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The course of lung inflation alters the central pattern of tracheobronchial cough in cat – the evidence for volume feedback during cough

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Abstract

The effect of volume-related feedback and output airflow resistance on the cough motor pattern was studied in 17 pentobarbital anesthetized spontaneously-breathing cats. Lung inflation during tracheobronchial cough was ventilator controlled and triggered by the diaphragm electromyographic (EMG) signal. Altered lung inflations during cough resulted in modified cough motor drive and temporal features of coughing. When *tidal volume* was delivered (*via* the ventilator) there was a significant increase in the inspiratory and expiratory cough drive (esophageal pressures and EMG amplitudes), inspiratory phase duration (CT_I), total cough cycle duration, and the duration of all cough related EMGs (*Tactive*). When *the cough volume* was delivered (*via* the ventilator) during the first half of inspiratory period (at $CT_I/2$ - early over inflation), there was a significant reduction in the inspiratory and expiratory EMG amplitude, peak inspiratory esophageal pressure, CT_I , and the overlap between inspiratory and expiratory EMG activity. Additionally, there was significant increase in the interval between the maximum inspiratory and expiratory EMG activity and the active portion of the expiratory phase (CT_{EI}). Control inflations coughs and control coughs with additional expiratory resistance had increased maximum expiratory esophageal pressure and prolonged CT_{EI} , the duration of cough abdominal activity, and *Tactive*. There was no significant difference in control coughing and/or control coughing when sham ventilation was employed. In conclusion, modified lung inflations during coughing and/or additional expiratory airflow resistance altered the spatio-temporal features of cough motor pattern *via* the volume related feedback mechanism similar to that in breathing.

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Keywords

cough control; stretch receptors; volume feedback; airflow resistance; cough motor pattern; impaired cough

1. INTRODUCTION

The role of pulmonary stretch receptors (PSR), specifically volume-related feedback in the regulation of cough is seen as controversial. Continuous positive airway pressure ventilation in anesthetized humans increased expiratory airflows in cough (Nishino et al., 1989), but reduced inspiratory cough efforts and number of coughs in anesthetized rabbits (Javorka et al., 1994). However, other studies yielded negative results (Romaniuk et al., 1997; Bolser and Davenport, 2000). PSR discharge rate during the inspiratory phase of cough reaches double that of eupnea. The discharge rate drops during the inspiratory-expiratory phase transition to a frequency slightly below eupnea maximum and further declines during the expiratory phase of cough, especially if a portion of functional residual capacity is exhaled (Jakus et al., 1983).

PSR activity also has a permissive effect on tracheobronchial cough, as the elimination of PSR signaling resulted in elimination of tracheobronchial cough in rabbit (Hanacek et al., 1984; Sant'Ambrogio et al., 1984). Additionally, cough performance is significantly impaired under several pathological conditions (pulmonary emphysema, fibrosis etc.; Langlands, 1967; Loudon and Shaw, 1967; Hope-Gill et al., 2003; Smith, 2006; Calverley, 2013); or following spinal cord injury and paralysis, where an inappropriate volume-related afferent feedback may contribute to decreased cough performance (Arora and Gal, 1981; Bolser D.C., personal communication).

In contrast, end-inspiratory occlusion, presumably increasing PSR discharge, has no effect on cough abdominal drive (Kobayashi et al., 1992; Romaniuk et al., 1997). Eupneic volume-timing relationships primarily attributed to PSR's (longer phase duration at lower lung volume; Zechman et al., 1976; Davenport et al., 1981), are not present in tracheobronchial cough in cat (Bolser and Davenport, 2000). Additionally, there are minimal correlations between cough amplitudes and phase durations in pentobarbital-anesthetized cats (Wang et al., 2009). These data suggest that PSR discharge does not significantly affect cough. Possibly, either the cough pattern generator itself, or other central mechanisms limit PSR/volume related feedback contribution. Various interventions have resulted in modified cough number and cough expiratory efforts, with no alteration of cough temporal features including neuronal blocking, administration of neuroactive agents and antitussives (Bolser et al., 1999; Jakus et al., 2004; Bongianini et al., 2005; Mutolo et al., 2008; Poliacek et al., 2010), as well as simultaneous stimulation of other motor behaviors (Poliacek et al., 2009; Simera et al., 2015). This is consistent with separate control of the cough motor drive and cough timing.

In this study we attempted to determine the effect of altered volume-related feedback (primarily through PSR feedback) by modulating inspiratory cough volume and expiratory airflow. We hypothesized that alterations in lung volume during the development of

individual coughs (inspiratory and/or expiratory volume other than naturally inhaled/exhaled at that time point of cough), which result in altered volume-related feedback, would alter cough motor drive and cough temporal features.

2. METHODS

Experiments were performed on 14 male and 3 female cats (3.76 ± 0.18 kg) under pentobarbital sodium anesthesia (Morbital Polfa or Pfannenschmidt GmbH; 40 mg/kg iv initially). Supplementary doses of 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) were given to reduce secretions and brain swelling, respectively. A Y-cannula was introduced into trachea (Figure 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%). Body temperature was maintained at $38.0 \pm 0.5^\circ\text{C}$ 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; Figure 1). The stimulator was inserted and moved periodically back and forth in the trachea 4–6 times for periods of 10 second 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. 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_1) 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 (Figure 1), under two control conditions: 1) with no ventilator attached to the cannula; and

2) with the ventilator connected to one-side of Y-cannula, while the remaining port was open (allowing free airflow). For coughs with controlled volumes, the ventilator was connected to the cannula, while the remaining side was sealed. The sealing plug was designed with a small port containing the stimulator (Figure 1). Of note, the plug was placed just prior to the cough stimulation and disconnected immediately following the last cough.

We conducted 2–4 stimulation trials under each testing condition: pre-ventilator control, closed-loop ventilator, and post-ventilator control. In order to avoid a measurement of the adaptation effects (tachyphylaxis) we pooled the pre- and post-ventilator control trials. The post-ventilator controls were: number of coughs 82.6%, ABD EMG amplitudes 96.1%, and DIA EMG amplitudes 97.0% of pre-ventilator controls. Defined volumes were delivered by the MERLIN digitally controlled Small Animal Ventilator (Vetronic Services Ltd, United Kingdom) 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 under 3 conditions (Figure 1): 1) tidal volume delivered during CT_I ; 2) typical (average) cough inspiratory volume delivered during the first half of CT_I (early over inflation); and 3) the typical (average) cough inspiratory volume delivered during the CT_I (positive control).

Ventilator resistance (tubings and valves) during expulsions of coughs putatively affected expiratory cough phase (see Results). In order to test these effects, the trials with spontaneous cough inspirations followed by expulsions diverted through the ventilator output pathway were performed.

All EMGs were amplified, filtered (100 – 3000 Hz), rectified, and integrated with the time constant of 200 ms. The number of coughs (average number of coughs per 10 s stimulation) in response to mechanical stimulation (cough number = CN), 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 overlapping of DIA and ABD burst (Over), the time between maxima of DIA and ABD activity (Dif), the duration of all cough related EMG activity (Tactive); and the total cough cycle duration (CT_{tot}) were analyzed (Figure 1). Additional temporal data were: the durations of cough related DIA and ABD activation (TDIA, TABD), augmenting - elevating (eleABD), and decrementing - descending segments of ABD EMG activity (desABD; Figure 1).

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).

Results are expressed as means $\pm$ 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 relationships between the dependent variables the Pearson correlation coefficients (r^2) were calculated with the amplitudes of DIA and ABD EMGs, CT_I, CT_E, CT_{E1}, CT_{tot}, and Tactive. Correlations were considered strong if $r^2 > 0.6$, moderate if $r^2 > 0.35$, weak if $r^2 > 0.25$.

3. RESULTS

For control, coughs were compared with the ventilator attached (remaining Y-cannula port left open) *vs.* disconnected, and there were no significant differences across all measures (all $P > 0.1$, $n=7$). For a positive control (ventilator controlled inflation, but typical cough volume delivered during regular CT_I), coughs had significantly increased maximum expiratory EP (Figure 2) and prolonged CT_{E1}, CT_E, TABD, desABD, Dif, CT_{tot}, and Tactive ($n=7$; Table 1). CN, amplitudes of DIA and ABD, and other parameters listed were not significantly different (Figure 2; Table 1). Of note, the additional resistance from the ventilator output tubings and valves was approximately 2 kPa.s.l⁻¹ (determined from flow-volume and pressure difference curves). Coughs with spontaneous inspirations *via* one-way valve, with their expirations guided through the ventilator, had similar alterations to coughs with inspiratory volume delivered during regular CT_I *via* the ventilator ($n=6$; Figure 2, Table 1).

Inspiratory and expiratory cough efforts increased (Figure 2 and 3) with the ventilator delivered tidal volume (15–35 ml, approximately 3-fold less than the regular cough volume; $n=7$). Such volume modulation also increased CT_I, TDIA, CT_{tot}, and Tactive representing modulations of the inspiratory cough phase duration (Figure 3; Table 2). CN and other temporal characteristics were not significantly different (Figure 2; Table 2).

Ventilator induced fast lung inflations during the first half of the cough inspiratory period (CT_I/2; $n=7$) with typical (average) cough volume significantly reduced inspiratory efforts and ABD EMG amplitudes (Figure 2 and 4). It also shortened CT_I, Over, eleABD and prolonged CT_{E1}, Dif, and desABD (Figure 4; Table 2).

The course of cough inspiration (and inflation) is not linear (e.g. there is less than 1/2 of maximum DIA activation at CT_I/2). The DIA EMG moving average at the time point of CT_I/2 was $43.7 \pm 4.4\%$ in coughs with tidal volume ventilator delivery *vs.* control $40.6 \pm 3.9\%$ ($P < 0.05$), consistent with increased amplitude of DIA EMG (at CT_I) under this condition. When cough volume was delivered fast, DIA EMG was $21.9 \pm 2.3\%$ *vs.* control $33.8 \pm 3.7\%$ ($P < 0.001$) at the time point of CT_I/2, consistent with the difference in the amplitude (at CT_I).

Selected positive correlations are listed in Table 3. Additional strong positive correlations were found between CT_{E1} and CT_I in coughs with tidal volume delivered by the ventilator

($r^2=0.66$, $P<0.05$) and for CT_{tot} with CT_E ($r^2>0.88$, $P<0.001$ in control coughs and when cough volume was delivered fast; $r^2=0.56$ for tidal volume delivered).

4. DISCUSSION

This study demonstrated the dependence of the cough motor pattern on volume related feedback and airflow resistance. Changes in lung inflation significantly modified cough motor drive and temporal features of mechanically induced cough in pentobarbital anesthetized cats. As such this experimental protocol unmasked the volume-timing relations not previously revealed with unimpeded cough (Bolser and Davenport, 2000).

The significance of volume feedback during cough was demonstrated by the increases in inspiratory and expiratory motor drive and CT_I , when tidal volume was delivered during the cough inspiratory phase (Figure 2 and 3; Table 2). These results are consistent with effects of volume feedback during eupnea (Davenport et al., 1981). Specifically, a reduction in lung volume results in higher DIA activation (St.John and Zhou, 1990) and prolongation of inspiratory duration (Davenport et al., 1981) during breathing. Regarding our cough data, longer CT_I likely contributed to prolonged Tactive ($Tactive = CT_I + CT_{E1}$), which is consistent with their high correlation (under all 3 conditions; Table 3).

The present results demonstrate a weak relationship between CT_I and CT_{tot} , but strong relationships between CT_E and CT_{tot} . These results are consistent with the fact that CT_E is the largest governing component of CT_{tot} (Wang et al., 2009). However, when the ventilator provided tidal volume there was a reduction in the $CT_E - CT_{tot}$ relationship and surprisingly there was an increase of $CT_I - CT_{E1}$ relationship. A possible explanation for such substantial changes might be a stabilizing effect of controlled (and low) volume delivered to the lungs (the same volume provided each cough by the ventilator, unlike for control coughs).

When fast ventilator cycles were performed, there was an inhibition of the cough inspiratory and expiratory drive and reduced CT_I (earlier peak of DIA activity occurred). This resulted in reduced co-activation of DIA and ABD (Over), increased the duration from the DIA to ABD peaks (Dif), and a reduction in the peak inspiratory EP. Additionally, a slight negative swing on EP occurred frequently during the late inspiration (Figure 4), which is consistent with DIA inhibition and does not support the possibility of significant “volume adjustment” at the peak of the phase. In contrast, early over-inflation during cough did not result in inspiratory termination, as seen in breathing (Bishop, 1977; Ehrhardt et al., 2001). This may be due to the significantly increased motor drive during cough as compared to breathing. Lastly, we believe that the ventilator output resistance significantly contributed to prolonged CT_{E1} and unchanged maximum of EP (Figure 2; Table 2, see later discussion).

There were weak correlations between inspiratory and expiratory cough efforts, and very weak correlations between the cough volume, CT_I , and CT_E as were previously published (Bolser and Davenport, 2000; Wang et al., 2009). Weak correlations were also found in coughs, with fast cough volume delivered by ventilator, between CT_{E1} and amplitudes of DIA and ABD EMG, while no such relation was seen for other conditions (Table 3). Perhaps the reduction in amplitudes of cough ABD activity, accompanied by prolonged CT_{E1} ,

lowered the variability of these parameters. Of note, both ventilator conditions increased contribution of CT_{E1} to Tactive compared to controls.

The volume feedback mechanism is accomplished mainly by PSR (Clark and von Euler, 1972; Canning et al., 2006). PSR discharge is highly correlated with the airway smooth muscle tension (Bartlett et al., 1976; Sant'Ambrogio and Mortola, 1977), thus is also dependent on volume (static component) following pressure changes (rate of volume changes; dynamic component; Bishop, 1977; Davenport et al., 1981). Additionally, there are strong correlations among PSR discharge frequency, transpulmonary tracheal pressure, and volume during cough (Jakus et al., 1981; 1983), as well as ventilator induced inflations and deflations (Davis et al., 1956). The discharge of individual PSR may differ depending on their location (Schelegle, 2003); however, in the cat the majority of PSR reside in bronchi with only a very low portion located extrapulmonary (Sant'Ambrogio and Miserochi, 1973; Schelegle, 2003).

The importance of PSR during cough has been demonstrated by its inhibition after elimination of PSR activation by SO_2 in rabbits (Hanacek et al., 1984; Sant'Ambrogio et al., 1984). Although Romaniuk et al. (1997) and Kobayashi et al. (1992) employing end-inspiratory occlusions found no effect on the cough inspiratory or expiratory activity, our findings are consistent with altered cough efforts due to modified inspiratory cough volumes. The difference, and advantage, of our present experimental protocol is that volume is still increasing during the inspiratory phase (although altered) with adequate PSR activity (supposedly similar to that during loading in breathing; Davenport et al., 1981).

Stimulation of rapidly adapting (irritant) receptors and nodose ganglion C fibers during hyperinflation could also contribute to the present findings (Pack and DeLaney, 1983; Canning et al., 2006; Canning, 2010). However, C-fiber thresholds for mechanical activation are substantially higher than that of rapidly adapting receptors and slowly adapting PSR (Coleridge and Coleridge, 1984). We also cannot exclude a contribution of extravagal spinal afferent pathways from the thoracic and abdominal structures (Shannon and Freeman, 1981; Hernandez et al., 1989). In particular, stimulation of intercostal muscle tendon organs results in the inspiratory inhibition (Shannon, 1980; Shannon and Lindsey, 1987; Bolser et al., 1987). However, no excitatory influence of these afferents on expiratory neurons, driving pump muscles, have been reported (Shannon and Lindsey, 1987; Shannon et al., 1987; Hernandez et al., 1989). The PSR are likely the dominant factor in modulation of cough ABD (expiratory efforts) in this study; the contribution of other vagal and non-vagal afferents seems very limited.

Regardless of the spontaneous cough expirations (following ventilator guided inspirations) the ventilator itself added additional expiratory airflow resistance. We hypothesize, that this expiratory resistance modified PSR discharge resulting in CT_E prolongation (as seen during occlusion; Romaniuk et al., 1997). The ventilator expiratory resistance resulted also in higher maximum EP (without an increase in ABD activation) and some temporal cough changes, which are similar to those when cough expulsions were guided through the ventilator (Table 1). The volume related feedback during expiratory threshold loads and positive pressure inflations resulted in prolonged expiratory phase in breathing (Zechman et

al., 1976; Bishop, 1977; Koehler and Bishop, 1979; Davenport et al., 1981). Additionally, the ventilator controlled linear increase in the lung volumes that differed from the inhalation pattern during control coughs (i.e. early ramp like filling of lungs followed by fast ballistic-like inhalation; Wang et al., 2009, Figure 1; Simera et al., 2015, Figure 1) had no effect on inspiratory cough characteristics (Figure 2; Table 1).

In conclusion, multiple factors are likely involved in the shaping of the cough motor pattern. We propose significant contribution of the PSR discharge (both slowly and rapidly adapting) and volume related feedback, in general, in the forming of the cough motor output. This could be one of mechanisms in pathologic conditions (emphysema, bronchospasm, asthma, etc.), where volume feedback is altered, which can modify cough motor drives. It subsequently results in further changes of the airflow, resistance, and lung volume during coughing (affecting cough performance and its efficacy).

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Figure 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/or expiratory airflow resistance (provided by the expiratory ventilator circuit). Dashed waveforms represent (expected) regular lung volume during cough; solid waveforms are (expected) ventilator controlled lung volumes during cough inspirations. Wider cross-hatch areas denote (expected) variability and prolongation of the cough expiratory phase duration due to the additional expiratory airflow resistance (ventilator output). Please, note that when fast inflation were conducted expulsion did not begin in the middle of regular CTI, even though the inspirations became shorter (see Results).

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

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

Figure 2. The effects of ventilator controlled cough inflations and/or expiratory airflow resistance on coughing

A: Positive control coughs with cough volume delivered by the ventilator (expulsions through the ventilator output circuit).

B: Coughs with spontaneous inspirations and expulsions diverted through the ventilator output circuit.

C: Coughs with tidal volume delivered by the ventilator in the inspiratory phase of cough.

D: Coughs with cough volume delivered by the ventilator during the first half of cough inspiration.

E: expiration; res: airflow resistance; I: inspiration; CTI: cough inspiratory time; CV: cough volume; VT: tidal volume; CN: cough number; ABD: abdominal EMG amplitude; DIA: diaphragm EMG amplitude; EP E: expiratory esophageal pressure amplitude; EP I: inspiratory esophageal pressure amplitude; *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$

Figure 3. The effects of inhaled tidal volume (inspiratory resistance) on coughing

Upper section: four cough trials, where the 1st and the 4th trial is a control, the 2nd and the 3rd trial is that with tidal volume delivered by the ventilator. Low cough inspiratory volume resulted in increased cough motor drive. Lower section: expanded waveforms of ventilator controlled inspiration low volume cough (on the left hand side) and control cough (on the right hand side) - in both cases the 2nd cough was taken. Please, retain that the control is on the right. Intervals of altered temporal characteristics are depicted. The onset, maximum, and offset of cough related EMG activities determine the interval durations.

Int: integrated moving average; DIA: diaphragm EMG; ABD: abdominal EMG; EP: esophageal pressure; BP: arterial blood pressure; CT_{tot}: total cough cycle duration; TDIA: DIA activity duration; CTI: inspiratory phase duration; Tactiv: duration of all cough related EMG activity

Figure 4. The effects of cough volume delivered fast by the ventilator (early over inflation) on coughing

<Upper section: cough trial on the left hand side represent a control, the trial on the right hand side is with cough volume delivered by the ventilator during the 1st half of cough inspiration (note increases in EP early in inspiratory phase of coughs). Lower section: expanded waveforms of control (on the left hand side) and early overinflated coughs (on the right hand side). Intervals of significant temporal characteristics are depicted.

Int: integrated moving average; DIA: diaphragm EMG; ABD: abdominal EMG; EP: esophageal pressure; BP: arterial blood pressure; CTI: inspiratory phase duration; Over: overlap of DIA and ABD; Dif: interval between DIA and ABD maximum; CTE1: active portion of the cough expiratory phase

Table 1

Temporal parameters of cough, in which expirations were guided through the ventilator. Coughs with typical cough volume delivered by the ventilator during regular inspiratory time (on the left) and coughs with spontaneous inspirations and only expulsions diverted through the ventilator output circuit (on the right). Primary data in bold.

	Control Free cough	Ventilator CT _I , CV	Control Free cough	Free I Ventilator E
CT _I [s]	0.81±0.07	0.80±0.08	0.88±0.09	0.96±0.08 W
Dif [s]	0.26±0.01	0.30±0.02 *	0.21±0.01	0.24±0.01 **
CT _{E1} [s]	0.68±0.05	0.86±0.06 **	0.61±0.08	0.86±0.10 ***
CT _E [s]	1.39±0.21	1.76±0.37 * W	1.51±0.24	1.81±0.24
Over [s]	0.33±0.07	0.34±0.11	0.42±0.12	0.42±0.12
CT _{E2} [s]	0.71±0.22	0.90±0.36 W	0.89±0.23	0.95±0.22
CT _{tot} [s]	2.21±0.24	2.56±0.36 *	2.39±0.31	2.77±0.26
Tactive [s]	1.50±0.10	1.66±0.11 **	1.50±0.15	1.82±0.18 *
TDIA [s]	1.00±0.07	1.01±0.11	1.01±0.10	1.11±0.09 W
TABD [s]	0.84±0.10	0.99±0.10 **	0.90±0.19	1.14±0.19 **
eleABD [s]	0.41±0.07	0.43±0.08	0.49±0.12	0.51±0.12
desABD [s]	0.43±0.04	0.55±0.04 **	0.41±0.09	0.63±0.11 **

CT_I: the duration of cough inspiratory phase; CV: cough volume; I: inspiration; E: expiration; Dif: duration between diaphragm and abdominal discharge maxima; CT_{E1}: duration of active expiratory phase; CT_E: duration of total expiratory phase; Over: duration of diaphragm and abdominal activities overlap; CT_{E2}: quiescent expiratory period; CT_{tot}: total cough cycle duration; Tactive: duration of all cough related EMG activity; TDIA: duration of cough diaphragm activity; TABD: duration of cough abdominal activity; eleABD: elevating segment of abdominal activity; desABD: descending segment of abdominal activity; W: Wilcoxon matched paired test;

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$

Table 2

Temporal parameters of coughing during ventilator guided inflations (low vs. fast). Primary data in bold.

	Control Free Cough	Ventilator CTI, VT	Control Free Cough	Ventilator CT _I / 2, CV
CT _I [s]	0.93±0.14	1.03±0.15 *	1.04±0.11	0.81±0.10 *
Dif [s]	0.25±0.01	0.27±0.02	0.24±0.01	0.30±0.01 **
CT _{E1} [s]	0.63±0.06	0.77±0.07	0.69±0.06	0.88±0.06 ***
CT _E [s]	1.39±0.14	1.62±0.19	2.00±0.33	2.59±0.67 W
Over [s]	0.30±0.06	0.30±0.07	0.35±0.09	0.24±0.07 *
CT _{E2} [s]	0.76±0.17	0.86±0.21	1.31±0.36	1.71±0.70 W
CT _{tot} [s]	2.29±0.20	2.70±0.21 **	3.03±0.37	3.40±0.64
Tactiv [s]	1.52±0.15	1.84±0.20 **	1.72±0.14	1.69±0.15
TDIA [s]	1.11±0.13	1.25±0.15 *	1.20±0.11	0.98±0.11
TABD [s]	0.74±0.10	0.85±0.09	0.88±0.15	0.96±0.13
eleABD [s]	0.36±0.06	0.36±0.07	0.43±0.09	0.38±0.08 *
desABD [s]	0.38±0.05	0.49±0.05	0.45±0.06	0.58±0.06 *

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

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$

Table 3

Selected positive correlations of the cough data – squares of Pearson's coefficient r^2 are listed.

		ABD	CT _I	CT _{E1}
ABD	Control		0.44 *	0.02
	Ventilator tidal volume		0.17	<0.01
	Ventilator cough volume		0.11	0.39
Tactive	Control	0.39	0.88 ***	0.30
	Ventilator tidal volume	0.05	0.94 ***	0.85 **
	Ventilator cough volume	0.25	0.88 **	0.68 *

ABD: amplitudes of cough abdominal EMG; CT_I: cough inspiratory phase; CT_{E1}: cough active expiratory phase; Tactive: the duration of all cough related EMGs; control: coughs under control conditions; Ventilator tidal volume and Ventilator cough volume: coughs with tidal volume delivered in inspiratory cough phase and coughs with cough volume delivered during the first half of cough inspiratory phase, respectively;

* P 0.05;

** P 0.01;

*** P 0.001 for the slope difference from 0