Effects of Bronchial Intermittent Constrictions on Explosive Flow during Coughing in the Dogs

Naoki Hayama, Tetsuri Kondo, Ichiro Kobayashi, Gen Tazaki, and Kenji Eguchi

Department of Medicine, Tokai University School of Medicine, Isehara, 259–1193 Japan

Abstract: This study tested the hypothesis that intrathoracic bronchi intermittently constrict during coughing and attempted to elucidate the effect on explosive flow. The subjects were 21 dogs that underwent tracheostomy. In the first group (n=7), the diameter of the fifth-generation bronchus was measured with a balloon-tipped catheter and the change during coughing was analyzed. In the other group (n=14), the dogs were vagotomized and coughing was simulated by sequential application of positive and negative airway pressures (sham cough). The effects of the bronchial constriction, elicited by the stimulation of vagus efferent fibers, on explosive flow and airway pressure of sham cough were analyzed. The bronchus was constricted in explosive phase of spontaneous coughing in all the dogs of the first group. When cough bouts were repetitively developed, bronchial constriction and phrenic burst developed simultaneously. The intermittent bronchial constrictions fused and virtually acted as tonic constriction. In the second group of dogs, the explosive flow of sham cough consisted of two phases; a short bout followed by a near-constant flow. When the bronchus was constricted, the explosive flow was still biphasic in 12 dogs and an exponential decay pattern formed in 2 of them. In these 12 dogs, the peak explosive flow slightly but significantly decreased (mean±SD, 1.39±0.23 vs. 1.34±0.23 l/s) and airway pressure in the segmental bronchus became smaller (−1.18±0.53 vs. −0.15±0.94 cmH₂O). We concluded that intermittent bronchial constrictions act as tonic one during coughing. Bronchial constriction slightly decreased the peak explosive flow and moved the choke point to the proximal airway. [The Japanese Journal of Physiology 53: 71–76, 2003]

Key words: vagus nerve, airway pressure, control of respiration.

Though cough is a non-respiratory event, it shares both neuronal mechanisms [1, 2] and respiratory muscles with those for respiration. The bronchus also participates in cough response as a pathway for gas conduction. The relationship between airway constriction and coughing has long been a matter of interest for physicians and physiologists. For example, cough is the most common symptom of patients with bronchial asthma, which is characterized by contraction of the airway smooth muscle. Numerous studies concerning the mechanism of cough in asthmatic patients have been published [3]. However, recent investigations on bronchial asthma revealed that the major parts of bronchoconstriction and airway narrowing can be mediated with chemical substances [4]. Thus, the older studies of cough in asthmatic patients should be reevaluated. Many physiologists have observed that some stimuli that provoke coughing fail to elicit bronchoconstriction [5, 6]. Separation of the mechanisms of cough response and reflex bronchial constriction is an example of physiological interest [7].

It has been reported that the tracheal smooth muscle contracts tonically during coughing [3, 8] and such contraction is thought to be partially a response to tonic inputs from the airway receptors [8, 9]. In a previous study, we observed that tracheal constriction during coughing included an intermittent component and that intermittent constriction developed in synchrony with phrenic nerve activity [8]. Since innervation, architecture and medullary neurons to the trachea and bronchus are distinct [10], whether intermittent constriction occurs in the intrathoracic bronchi re-
mains to be investigated. In the present study we hypothesized that the intrathoracic bronchus also constricts during coughing because its caliber is controlled by respiratory-related descending commands [11, 12]. Since the intermediate-size bronchus is the major part to generate airway resistance, constriction of this size of bronchus may control airflow during coughing. Thus, we analyzed the effects of bronchial constriction on explosive flow during coughing.

MATERIALS AND METHODS

Subjects were 21 beagle dogs (5–12 kg in weight). In seven of them, coughing commanded by the central neuronal structure were analyzed (group A). In the remaining 14 dogs (group B), coughing was simulated by sequential application of positive and negative pressures to the airway, i.e., sham cough. Gas flow and pressure in the segmental bronchus were analyzed during sham coughing. This study was approved by the Animal Ethics Committee of Tokai University School of Medicine.

The experimental setup was similar to that in a previous study [12]. In brief, decerebration was made by transection of the mid-brain at the rostral margin of the superior colliculi. Then the dogs were placed in a supine position and a tracheostomy was conducted in the lower neck. Respiratory flow \( (\dot{V}) \) was measured with a pneumotachometer (TV122T, Nihon Kohden, Tokyo, Japan) connected to the tracheal tube. A special tracheal connector was made to stimulate tracheal bifurcation without disturbing airflow measurement [8].

In group A dogs, activity of the proximal end of the transected phrenic nerve was continuously measured (PNA). Tension of the tracheal smooth muscle (7tr) was measured with an isometric transducer (TB611T, Nihon Kohden) after longitudinally cutting the anterior 3rd through 8th tracheal cartilaginous rings. One end of the dorsal tracheal smooth muscle was tied to a rod with 4 silk strings and the other end was connected to the transducer [11, 12]. Bronchial dimension (Pbr) was measured with a donut-shaped balloon-tipped catheter [12] implanted in the fifth-generation bronchus of the right lower lobe. The pleural pressure (Ppl) was also measured with an esophageal balloon. In group B dogs, tracheal pressure (Ptr), Ppl, and intramural pressure in the fifth-generation bronchus of the right lower lobe (Pseg) were measured.

After recording the parameters during spontaneous respiration, the dogs were paralyzed with pancuronium bromide (2.0 mg/kg/h). We made a partial arterial-venous bypass to maintain blood gases without using mechanical ventilation. Venous blood was withdrawn from the bilateral femoral veins and right subclavian vein, oxygenated with a blood oxygenator (D-705, Medifilo, Dideco, Mirandra, Italy), and then projected by a pulsating pump (1421, Harvard, Southnatick, MA, USA) into the aortic arch through the right subclavian artery. Before starting extracorporeal circulation, dogs were mechanically ventilated (613, Harvard) with 100% O₂. This procedure provided complete immobilization with steady \( P_{a\text{CO}_2} \) and pH and \( P_{a\text{O}_2} > 150 \text{mmHg} \) for least 20 min [11].

During extracorporeal circulation, coughing was provoked by mechanical stimulation of tracheal bifurcation in the group A dogs.

In the group B dogs, bilateral vagus trunks were transected and then positive and negative pressures were sequentially applied to the airway through the tracheal tube (sham cough). This simulation method has been used by several authors [13, 14]. To simulate an inspiratory phase of coughing, positive airway pressure (10 cmH₂O) was initially applied for 3–5 s, and then the airway pressure was suddenly switched to \( -40 \text{cmH}_2\text{O} \) (simulation of explosive phase of coughing). Negative pressure was maintained for 8 s. To provoke bronchoconstriction, distal ends of the bilateral vagus nerves were stimulated at the onset of positive pressure application with train pulses (30 Hz, 40 V, 1 ms, duration 13 s). The same procedure was repeated without stimulation of the vagus efferent fibers. The stimulus intensity was decided to give the maximal tracheal constriction referring to our previous study [8].

All the data are expressed as mean±SD. Statistical analyses were performed by Student’s paired t-test. A \( p \) value less than 0.05 was considered to indicate statistical significance.

RESULTS

Figure 1 shows a cough accidentally developed during spontaneous respiration in a non-paralyzed dog. In each inspiratory phase of quiet breathing, \( P_{br} \) deflected downward. Bronchial dilation, i.e., \( P_{br} \) deflection, developed almost in parallel with \( P_{pl} \) changes during early-inspiratory through mid-inspiratory phases, suggesting that bronchial dilation was provided by lung inflation driven by negative \( P_{pl} \). However, in late-inspiratory through expiratory phases, there was an apparent difference between \( P_{pl} \) and \( P_{br} \). In the late-inspiratory phase, \( P_{pl} \) continued to drop in a negative direction while \( P_{br} \) returned to positive. In the expiratory phase, \( P_{pl} \) immediately returned to the zero level and remained at there while \( P_{br} \), once it
reached the positive peak gradually returned to the zero the level. During spontaneous coughing, indicated by the arrow, patterns of change in $P_{br}$ and $P_{pl}$ were similar to those seen during quiet breathing. In the explosive phase, the $P_{br}$ and $P_{pl}$ reached the maximum level at the same time, suggesting that positive changes in $P_{br}$ reflected by bronchial compression are caused by change in $P_{pl}$. Soon after reaching the peak, $P_{br}$ returned to zero, suggesting that the bronchus lacked the tonic component of constriction. This pattern of bronchial constriction was seen in all group A dogs.

Figure 2 shows coughing provoked by mechanical stimulation of tracheal bifurcation in a paralyzed dog and its blood gases were maintained with extracorporeal circulation. In this particular dog, activity of the abdominal nerve (ANA) was recorded using a pair of fine-wire electrodes. $T_{tr}$, tension of the tracheal smooth muscle; $P_{br}$, bronchial constriction measured with balloon-tipped catheter; PNA, phrenic nerve activity.

Fig. 2. A cough provoked by mechanical stimulation of tracheal bifurcation in a paralyzed dog and its blood gases were maintained with extracorporeal circulation. In this particular dog, activity of the abdominal nerve (ANA) was recorded using a pair of fine-wire electrodes. $T_{tr}$, tension of the tracheal smooth muscle; $P_{br}$, bronchial constriction measured with balloon-tipped catheter; PNA, phrenic nerve activity.

data strongly suggested that the response was a cough [1]. During and after stimulation, activities of the phrenic and abdominal nerves became larger. The bronchus constricted intermittently in synchrony with each phrenic bursts. This type of bronchial intermittent constriction during coughing was observed in five out of the six dogs analyzed. It should be noted that bronchial constrictions were superimposed on the previous ones during coughing. As a result, the peak of $P_{br}$ during coughing was always higher than that during spontaneous respiration. Figure 3 shows the peak values of bronchial constrictions during coughing expressed as times of those during spontaneous respira-

In group B dogs, cough was simulated by the sequential application of positive and negative pressures to the airway. Figure 4 shows examples of changes in $P_{tr}$, $P_{pl}$, $P_{seg}$, and $V$ of the sham cough with (Fig. 4B) and without vagal nerve stimulation (Fig. 4A). When positive pressure ($13.9 \pm 3.4 \text{ cmH}_2\text{O}$) was applied to the airway, $P_{tr}$ gradually increased and reached a steady level in a few seconds. By switching airway pressure from positive to negative ($-43.5 \pm 10.4 \text{ cmH}_2\text{O}$), $P_{tr}$ decreased to the maximum negative level within 1.0 s, kept this level for $\sim 0.8$ s, and then returned to the zero level. In $P_{seg}$, trace negative deflection developed approximately 0.8 s after the application of negative airway pressure and this deflection suggested transmission of negative $P_{tr}$ to the distal bronchus. During the application of positive airway pressure, $V$ changed steeply to the negative maximum and then gradually decreased with a long-time constant ($>5$ s). Immediately after switching the airway pressure from positive to negative, an explosive expi-
Cough-related flow developed. The pattern of explosive flow was consistent with that in a previous report [14]. It consisted of: (1) An ascending part until peak flow was reached, (2) A first descending part, (3) A plateau with a negative slope, (4) A second, steeper descending section, and (5) A final plateau part with small flow. The explosive flows in group B dogs were classified as typical “plateau pattern” in 12 dogs while for two dogs the descending part was “exponential decay pattern.”

When bilateral vagus efferent fibers were stimulated during the sham coughing (Fig. 4B), \( P_{pl} \) and \( P_{seg} \) traces changed remarkably. In the \( P_{pl} \) trace, a small hump appeared at the onset of vagal stimulation, which represented contraction of the esophageal smooth muscle, and thus \( P_{pl} \) was no longer an indicator of pleural pressure in this condition. The negative deflection of \( P_{seg} \) markedly and significantly diminished \((-1.18 \pm 0.53 \text{ vs. } -0.15 \pm 0.94 \text{ cmH}_2\text{O})\) during sham coughing with vagal nerve stimulation.

\( P_{tr} \) did not change with vagal nerve stimulation. Furthermore, the time course of \( \dot{V} \) did not change in the inspiratory phase of sham coughing, but some changes were observed in the expiratory phase. In one dog whose explosive flow was the plateau pattern in the cough without vagal stimulation, an exponential pattern formed while vagal nerves were stimulated. In the remaining 11 dogs, explosive flows during vagal stimulation were classified as plateau pattern. However, among these 11 dogs, one dog in one out of five trials developed an exponential decay pattern. When vagus efferent fibers were stimulated, the peak explosive flow became slightly smaller and the duration of the “plateau” phase was shortened.

Figure 5 shows the changes in explosive flow parameters for 14 dogs during sham coughing with or without vagal stimulation (Cont). Mean and SDs are drawn in the figure.
Bronchial Constriction during Cough

was significantly shorter than that without stimulation (0.37±0.17 s vs. 0.43±0.14 s). The decrease in peak of plateau phase flow during stimulation did not reach statistical significance (1.01±0.20 l/s vs. 1.06±0.25 l/s).

DISCUSSION

In the present study we found that the bronchial caliber represented by \( P_{br} \) was intermittently narrowed during the coughing. Such bronchial constrictions were synchronized with phrenic bursts. Individual constrictions fused and acted as a tonic constriction. The bronchial constriction caused a slight decrease in peak explosive flow. The analysis of \( P_{seg} \), i.e., intramural pressure of fifth-generation bronchus, further suggested that bronchial constriction moved the choke point of the explosive flow to the proximal site of the airway.

Analysis of short term-changes in bronchial caliber is difficult in alive animals because respiratory motions considerably interfere with the analysis. In a previous study, we completely eliminated respiratory motions using extracorporeal circulation and found that the bronchus rhythmically constricted in phase with respiratory rhythm [12]. The present study showed that the bronchus constricted intermittently in phase with phrenic burst during coughing as well. The intermittent constrictions fused and actually acted as tonic constriction. The behavior of bronchial constrictions was quite similar to that in acute hypercapnia observed in the previous study [12]. In that study both the trachea and bronchus constricted tonically but bronchial tonic constriction was the summation of a few rhythmic constrictions. Usually the cough response consists of a few bouts and thus both the trachea and bronchus practically continuously constrict during cough response. This speculation is supported by a report by Tomori and Widdicombe [15], who reported that airway resistance increased during mechanically provoked cough in paralyzed and artificially ventilated cats. The present study directly showed an indirect presentation of constriction of the intrathoracic bronchi during coughing.

The cough shares its neuronal mechanisms with respiration but precise integration in the central architecture is not yet clear. Jakus et al. [16] reported that medullary inspiratory and expiratory neurons are sequentially activated during mechanically provoked cough. Bastel [17] analyzed medullary neuronal activities during electrically provoked sneeze in cats. He suggested that many expiratory neurons were activated before an increase in pleural pressure. Shannon et al. [1] and Bakey et al. [2] further investigated neural relationships among respiratory neurons in the ventral medulla during fictive cough. They proposed that the pattern of cough is generated by a network of these neurons. The pulmonary branch of the vagus nerve, which controls the bronchial caliber, is projected from the ventral neurons [18], but the relation between these neurons and respiratory-related neurons remains to be investigated.

To investigate the function of bronchial constriction, we compared the flow and intra-luminal pressure during simulated coughing with and without vagal stimulation. Patterns of \( P_{aw} \) and \( V \) of sham cough were consistent with those reported during human coughing [19–21] or simulated coughing [14]. During the stimulation of vagus efferent fibers, the peak explosive flow slightly but significantly decreased and the duration of plateau phase shortened significantly. In two dogs, the flow pattern changed from plateau to exponential decay while the vagus nerves were stimulated. These findings suggested that bronchial constriction had a small but significant effect on explosive flow during coughing. The reduction of the peak expiratory flow may be attributed to narrowing of the large airway because stimulation of the cervical vagus nerves excited both pulmonary branches of the vagus nerves and recurrent laryngeal nerves.

It is possible that extreme lung deflation and vagal nerve stimulation facilitated the release of catecholamines from adrenal medulla. Leff et al. [22] have reported that intrinsic catecholamines have a significant effect on contraction of the airway smooth muscle. In this study adrenectomy had not been done and thus our results may include effects of intrinsic catecholamines.

Pedersen et al. [14] measured the airway pressure of sham coughing in the dog model. They found that the choke point existed in the caudal trachea at the onset of cough, moved more caudally during coughing and abruptly jumped to the segmental bronchi at the end of the plateau phase [14]. In the present study, when the bronchus was not constricted, \( P_{seg} \) was negative at the middle phase of explosive flow suggesting that there was a pressure gradient between the trachea and peripheral bronchus. In contrast, when the bronchus was constricted, \( P_{seg} \) became much less negative suggesting that bronchial constriction moved choke point to the more proximal airway. Such excursion of the choke point may shorten the distance between the airway opening and choke point, and thus augment the pressure gradient in proximal airways. We speculated that excursion of the choke point has a function to facilitate airway clearance in larger air-
ways. Thoracic volume decreases during coughing and the airway narrowing produced by lung deflation may also have an effect on choke point [21]. Our speculation does not conflict with this hypothesis. Since either during sham coughing with or without vagal nerve stimulation lung deflation level was the same in this study, the effect of bronchial constriction on the choke point may be independent of lung inflation.

It should not be forgotten that the plateau phase shortened, and in some instances, the flow pattern changed from plateau to exponential during bronchial constriction. O’Donnel et al. [23] analyzed flow–volume curve in patients with bronchial asthma. They reported that the plateau phase in flow–volume disappeared after challenge with bronchoconstrictive agents. This report suggests that excessive bronchial constriction reduces expiratory flow, both at its peak and in the middle phase of expiration. The mechanism of expiratory flow limitation in cough response is thought to be the same as that in forced expiration. Therefore, excessive bronchial constriction during coughing may also deteriorate the explosive function of the cough. We presume that there are some neuronal mechanisms that balance expiratory forces and bronchial caliber during coughing. Finally, although in vivo studies simulate exact cough, there are numerous limitations we should be careful of when applying experimental results to real cough.

In conclusion, this animal study revealed that bronchial smooth muscle intermittently constricted in synchrony with individual bursts of cough. Such constrictions fused and acted as a tonic constriction, which slightly decreased peak explosive flow and moved the choke point to proximal airway.

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Sciences and Technology of Japan (No. 13670618).

REFERENCES