occlusion were applied for single inspiratory or expiratory cycles. Each magnitude of load was presented five times, with the order of presentation randomized. A minimum of five unloaded ventilatory cycles was allowed to elapse between each loaded cycle. Resistive loads were not applied during cough.

$P_{es}$, airflow, $V_I$, and $V_E$ were displayed on a chart recorder and recorded on magnetic tape for later analysis. $T_I$ and $T_E$ during eupnea or loaded breaths and inspiratory ($CT_I$) and expiratory ($CT_E$) durations during cough were determined from the airflow record, except during inspiratory occlusion, for which $P_{es}$ was used to determine $T_I$. $V_I$ and $V_E$ were measured during eupnea, loaded breaths, and cough.

All values are expressed as means ± SE. Statistical differences between means were evaluated with Student’s $t$-test. Relationships between $V_I$ or $V_E$ and phase timing during loaded breaths or cough were evaluated by linear regression analysis. Differences were considered significant if $P < 0.05$.

**RESULTS**

A total of 400 coughs were elicited in the five cats. Cough was associated with large increases in $V_I$ and $V_E$ but with relatively little change in phase timing compared with eupnea. $V_I$ during cough averaged 91 ± 5 ml, and $CT_I$ averaged 0.93 ± 0.05 s. $V_E$ values during cough were 84 ± 11 ml, and $CT_E$ averaged 0.54 ± 0.09 s. During eupnea, $T_I$ averaged 1.1 ± 0.08 s and was not significantly different from $CT_I$ ($P > 0.05$). $T_E$ averaged 0.5 ± 0.16 and also was not significantly different from $CT_E$ ($P > 0.05$). However, $V_I$ during eupnea (28 ± 3 ml) was significantly different from during cough ($P < 0.001$). Similarly, $V_E$ during eupnea (31 ± 5 ml) was significantly different from during cough ($P < 0.001$).

Figure 1 shows an example of $V_I$, $V_E$, airflow, and $P_{es}$ during eupnea and a series of tracheobronchial coughs. $V_I$ increased by approximately threefold during cough, whereas $CT_I$ and $T_I$ were similar for most of the
coughs. CT\textsubscript{E} during these coughs was approximately one-half of T\textsubscript{E}, but V\textsubscript{E} during coughing was approximately threefold larger than during eupnea (Fig. 1).

Although T\textsubscript{I} lengthened and V\textsubscript{I} declined during graded resistive loading, there was little relationship between V\textsubscript{I} and CT\textsubscript{I} during cough. This observation is illustrated for one animal in Fig. 2A, in which T\textsubscript{I} during cough overlap those during control eupneic cycles and all loading cycles, including tracheal occlusion. However, V\textsubscript{I} during cough was as high as 150 ml. Furthermore, T\textsubscript{E} and V\textsubscript{E} declined during graded resistive loading, but CT\textsubscript{E} was essentially fixed during cough, regardless of V\textsubscript{E} (Fig. 2B).

Averaged data for the relationship between volume and phase timing are shown in Figure 3 for all coughs in all animals. There was a linear relationship between V\textsubscript{I} and T\textsubscript{I} during resistive loading and control trials (Fig. 3A). Averaged data for V\textsubscript{I} and CT\textsubscript{I} fell outside this relationship. Linear regression analysis indicated a slope for the V\textsubscript{I}/T\textsubscript{I} relationship that was significantly different from zero (2.196 ± 4 ml/s; P < 0.001, r\textsuperscript{2} = 0.72 ± 0.07) and significantly different from the slope for the V\textsubscript{I}/CT\textsubscript{I} data (0.003 ± 0.001 ml/s; P < 0.003, r\textsuperscript{2} = 0.08 ± 0.03). There also was a significant linear relationship between V\textsubscript{E} and T\textsubscript{E} during resistive loading and control trials (Fig. 3B). Averaged data for V\textsubscript{E} and CT\textsubscript{E} fell outside this relationship. The slope of the V\textsubscript{E}/T\textsubscript{E} relationship was significantly different from zero (−18 ± 2 ml/s; P < 0.001, r\textsuperscript{2} = 0.75 ± 0.08) and also significantly greater than the slope for the V\textsubscript{E}/CT\textsubscript{E} data (0.005 ± 0.002 ml/s; P < 0.001, r\textsuperscript{2} = 0.01 ± 0.02).

Many mechanical stimulation trials resulted in sustained multiple coughing over a period of 10–25 s. To control for the potential influence of altered blood gases on the volume-timing relationship, we analyzed both...
single coughs and the first cough from trials resulting in multiple coughs (n = 71 coughs). Neither Vi (97 ± 7 ml; P > 0.05) nor Ve (91 ± 12 ml; P > 0.05) during single or first coughs in a series was significantly different from those values for all coughs. However, CTI (1.21 ± 0.1 s; P < 0.05) during single or first coughs was significantly longer than this value during all coughs. There was no significant difference between CTE (0.61 ± 0.09; P > 0.05) for single or first coughs and all coughs. The slope of the Vi/CTI relationship for single and first coughs (5 ± 4 ml/s; P > 0.05, r² = 0.09 ± 0.04) also was not significantly different from that for all coughs. However, the slope of the Ve/CTE relationship (40 ± 16 ml/s; P < 0.05, r² = 0.29 ± 0.09) for single and first coughs was significantly greater than that for all coughs.

CTI was only weakly related to CTE during all coughs (slope = 0.19 ± 0.05 ml/s; P < 0.05, r² = 0.14 ± 0.04). During single or first coughs, CTI was unrelated to CTE (slope = 0.06 ± 0.04 ml/s; P > 0.05, r² = 0.07 ± 0.03).

DISCUSSION

The major findings of this study were that Vi and Ve were much larger during cough than during eupneic cycles but that inspiratory and expiratory phase durations were not different between the two conditions. There was no relationship between Vi and phase timing during cough. In contrast, significant relationships were observed in the same animals between Vi or Ve and phase timing during resistive loading. There was a relationship between Ve and CTE during single coughs, but this relationship was different than the Ve/TE relationship during resistive loading. Furthermore, the relationship between Ve and CTE was not present when the analysis was expanded to include all coughs. Thus the ventilatory pattern during cough does not fit the volume-timing relationship during eupneic breathing, suggesting a ventilatory pattern control that bypasses normal regulatory mechanisms present during eupnea.

This is the first report investigating the relationship between volume and phase timing during the cough reflex. The considerable overlap of phase durations between cough, eupnea, and resistive loading, despite much larger Vi and Ve, indicates that larger volumes were not associated with shorter phase durations during coughing in our experiments, as would be predicted on the basis of previous studies (7, 15, 32, 33). Therefore, our findings support separate ventilatory pattern regulation during eupneic breathing and the cough reflex. This finding clearly contrasts with the active modulation of phase timing by pulmonary volume-related feedback that has been demonstrated in animals and humans under a variety of experimental conditions (7, 15, 32, 33). However, it is clear that pulmonary volume-related feedback does have an important regulatory role in the production of cough. Other investigators have established that pulmonary volume-related feedback has an important permissive effect on the cough reflex that is not present during eupneic breathing (13, 22). Our results, when combined with the findings of these previous studies, indicate that the central regulation of the cough reflex is far different from that of breathing.

Single-breath alterations in respired volumes and phase durations have been used to minimize the potential influence of changes in arterial blood gases elicited by perturbations, such as mechanical loading, on the volume-timing relationship (8, 33). These single mechanically loaded breaths are typically shorter than the lag time to a chemoreceptor response after a change in ventilation (18). In the present study, we compared the characteristics of the first cough in a series or single coughs with the population cough data to address the possibility that changes in blood gases induced by repetitive coughing may have altered the relationship between volume and phase timing. Although CTI was longer during single or first coughs, there was no evidence of a relationship with a negative slope between cough volumes and phase timing. However, a weak positive relationship existed during single or first coughs between Ve and CTE, but this relationship was very different from the negative relationship between Ve and Tc.

Clark and von Euler (7) reported a linear relationship between Tc and Ti that they called the “timing relationship.” These investigators suggested that the relationship between Tc and Ti could be altered by volume perturbations during the expiratory phase. Zechman et al. (33) and Davenport and Wozniak (9) showed that expiratory resistive loads did indeed result in prolongation of Tc without alterations in Ti. We did not find a relationship between CTE and CTI. This observation also provides further support of our conclusion that pulmonary volume-related feedback does not modulate phase timing during the cough reflex.

Cough is widely regarded as an expulsive reflex, associated with active and vigorous expiratory airflow that is produced by an increased expiratory motor drive to abdominal and chest wall expiratory muscles (3, 31). However, the manner and extent to which inspiratory motor drive increases during cough are less well understood. It is possible that the increased Vi during cough is due to a prolonged Ti and thus does not represent an elevated rate of increase in inspiratory motor drive. Our data indicate that the rate of rise of inspiratory motor drive was elevated during cough, given that Ti did not change, whereas Vi was increased. In other words, the increased Vi was not simply due to an increased Ti. An increased rate of rise of inspiratory motor drive during cough also has been demonstrated in the phrenic neurogram during fictive cough (3) and the diaphragm electromyogram in unparalyzed animals (30).

We observed the well-known relationship (7, 15, 32, 33) between pulmonary volume-related feedback and respiratory phase durations in our animals during resistive loading. This was an important component of the study, given that pentobarbital sodium anesthesia can suppress the relationship between volume and phase timing during eupnea (11). Therefore, our re-
results cannot be explained by suppression of the volume-timing relationship by the anesthetic.

Although we did not record the activity patterns of SARs during cough, the preponderance of literature on the behavior of this afferent group clearly indicates that the large V1 we observed during cough almost certainly resulted in large increases in their discharge (1, 2, 10, 21). However, the only report describing the behavior of SARs during cough indicates that the discharge pattern of this afferent group did not change significantly (17). It is important to note that Matsunoto (17) did not report V1 values during cough, so the magnitude of lung inflation during his experiments is unknown. Indeed, the airflow records shown in his study are more consistent with the production of expiration reflexes than cough. Expiration reflexes are not associated with large inspiratory efforts (16) and thus would not be expected to result in large increases in SAR activity.

Intercostal muscle tendon organs, costovertebral joint mechanoreceptors, and cutaneous afferents from the chest wall can have profound actions on respiratory phase timing, primarily by shortening Ti and/or Te (6, 24, 25). The effects of these afferent groups on phase timing have usually been studied in vagotomized animals to eliminate the actions of SARs on the respiratory pattern, but they can be demonstrated in vagally intact animals and humans (14, 19). The large volumes and active chest wall movements that occurred during cough are likely to have stimulated one or more of these afferent groups (6, 12, 23). However, phase durations were not significantly shorter during cough than during eupnea, suggesting that chest wall afferents did not influence phase timing in our experiments.

Our laboratory has recently proposed a model of the central organization of the cough reflex that was created to account for the actions of centrally active antitussive drugs on the cough motor pattern (5). This model does not include modulation of phase timing mechanisms by SAR afferent feedback. Instead, SAR afferent feedback, through pump cells, alters the excitability of a gate mechanism that transmits excitatory afferent input to the central cough pattern generator. The altered excitability of the gate mechanism produced by SAR afferent feedback accounts for the permissive effect of SARs on the cough reflex (13, 22). Results from the present study are consistent with this model in that our findings do not support a direct action for afferent feedback from SARs in modulation of the central pattern generation system during cough. The detailed cellular model of the cough pattern generator proposed by Shannon and co-workers (26–28) includes modulation of cough phase timing by SAR afferent input via pump cell-mediated excitation of expiratory decrementing neurons. Expiratory decrementing neurons increase their discharge rate during cough and have widespread inhibitory actions on inspiratory and expiratory neurons in the brain stem (26, 28). Our findings are consistent with idea that excitation of expiratory decrementing neurons by SARs is not functionally manifest during cough.

The suppression of the influence of pulmonary volume-related feedback on phase timing is necessary because large, rapid inflations and deflations are an essential component of the ventilatory pattern that produces a cough. If SARs functioned during cough as they do in eupneic breathing, a large change in inspiratory motor drive with a decreased Ti and associated increased V1 would be required to achieve the volume necessary for cough. However, Ti does not change during cough, so the large volumes necessary for cough would be inhibited (or restricted) by the SARs. Thus a transient large increase in inspiratory motor drive occurs with suppression of SAR-mediated inhibition of inspiration to allow the ventilatory pattern of cough to manifest. In essence, release of the cough pattern generation system from the “off-switch” action of pulmonary volume-related feedback allows large volumes to be produced over a wider range of phase durations.

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