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The motor pattern of tracheobronchial cough is affected by inspiratory resistance and expiratory occlusion – The evidence for volume feedback during cough expiration

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ABSTRACT

The role of pulmonary stretch receptor discharge and volume feedback in modulation of tracheobronchial cough is not fully understood. The current study investigates the effect of expiratory occlusion with or without preceding inspiratory resistance (delivery of tidal or cough volume by the ventilator lasting over the active cough expiratory period) on the cough motor pattern.

Experiments on 9 male cats under pentobarbital sodium anesthesia have shown that inspiratory resistance followed by expiratory occlusion increased cough inspiratory and expiratory efforts and prolonged several time intervals (phases) related to muscle activation during cough. Expiratory occlusion (at regular cough volume) decreased number of coughs, increased amplitudes of abdominal electromyographic activity, inspiratory and expiratory esophageal pressure during cough and significantly prolonged cough temporal features. Correlation analysis supported major changes in cough expiratory effort and timing due to the occlusion.

Our results support a high importance of volume feedback, including that during cough expulsion, for generation and modulation of cough motor pattern with obstruction or expiratory airway resistances, the conditions present during various pulmonary diseases.

1. Introduction

Cough performance can be significantly impaired in lung diseases such as pulmonary emphysema, fibrosis, etc. (Langlands, 1967; Loudon and Shaw, 1967; Hope-Gill et al., 2003; Smith, 2006; Calverley, 2013). Under such conditions insufficient volume, airflow, and related afferent feedback decreases cough performance (Arora and Gal, 1981; Bolser, 1991). Afferent feedback from the airways is primarily achieved by vagal nerve fibers (e.g. slowly and rapidly adapting receptors).

The role of pulmonary stretch receptors (PSRs) in tracheobronchial cough modulation has not been fully elucidated. Controversial results have been obtained when volume-related feedback is varied, and likely these are due to the 1) narrow focus on specific aspects of cough, and/or 2) extreme experimental conditions. For example, Nishino et al (1989) demonstrated that continuous positive airway pressure ventilation in anesthetized humans increased expiratory cough airflows, however Javorka et al. (1994) showed reduced inspiratory cough efforts and cough number in anesthetized rabbits. Additionally, several groups have shown no changes in abdominal motor drive with end-inspiratory occlusions (Kobayashi et al., 1992; Romaniuk et al., 1997), and no volume-timing relationships in anesthetized cats (Bolser and Davenport, 2000). These studies suggest that cough is not significantly impacted by the PSR discharge. In contrast, we reported significant changes in cough motor pattern with expiratory and/or inspiratory resistance and early over-inflation during cough trials (Poliacek et al., 2016). Our recent work suggests that there may be central mechanisms that can limit PSR / volume-related feedback contribution.

The current study extends Poliacek et al. (2016) and investigates the effect of functional occlusion during cough expulsion on cough motor drive and pattern. We hypothesized that 1) expiratory occlusion significantly alters cough motor pattern, 2) additional effects of inspiratory resistance (when applied) on cough will occur, 3) volume feedback variations during cough are needed for the development of regular cough motor pattern, and 4) the volume feedback is significant for cough regulation under irregular volume / flow conditions.

2. Methods

Experiments were performed on 9 male cats (3.79 ± 0.21 kg) under pentobarbital sodium anesthesia (Pfannenschmidt GmbH; 40 mg/kg iv initially). Supplementary doses of the anesthetic were administered (1–3 mg/kg iv) as needed (depending on the presence of corneal and pull back reflexes, jaw tone, respiratory rate and blood pressure). Atropine (0.1 mg/kg iv) and hydrocortisone (2 mg/kg iv)

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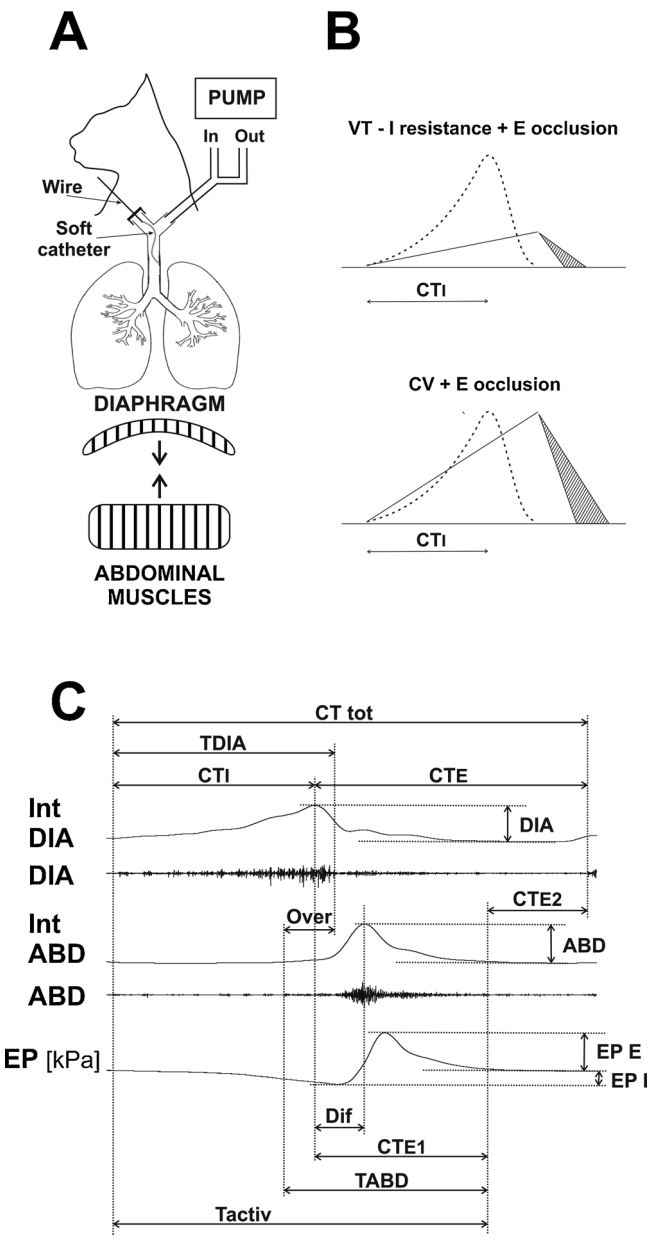

Fig. 1. The scheme of volume modifications during coughing and cough analysis.

A: The scheme of ventilator and stimulating tool connections to the Y-cannula during ventilator controlled cough trials.

B: Schemes of modified volume and "expiratory occlusion" during cough. Dashed waveforms represent (expected) regular lung volume during cough; solid waveforms are ventilator delivered volumes during cough. They could be slightly modified by muscle activity during cough, mainly expulsion against ventilator providing inflation (functional occlusion), however, into the ventilator tubing. Wider cross-hatch areas denote (expected) variability and prolongation of the cough expiratory phase duration due to the occlusion and additional expiratory airflow resistance (ventilator output).

C: The scheme of cough analysis. Amplitudes of EMG activities and esophageal pressure as well as temporal parameters measured on cough are depicted.

ABD: abdominal EMG (also the amplitude of abdominal activity in C with arrow); CTE: expiratory phase duration; CTE1: active portion of the cough expiratory phase; CTE2: quiescent expiratory period; CTI: inspiratory phase duration; CTtot: total cough cycle duration; CV: cough volume; DIA: diaphragm EMG (also the amplitude of diaphragm activity in C with arrow); Dif: interval between DIA and ABD maximum; E: expiratory; EP: esophageal pressure; EP E: amplitude of expiratory EP; EP I: amplitude of inspiratory EP; I: inspiratory; Int: integrated moving average; Over: overlap of DIA and ABD; TABD: duration of cough ABD activity; Tactiv: duration of all cough related EMG activity; TDIA: DIA activity duration; VT: tidal volume

were given to reduce secretions and brain swelling, respectively, neither of which are known to adversely alter volume feedback mechanisms in cats (Richardson et al., 1984; Yu et al., 1987 Iscoe and Gordon, 1992; Matsumoto, 1998). A Y-cannula was introduced into trachea (Fig. 1), catheters were placed into the femoral artery in order to measure blood pressure and the femoral vein to inject drugs as needed. A balloon catheter was inserted into the esophagus for the measurement of esophageal pressure (EP). Animals spontaneously breathed oxygen-enriched air (30%) in order to avoid unexpected changes in cough response due to the reduced oxygen supply. Body temperature was maintained at 38.0 ± 0.5 °C by a heating pad and continuously monitored together with blood pressure, EP, respiratory rate and end-tidal CO_2 concentration ($ETCO_2$). Samples of arterial blood were periodically removed, in order to monitor blood gases and pH (and maintain it within appropriate range). Animal care as well as all procedures were performed in accordance with the Animal Welfare Guidelines of the Comenius University and the legislation for animal use and welfare of Slovak Republic and European Union (Directive 2010/63/UE).

Electromyograms (EMGs) were recorded from expiratory abdominal muscles (transversus abdominis and/or obliquus abdominis externus; ABD), and an inspiratory muscle (sternal diaphragm; DIA), with bipolar teflon insulated fine steel wire hook electrodes. Tracheobronchial cough was elicited by mechanical stimulation of the intrathoracic airways with 8 cm long soft polyethylene catheter attached to the steel wire (stimulator; Fig. 1). The stimulator was inserted and moved periodically back and forth in the trachea 4–6 times for periods of 10 s to elicit repetitive coughing (the stimulation was performed in the same way by the same experimenter in each animal).

Cough was defined by a large burst of inspiratory related DIA EMG activity, immediately followed by a burst of expiratory ABD EMG activity, and by a related negative to positive EP change (Fig. 1). These criteria separate cough from other defensive airway behaviors such as expiration reflex (Poliacek et al., 2008) or swallow (Pitts et al., 2013). During cough, the inspiratory phase duration (CT_I) was defined as the period of time from the onset to the maximum DIA EMG activity. The active expiratory phase (CT_{E1}) was defined as the period of time from the maximum of the DIA EMG activity to the end of the cough ABD EMG activity. The duration of the quiescent expiratory phase (CT_{E2}) was defined as the period of time from the end of the cough ABD EMG activity to the onset of the DIA EMG activity for the next cough (behavior). The time from the maximum DIA EMG activity to the end of the cough cycle was defined as the total expiratory phase duration (CT_E).

Cough stimulation was conducted *via* one of two openings in the Y-shape tracheal cannula sealed by a plug with a small port containing the stimulator (Fig. 1). For ventilator "controlled "cough, the ventilator was connected to the other port of cannula (Fig. 1). The plug was placed in the port of cannula just prior to the cough stimulation and disconnected immediately following the last cough.

We conducted 2–4 stimulation trials under each testing condition: a) pre-ventilator control, b) closed-loop ventilator, and c) post-ventilator control. In order to avoid a measurement of the adaptation effects (tachyphylaxis) we pooled the pre- and post-ventilator control trials. Defined volumes were delivered by the MERLIN digitally controlled Small Animal Ventilator (Vetronic Services Ltd, United Kingdon) modified to trigger the ventilatory cycle by an external voltage. The DIA EMG was used to signal / trigger the ventilator.

Tidal and cough-related volumes were measured by a pneumotachograph (LBL 50, Commet). Majority of coughs in the trial had very similar cough volume, which has been taken as "typical (average)" cough volume. Ventilator controlled cough trials were performed either with 1) tidal volume or 2) typical (average) cough inspiratory volume delivered during the time of approximately 140% of CT_I (Fig. 1). The first condition represents *inspiratory resistance* followed by *expiratory occlusion*, the second condition represents *expiratory occlusion*. Controls were performed with the ventilator attached and an open port, as well as, with the average cough volume delivery during CT_I following by

expiratory resistance (ventilator tubings) and are described in our previous study (Poliacek et al., 2016).

All EMGs were amplified, filtered (100–3000 Hz), rectified, and integrated with the time constant of 200 ms. The number of coughs (CN = average number of coughs per 10 s stimulation) in response to mechanical stimulation, amplitudes of DIA and ABD EMG moving averages, amplitudes of EP during the appropriate phases of cough, CT_I, CT_{E1}, CT_{E2}, CT_E, the time between maxima of DIA and ABD activity (Dif), the duration of all cough related EMG activity (Tactiv), and the total cough cycle duration (CTtot) were analyzed (Fig. 1). Additional temporal data were (Fig. 1): the durations of cough related DIA and ABD activation (TDIA the time from the beginning to the end of inspiratory related DIA cough discharge, TABD the time from the beginning to the end of cough related ABD discharge), augmenting - elevating (eleABD from the beginning to the maximum of cough related ABD discharge), and decrementing - descending segments of ABD EMG activity (desABD from the maximum to the end of cough related ABD discharge).

Magnitudes of the moving averages during coughing were normalized relative to the mean (EMGs) amplitudes of the first control pre-ventilator coughs (the average magnitudes of all control coughs for each particular EMG). The beginning and the end of the muscle activity were determined from the raw EMG signals. The ventilator was in "close "mode only during the necessary cough trials. Thus, we did not analyze the cardiorespiratory parameters that might be altered by ventilator action (presence of cough and ventilator mode lasted only for 10–15 s). Cardiorespiratory changes induced by coughing have been previously described (e.g. Korpas and Tomori, 1979).

The results are expressed as means ± standard error (SE). All cough parameters were averaged over each group of trials within the stimulation sequence (pre- and post-controls vs. ventilator mode). For statistical analysis paired *t*-test or Wilcoxon matched paired test (W) were employed as appropriate for testing the differences. Differences were considered significant if $p < 0.05$. To assess the relationships between the dependent variables Pearson correlation coefficients (r) were calculated across the following variables: amplitudes of DIA and ABD EMGs, CT_I, CT_E, CT_{E1}, TDIA, TABD, CTtot, and Tactiv. Correlations were typically reported when significant difference of the dependence slope from 0 occurred.

3. Results

When the tidal volume was delivered by the ventilator during the inspiratory phase of cough (inspiratory resistance) lasting over active cough expiration (expiratory occlusion) cough inspiratory and expiratory efforts increased (Fig. 2 and 3). Among cough temporal features CT_I, CT_{E1}, Tactiv, TDIA, TABD, and desABD were significantly prolonged (Table 1). The CTtot was also prolonged (Table 1) with the p value at the limit of statistical significance (p = 0.052).

When the typical cough volume was delivered during the time exceeding the regular CT_I by approximately 40%, representing the occlusion during the active expiratory phase the CN decreased and amplitudes of ABD EMG, inspiratory and expiratory EP increased (Fig. 2 and 3). The significant prolongation of CT_I, CT_{E1}, CT_E, CTtot, Tactiv, TDIA, TABD, eleABD, desABD (Table 1) and Dif (from 0.22 ± 0.01to 0.34 ± 0.04 s, $p < 0.05$) was seen.

The only correlation of EMG amplitudes data with the slope significantly different from 0 was that of DIA and ABD ($r = 0.83$, $p < 0.05$) when cough volume was applied. Pearson correlation coefficients for other characteristics are listed in Table 2 for tidal volume and Table 3 for cough volume delivered by ventilator.

4. Discussion

The present results clearly demonstrate that the motor pattern of tracheobronchial cough is modulated by alterations in lung volume

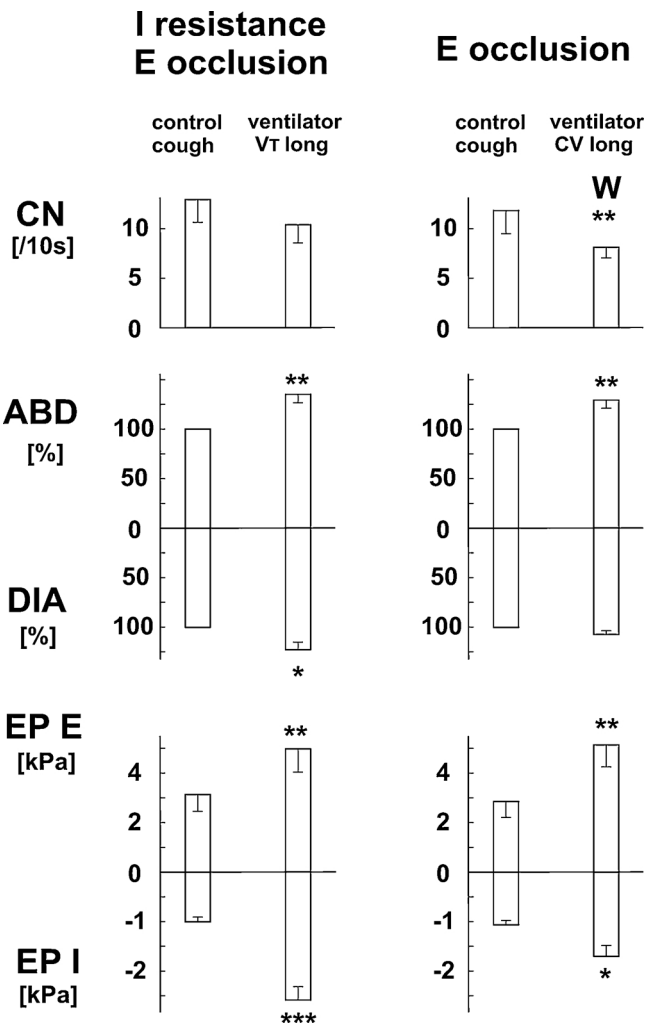

Fig. 2. The effects of ventilator controlled cough inflations and expiratory occlusion on coughing.

Coughs with tidal volume delivered by the ventilator over the inspiratory (resistance) and active expiratory (occlusion) phase of cough (left charts) and coughs with cough volume delivered by the ventilator over the inspiratory and active expiratory (occlusion) phase of cough (right charts).

ABD: abdominal EMG amplitude; CN: cough number; CV: cough volume; DIA: diaphragm EMG amplitude; E: expiratory; EP E: expiratory esophageal pressure amplitude; EP I: inspiratory esophageal pressure amplitude; I: inspiratory; VT: tidal volume; W: Wilcoxon matched pairs test; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

feedback during the expiratory phase of cough. This report, together with our previous (Poliacek et al., 2016), provides detailed information about cough modulation resulted from altered inspiratory volumes and expiratory resistances during cough. These results suggest in conditions with cough impairments, airway obstruction and airway resistance can deleteriously impact cough motor performance (Fig. 3).

Expiratory occlusion during cough induced a pronounced increase in the expiratory EP maximum, CT_{E1}, CT_E, Tactiv, and CTtot, surpassing the effects of expiratory resistance (Poliacek et al., 2016). Additionally, there was increased CT_I, TDIA, Dif and ABD motor recruitment resulting in significant increase in ABD EMG amplitudes and TABD (Fig. 2, Table 1). The occlusion protocol reduced CN due to a prolongation of cough phases (Table 1) and increased the inspiratory EP amplitude (Fig. 2), likely because ventilator controlled cough inspirations. The expiratory occlusion following inspiratory resistance did not alter CN. Cough regulatory circuits may respond to low inspiratory volume and attempt to compensate by reducing CT_{E2} and effectively

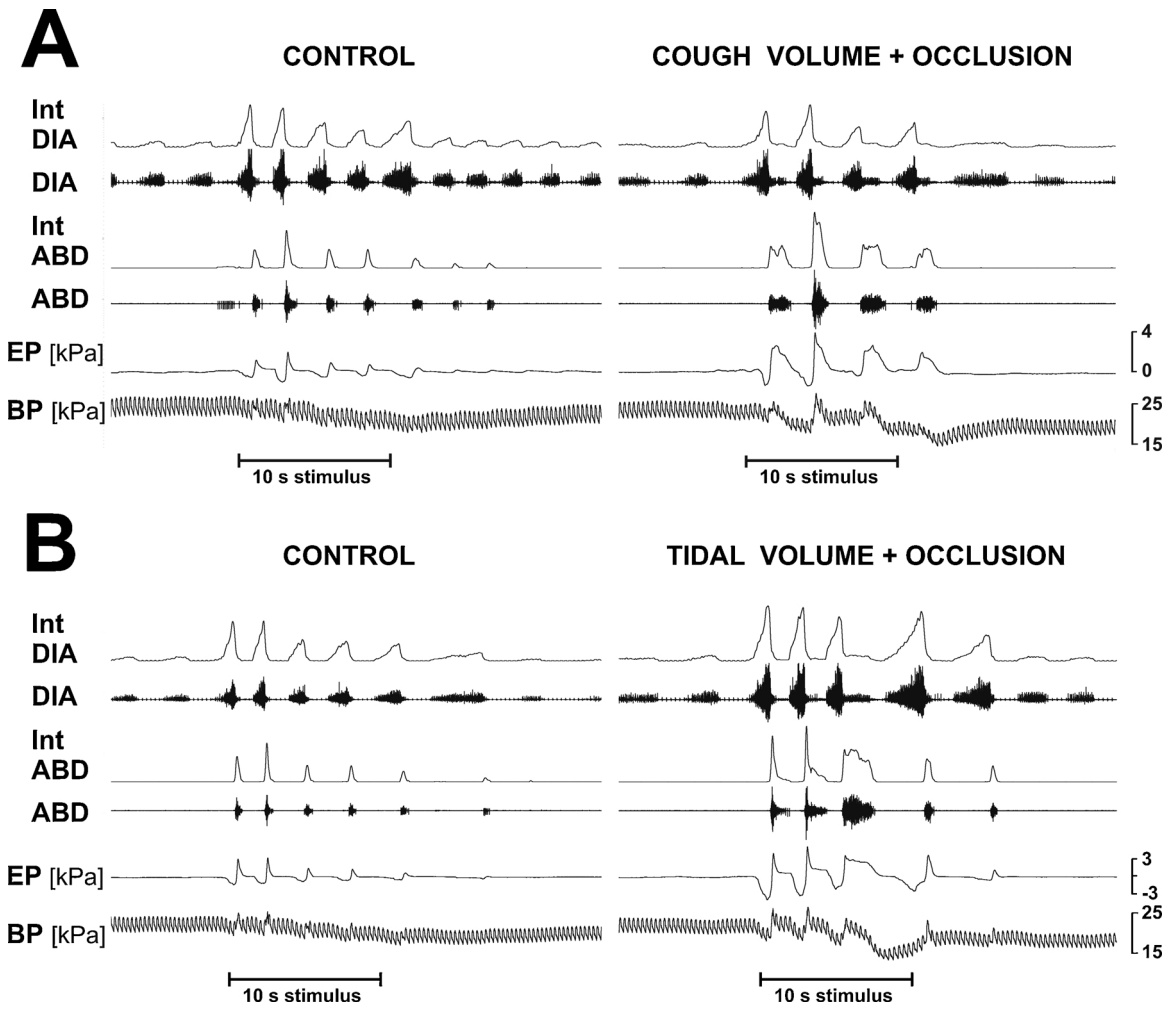

Fig. 3. Examples of coughing in control and when cough or tidal volume were delivered by ventilator over inspiratory and early expiratory stage (occlusion) of cough.

A: Occlusion at cough volume resulted in lower number of cough, increased and prolonged abdominal motor drive.

B: Occlusion at tidal volume induced increased and prolonged abdominal motor drive. Low lung volume representing inspiratory resistance resulted in increased inspiratory motor drive as well.

ABD: abdominal EMG; BP: arterial blood pressure; DIA: diaphragm EMG; EP: esophageal pressure; Int: integrated

Table 1

Temporal features of coughing during ventilator guided inflations that lasted over cough active expirations. Primary data in bold.

	Control Free Cough	Ventilator VT	Control Free Cough	Ventilator CV
CT_I [s]	**0.75 ± 0.07**	**0.87 ± 0.10** *	**0.79 ± 0.07**	**0.88 ± 0.06** **
CT_{E1} [s]	**0.60 ± 0.05**	**1.04 ± 0.09** ***	**0.59 ± 0.05**	**1.16 ± 0.07** ***
CT_E [s]	**1.12 ± 0.07**	**1.42 ± 0.10**	**1.18 ± 0.06**	**1.93 ± 0.27** ** **W**
CT_{E2} [s]	**0.52 ± 0.08**	**0.38 ± 0.09**	**0.58 ± 0.09**	**0.77 ± 0.31**
CTtot [s]	**1.88 ± 0.09**	**2.30 ± 0.18**	**1.96 ± 0.08**	**2.81 ± 0.24** ** **W**
Tactiv [s]	**1.36 ± 0.11**	**1.92 ± 0.17** ***	**1.38 ± 0.10**	**2.04 ± 0.08** ***
TDIA [s]	0.86 ± 0.08	1.01 ± 0.11 **	0.90 ± 0.07	1.00 ± 0.07 **
TABD [s]	0.79 ± 0.09	1.22 ± 0.11 ***	0.79 ± 0.09	1.38 ± 0.09 ***
eleABD [s]	0.40 ± 0.06	0.45 ± 0.09	0.41 ± 0.06	0.56 ± 0.07 **
desABD [s]	0.40 ± 0.05	0.77 ± 0.08 ***	0.38 ± 0.05	0.82 ± 0.07 ***

CT_E: duration of total expiratory phase; CT_{E1}: duration of active expiratory phase; CT_{E2}: quiescent expiratory period; CT_I: the duration of cough inspiratory phase; CTtot: total cough cycle duration; CV: cough volume; desABD: descending segment of abdominal activity; Dif: duration between diaphragm and abdominal discharge maxima; eleABD: elevating segment of abdominal activity; Over: duration of diaphragm and abdominal activities overlap; TABD: duration of cough abdominal activity; Tactive: duration of all cough related EMG activity; TDIA: duration of cough diaphragm activity; VT: tidal volume; W: Wilcoxon matched paired test; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 2
Pearson correlation coefficients for selected cough characteristics in control (upper line) and when tidal volume was delivered by the ventilator (lower line).

	CT_{E1}	CT_E	CT_{E2}	CTtot	Tactive	TDIA	TABD
CT_I	0.51	−0.23	−0.52	0.62	**0.91****	**0.99*****	0.46
	0.66	0.61	0.03	**0.90****	**0.92****	**0.99*****	0.58
CT_{E1}		−0.20	−0.42	0.59	**0.81***	0.54	**0.78***
		0.53	−0.39	0.66	**0.90****	0.69	**0.72***
CT_E			**0.81***	0.62	−0.06	−0.18	−0.16
			0.58	**0.90****	0.62	0.56	0.16
CT_{E2}				0.23	−0.55	−0.49	−0.62
				0.34	−0.19	−0.05	−0.52
CTtot					0.69	0.66	0.25
					0.86**	**0.86****	0.41
Tactiv						**0.93*****	0.68
						0.93***	**0.72***
TDIA							0.47
							0.63

CT_E: duration of total expiratory phase; CT_{E1}: duration of active expiratory phase; CT_{E2}: quiescent expiratory period; CT_I: the duration of cough inspiratory phase; CTtot: total cough cycle duration; TABD: duration of cough abdominal activity; Tactiv: duration of all cough related EMG activity; TDIA: duration of cough diaphragm activity; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ for the slope significantly different from 0.

Table 3
Pearson correlation coefficients for selected cough characteristics in control (upper line) and when cough volume was delivered by the ventilator (lower line).

	CT_{E1}	CT_E	CT_{E2}	CTtot	Tactive	TDIA	TABD
CT_I	0.54	−0.25	−0.49	0.69	**0.91****	**0.99*****	0.41
	−0.27	−0.55	−0.43	−0.37	0.54	**0.99*****	−0.11
CT_{E1}		−0.28	**−0.77***	0.27	**0.84****	0.56	**0.80***
		0.43	−0.61	−0.55	0.66	−0.33	0.29
CT_E			**0.83***	0.53	−0.30	−0.21	−0.36
			0.98***	**0.98*****	**−0.81***	−0.48	−0.26
CT_{E2}				0.19	−0.69	−0.47	**−0.71***
				0.99***	**−0.86****	−0.35	−0.29
CTtot					0.58	**0.71***	0.09
					−0.76**	−0.28	−0.31
Tactiv						**0.91****	0.66
						0.48	0.17
TDIA							0.41
							−0.18

CT_E: duration of total expiratory phase; CT_{E1}: duration of active expiratory phase; CT_{E2}: quiescent expiratory period; CT_I: the duration of cough inspiratory phase; CTtot: total cough cycle duration; TABD: duration of cough abdominal activity; Tactiv: duration of all cough related EMG activity; TDIA: duration of cough diaphragm activity; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ for the slope significantly different from 0.

initiating the next cough inspiration sooner (Table 1). When there is inhaled volume similar to regular cough volume (present protocol), exhalation dominates resulting in lower CN (see results). Consistently, CTtot was significantly prolonged with cough volume, but the marginal change occur with tidal volume ($p = 0.052$; Table 1). Combining inspiratory resistance (low lung volume during cough inspiration) with either expiratory resistance (Poliacek et al., 2016) or occlusion (present data) showed identical effects on inspiratory cough phase.

Interpretation of the correlation analysis is limited due to low sample numbers, however, some of results may provide additional evidence and/or explanations for the present results. Only weak correlation among DIA and ABD EMG cough amplitudes and their no relation to the cough time phases was found in anesthetized cat (Wang et al., 2009; Pitts et al., 2016). The correlation of cough DIA and ABD amplitudes ($r = 0.83$, $p < 0.05$ for cough volume delivered, $r = 0.51$ for tidal volume delivered) represent particularly (due to the EMG signal normalization) the preservation of this relation in coughs with and without expiratory occlusion.

Some cough variables are known to be related (CT_I represents main part of TDIA, CT_{E1} for TABD, etc.), which produced strong correlations (Tables 2 and 3). However, the relationship between CT_{E1} and TABD (similar for TABD and Tactiv) was completely lost when cough volume was delivered (Table 3). It suggests significant (and irregular) alterations of these parameters with cough volume delivery and expiratory occlusion (of note, the average timing changes did not show increased irregularity - SE values; Table 1). Extended and sometimes uneven effect of cough volume delivered by ventilator on expiratory phase may explain the strong negative relationships for CT_E (CT_{E2}, CTtot) and Tactiv (Table 3). Consistent with pronounced effects of occlusions at cough volume, only when cough volume was applied CT_{E2} was strongly correlated with CTtot in this study. Both CT_I and CT_{E1} significantly contributed to Tactiv and express correlations to Tactiv (as does TDIA and TABD). However, a similar reduction in correlation strength for CT_{E1} and TABD was seen for CT_I (and TDIA) and Tactiv when cough volume was employed (Table 3). In the present study, differently from the previous report (Poliacek et al., 2016), prolonged delivery of tidal volume resulted in increased correlation of CT_I (and TDIA) and CTtot (Table 2). Wang et al. (2009) and Pitts et al. (2016) both reported weak relationships between CT_I and CTtot in anesthetized cats. Additionally, there was a reduction in the relationship between CT_E and CT_{E2} when tidal volume was delivered (Table 2), which is likely due to increased contribution from CT_{E1} to CT_E (Table 2,3). Of note, Wang et al. (2009) and Pitts et al (2016) reported correlations of CT_E, CT_{E2} and CTtot and weak-no relationship between CT_E and CT_{E1}.

We hypothesize that expiratory prolongation with expiratory occlusion resulted in higher contribution of CT_E to the cough timing. Additionally, occlusion at cough volume was more efficient in modifying cough motor pattern (consistent with higher PSR activity and their no reduction in discharge rate during expiration; Jakus et al., 1983). This fact supports the notion that even though our occlusion was not executed by a closure of tracheal cannula, there was no significant alteration in tracheal pressure or movement of air. Our results demonstrate a significant role of PSR during the expiratory phase of cough. Jakus et al. (1983) showed that PSR's activity in anesthetized cats corresponds to the lung volume changes during cough and Davis et al. (1956) their relation to ventilator induced inflations and deflations. The airway smooth muscle tension (Bartlett et al., 1976; Sant'Ambrogio and Mortola, 1977) as well as the rate of volume changes (Bishop, 1977; Davenport et al., 1981) contribute to the discharge of PSR's, indeed, PSR's represent main component of volume feedback mechanism (Clark and vonEuler, 1972; Canning et al., 2006). However, we cannot exclude the contribution of rapidly adapting PSR's, vagal C-fibers (Canning et al., 2006; Canning, 2010) and extravagal spinal afferent pathways from the thoracic and abdominal structures (Shannon and Freeman, 1981; Hernandez et al., 1989) to the observed changes. Of note, the role of rapidly adapting receptors in cough control is unclear (Mazzone and Undem, 2009), the C-fibers have high threshold for mechanical stimulation (Coleridge and Coleridge, 1984) and extravagal afferents e.g. intercostal muscle tendon organs influence on expiratory performance has never been reported (Shannon et al., 1985; Hernandez et al., 1989).

Our results support the importance of volume feedback during cough, specifically, its modulation during expulsion can result in the altered cough motor pattern. Under pathologic conditions of irregular cough volumes and / or inspiratory and expiratory airway resistances, cough may be significantly impacted also by this mechanism.

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