Coughing induced by airway irritation modulates the sensation of air hunger

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The aim of this study was to clarify whether coughing elicited by airway irritation can modulate the sensation of air hunger. Using a visual analog scale (VAS), we measured air hunger for 30 s following breakpoint of a breath-hold in healthy young subjects who were asked to resume their breathing according to four patterns (free breathing, citric acid inhalation, voluntary cough, and panting) before and/or after airway anaesthesia. We also measured air hunger for citric acid-induced coughing and voluntary coughing without the preceding breath-holding. The free breathing after breakpoint of breath-holding causes an immediate relief of air hunger (VAS median values at 5, 15 and 25 s after breath-hold: 39, 0 and 0), whereas voluntary coughing causes a delay in the relief of air hunger (67, $P < 0.05$; 17, $P < 0.05$; and 0, NS) and a slower relief occurred during citric acid-induced coughing (81, $P < 0.01$; 49, $P < 0.05$; and 12, $P < 0.05$). Conversely, the voluntary coughing and citric acid-induced coughing *per se* failed to induce air hunger. Inhalation of lidocaine aerosol completely abolished the cough response to citric acid inhalation causing an immediate relief of air hunger, whereas airway anaesthesia alleviated only slightly the air hunger during voluntary coughing. The changes in air hunger during the panting were similar to those during the voluntary coughing observed before airway anaesthesia and were not affected by airway anaesthesia (VAS at 15 s point before *versus* after anaesthesia: 18 *versus* 15; NS). Coughing induced by airway irritation *per se* does not generate the sensation of air hunger but can aggravate it, presumably by vagally mediated mechanisms and/or central mechanisms.

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It is generally accepted that the vagus nerve plays a significant role not only in generation of cough reflex but also in modulation of respiratory sensations. For example, while mechanical stimulation of the large airway can easily elicit cough reflex (Sant'Ambrogio & Widdicombe, 2001), mechanical or electrical stimulation of the large airways is perceived as irritating, tickling, uncomfortable, or painful (Morton *et al.* 1950). Dyspnoea with coughing is a devastating symptom observed frequently in patients with severe cardiopulmonary disorders as well as in patients with advanced cancers. Although the precise origin of dyspnoea remains unknown, it is quite possible that the vagal afferents may greatly contribute to its generation and modulation. In fact, it is generally accepted that stimulation of pulmonary stretch receptors probably decreases the sensation of dyspnoea (Manning *et al.* 1992). Compared with the contribution of pulmonary stretch receptors to modulation of dyspnoea, relatively little is known as to the contribution of vagal irritant receptors and vagal C-fibre receptors, stimulation of which is known to induce defensive airway reflexes including cough reflex.

Recent evidence shows that dyspnoea is a multidimensional sensation that may include several different respiratory sensations such as a sensation of air hunger, a sensation of work/effort, and a sensation of chest tightness (American Thoracic Society, 1999). Among these sensations, the sensation of air hunger appears to be the most threatening sensation that is felt at the end of a long breath-hold.

It is a common clinical observation that in patients with dyspnoea the sensation of dyspnoea is aggravated by coughing (Grandas *et al.* 2005). However, to our knowledge there has been no study showing the severity or extent of this problem. Moreover, mechanisms responsible for the aggravation of dyspnoea with coughing have not been explored. We hypothesized that the aggravation of dyspnoea during coughing may be due to the aggravation of air hunger brought about by some vagally mediated mechanisms.

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The purpose of the present study was to clarify whether the vagally mediated cough reflex can modulate the sensation of air hunger. Results of our study might provide a clue for inferring the possible mechanisms responsible for the aggravation of dyspnoea with coughing. We studied changes in relief of air hunger immediately after the breaking point of breath-holding when the subjects resumed their breathing according to four patterns (free breathing, citric acid inhalation, voluntary cough and panting) with or without airway anaesthesia. We also measured air hunger for citric acid-induced coughing and voluntary coughing without the preceded breath-holding.

Methods

Studies were carried out in 58 young healthy subjects (46 males and 12 females) whose ages ranged from 22 to 34 year. The subjects were medical college students with no prior clinical training. Their average heights and weights were 169.8 ± 6.8 cm and 62.4 ± 8.8 kg (mean ± S.D.), respectively. The study protocols were approved by the Institutional Ethical Committee of Chiba University, which conforms to the standard set by the *Declaration of Helsinki* (last modified in 2004) of the World Medical Association. Each subject gave informed consent to the methodology of the study. None of them was a current smoker or was aware of the hypothesis tested in the studies.

The subjects were tested in the sitting posture. They breathed through an experimental apparatus containing a face mask, a pneumotachograph, and a T piece system supplied with 100% oxygen. Details of the experimental setup are given elsewhere (Nishino *et al.* 2000). In brief, ventilatory airflow was measured with the pneumotachograph (CP-100; Allied Health Care Product Inc., St Louis, MO, USA), and tidal volume (V_T) was obtained by electrical integration of the inspired flow signal. Mask pressure (P_{mask}) was measured with a pressure transducer (Transpac IV; Abbott Critical Care Systems, Chicago, IL, USA). End-tidal carbon dioxide tension (P_{ETCO_2}) was measured with an infrared CO_2 analyser (NEC-Sanei-1H21A, Tokyo, Japan) through a port in the face mask.

Each subject was asked to rate continuously the intensity of sensation of air hunger, which was defined as the sensation of respiratory discomfort developed during breath-holding by using a visual analog scale (air hunger VAS). The analog scale consisted of a horizontal 10 cm line with equally spaced markers. The subjects could control the position of the knob of the linear potentiometer along this line. The numerical VAS value of zero indicated 'none', and 100 indicated a sensation of 'intolerable discomfort'. During the experiments, airflow, V_T, P_{mask}, P_{ETCO_2} and the VAS score were all recorded on a thermal array recorder (Omniace RT 3424; NEC, Tokyo, Japan) and stored on a magneto-optical disk for later analysis of the data with a computer program (Omni Win RT34–704; NEC).

The experimental protocols are described below.

Experiment 1

In this experiment studies were carried out in 22 (15 male and 7 female) subjects. The subjects were given a short training period to accustom them to the apparatus, changes in respiratory sensation, and the use of the VAS while performing two or three preliminary trials of maximum breath-holding.

When all of the respiratory variables were stable after the preliminary trials of breath-holding, the subject was asked to stop breathing at end-expiration and to hold his or her breath for as long as possible while rating continuously the sensation of air hunger using the VAS. At the breaking point of breath-holding, the subject resumed spontaneous breathing while rating continuously the sensation of air hunger for 30 s (free breathing trial). After completion of this control breath-holding trial, two additional experimental trials were performed with an interval of 5–7 min. In these trials, the subject either inhaled citric acid aerosol (the acid inhalation trial) or performed voluntary coughing (the voluntary coughing trial) immediately after the breaking point in a random order. Citric acid aerosol was delivered for 20 s by an ultrasonic nebuliser (Soniclizer 305, Atom Medical Co., Tokyo, Japan) at maximum output (6 ml min^{-1}) after placing 20 ml of a 30% w/v solution of citric acid in a nebulizing chamber. The voluntary coughing was started at the breakpoint by experimenter's signal and continued for 20 s. The pattern of coughing was left to the subjects, but the subject was instructed to maintain the strongest cough until the signal for its cessation. The subject was also instructed to rate continuously the sensation of air hung during inhalation of citric acid aerosol and during voluntary coughing.

Immediately after each experimental trial, the subjects were asked to assess their ability to use the VAS to indicate the intensity of the sensation of air hunger.

Experiment 2

The effects of coughing on air hunger VAS without the preceded breath-holding and the effects of airway anaesthesia on coughing and air hunger VAS were evaluated separately in an additional 21 (18 male and 3 female) subjects. In this experiment, the free breathing trial was performed first, and then either inhalation of citric acid aerosol or voluntary coughing was performed for 20 s with an interval of 5–7 min without the

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preceding breath-holding when the subject was breathing spontaneously. Then, 10 ml of 4% lidocaine was nebulized with an ultrasonic nebuliser (Omron NE-U07, Tokyo, Japan) and the subjects breathed the aerosol from a mouth-piece for 10 min while they were instructed to take slow, deep breaths. Immediately after the completion of inhalation of lidocaine aerosol, the three experimental trials including the free breathing trial, voluntary coughing trial, and acid inhalation trials were performed in the same manner as in protocol 1. After these trials, the subject inhaled citric acid aerosol again to confirm the effectiveness of airway anaesthesia.

Experiment 3

In addition to the aforementioned experiments, another series of experiment was conducted in an additional 15 (13 male and 2 female) subjects. Following breakpoint of a breath-hold, the subjects were asked to resume their breathing according to three patterns (free breathing, voluntary cough, and volitional panting without the explosive flows associated with coughing) while rating air hunger VAS. The rationale for conducting this experiment was to see how the breathing pattern having small V_T that is different from the coughing pattern can influence the air hunger intensity after the breakpoint of breath-holding. Like the voluntary coughing, the panting was started at the breakpoint by the experimenter's signal and continued for 20 s. The pattern of panting was left to the subject, but the subject was instructed to maintain very rapid, shallow breathing without taking deep breaths until the signal for its cessation. The experimental trials were repeated after the completion of airway anaesthesia performed in the same manner as in Experiment 2.

Data analysis

The values of air hunger VAS obtained at 5, 15 and 25 s after the breakpoint of breath-holding were analysed by comparisons of different conditions. The changes in air hunger VAS were also evaluated by calculating the area under the curve (AUC_{VAS}) by the trapezoidal method over the period of the first 30 s after the breakpoint of breath-holding.

AUC_{VAS} describes the integrated air hunger intensity such that the greater the value of ACU_{VAS}, the greater the air hunger sensation.

Data on the respiratory variables after the breakpoint of breath-holding were analysed by comparisons of 10 s intervals during 30 s immediately after the breakpoint. Data were expressed as median (interquartile range), and statistical analysis was performed by the use of Friedman's repeated measures ANOVA followed by Student–Newman–Keuls test and a signed rank test. $P < 0.05$ was considered significant.

Results

Experiment 1

All subjects tolerated the inhalation of 30% citric acid aerosol and completed the experimental protocol. All subjects showed vigorous cough responses to inhalation of citric acid aerosol, which lasted for longer than 20 s.

The maximal breath-holding times in the three experimental trials were as follows (median (interquartile range)): free breathing, 55 s (48–62 s); voluntary coughing, 58 s (46–75 s); and citric acid inhalation, 61 s (54–73 s). There were no significant differences among these values. The air hunger VAS always reached a value of 100 at the breakpoint of breath-holding.

Figure 1 shows experimental records illustrating changes in respiratory variables and VAS score before, during and after breath-holding in a single subject. In the free breathing trial (Fig. 1*A*), the air hunger VAS gradually increased during breath holding and finally reached a maximum value of 100 at the breaking point of breath-holding. Upon the resumption of breathing, the air hunger VAS rapidly decreased. In the voluntary coughing trial (Fig. 1*B*) and the acid inhalation trial (Fig. 1*C*), the rise in air hunger VAS was similar to that observed in the control trial whereas in both these trials the decrease in air hunger VAS after the breaking point was much slower than that observed in the free breathing trial, indicating the slow relief of the air hunger sensation.

Changes in respiratory variables after the resumption of breathing are summarized in Table 1. In the free breathing trial, the resumption of breathing started with hyperpnoea consisting mainly of large V_T breaths. The ventilatory activity decreased progressively in time. In contrast, both in the voluntary coughing trial and in the acid inhalation trial, the resumption of breathing started with a burst of coughing, the breathing pattern of which can be characterized by a high frequency with a relatively small V_T. No significant differences were observed in the values of peak expiratory flow ($\dot{V}_E$), V_T and f in the first 20 s after the breakpoint of breath-holding between the voluntary coughing trial and the acid inhalation trial, indicating that the coughing pattern during the voluntary coughing trial is quite similar to that of involuntary coughing induced by inhalation of citric acid. During the irregular patterns of breathing associated with the act of coughing, the values of P_{ETCO_2} were either similar to or slightly lower than the corresponding values of P_{ETCO_2} in the free breathing trial, indicating that relative hypoventilation did not occur during the act of coughing.

The changes in air hunger VAS score obtained from all subjects after the breaking point are shown in Fig. 2. Although the air hunger VAS after the breakpoint of breath-holding rapidly decreased in all three experimental trials, there was a difference in the rapidity of relief among the three trials. The values of air hunger VAS in the

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Table 1. Changes in respiratory variables before and after breaking point (Experiment 1: $n = 22$)

	Baseline	0–10 s	10–20 s	20–30 s
Free breathing				
V_T (l)	0.69 (0.63–0.78)	1.45 (1.32–1.73)	1.08 (0.89–1.31)	0.97 (0.82–1.09)
f (bpm)	14.3 (12.5–15.5)	13.5 (12.0–16.4)	14.8 (13.7–17.4)	14.8 (12.9–17.1)
$\dot{V}_I$ (l min^{-1})	10.2 (8.5–10.7)	23.2 (17.4–25.1)	16.5 (14.0–18.0)	13.1 (12.0–17.1)
P_{ETCO_2} (mmHg)	40.0 (38.9–41.0)	45.4 (42.7–48.8)	42.5 (39.6–44.1)	42.3 (40.3–44.0)
Voluntary coughing				
V_T (l)	0.69 (0.63–0.80)	0.75 (0.60–0.95)*	0.76 (0.49–1.02)*	1.09 (0.90–1.23)
f (bpm)	14.5 (13.1–15.2)	33.2 (28.0–48.0)*	36.0 (24.0–42.8)*	19.0 (17.0–23.1)*
$\dot{V}_I$ (l)	9.8 (8.6–11.0)	24.4 (19.8–31.0)	24.4 (18.6–30.2)*	20.7 (17.6–25.2)*
Peak V_E (l s^{-1})	nd	3.502.60–4.50	3.15 (2.4–4.1)	nd
P_{ETCO_2} (mmHg)	40.0 (39.0–41.1)	44.1 (41.3–48.7)	36.6 (31.6–42.0)*	39.0 (34.3–40.6)*
Citric acid inhalation				
V_T (l)	0.70 (0.61–0.82)	0.66 (0.50–0.89)*	0.59 (0.46–0.93)*	0.63 (0.50–1.00)*
f (bpm)	13.6 (12.5–15.4)	31.5 (27.3–42.0)*	28.3 (23.1–36.0)*	25.2 (18.8–32.3)*
$\dot{V}_I$ (l)	10.2 (8.9–11.0)	22.9 (15.3–29.6)	19.2 (13.2–22.5)	17.1 (13.2–25.0)
Peak $\dot{V}_E$ (l s^{-1})	nd	3.50(2.90–4.4)	3.30 (2.9–4.2)	nd
P_{ETCO_2} (mmHg)	40.0 (38.0–41.0)	46.8 (43.0–50.1)	39.8 (38.2–43.0)	40.2 (36.1–42.4)

*$P < 0.05$, compared with the corresponding values of free breathing; nd: not determined.

free breathing trial were significantly lower ($P < 0.05$) than those in the acid inhalation trial at 5, 15 and 25 s after the breakpoint of breath-holding (VAS at 5, 15, 25 s points: free breathing 39 (0–70), 0 (0–0), 0 (0–0), *versus* citric acid inhalation 81 (65–93), 49 (29–74), 12 (0–44)) and were also significantly lower ($P < 0.05$) than those in the voluntary coughing trial at 5 and 15 s points (voluntary coughing 67 (47–90), 17 (0–50), 0 (0–2)), indicating that

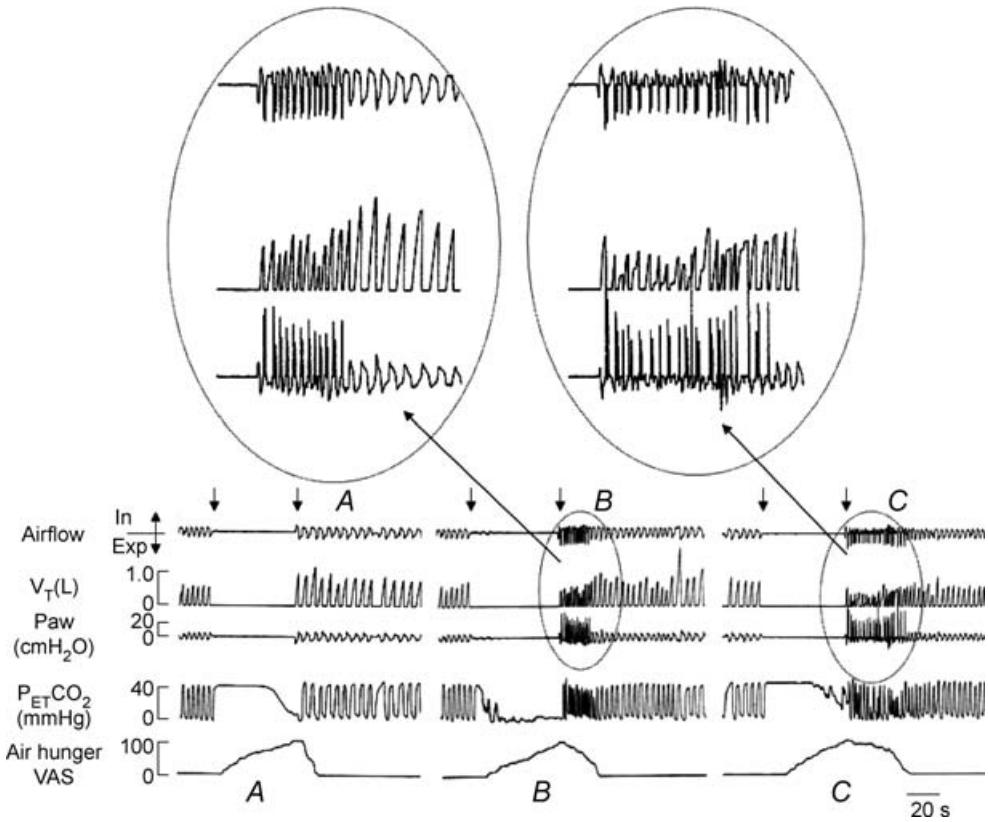


Figure 1. Experimental recordings illustrating changes in respiratory variables and the VAS score: free breathing trial (*A*), voluntary coughing trial (*B*) and acid inhalation trial (*C*)
Arrows indicate the start and end of breath-holding. Insets: magnified recordings of respiratory variables during coughing trials.

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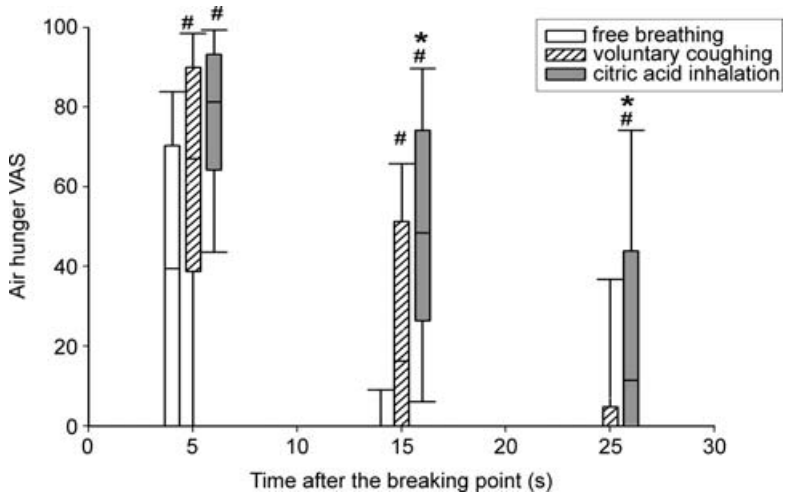


Figure 2. Changes in the air hunger VAS after the breakpoint of breath-holding
#$P < 0.05$, significantly different from the corresponding values in the free breathing trial. *$P < 0.05$, significantly different from the corresponding values in the voluntary coughing trial.

the relief occurred more rapidly in the free breathing trial than in the coughing trials. Comparison between the voluntary coughing trial and the acid inhalation trial showed that there was no significant difference in the value of air hunger VAS at 5 s after the breakpoint of breath-holding. However, the values of air hunger VAS at 15 and 25 s after the breakpoint of breath-holding were significantly higher ($P < 0.05$) in the acid inhalation trial than in the voluntary coughing trial, indicating that the relief occurred more slowly during the citric acid-induced coughing than during the voluntary coughing. The values of AUC_{VAS} after the breakpoint of breath-holding in the voluntary coughing trial (969 (605–1408) VAS s) were also significantly greater than those in the free breathing trial (545 (250–775), $P < 0.01$) but significantly smaller than those in the acid inhalation trial (1500 (975– 1980), $P < 0.01$).

Experiment 2

When the effects of coughing on air hunger VAS were evaluated without the preceding breath-holding, none of 21 subjects had the sensation of air hunger either during voluntary coughing or during citric acid-induced coughing (Fig. 3).

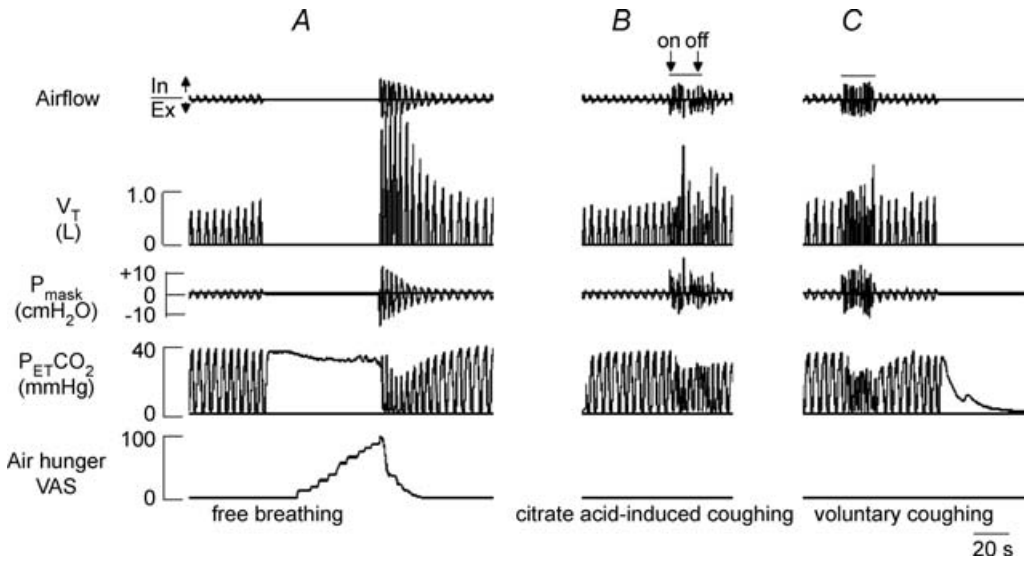


Figure 3. Experimental recordings illustrating changes in respiratory variables and the VAS score after breath-holding, during voluntary coughing, and during citric acid inhalation
A, the subject resumed free breathing at the breakpoint of breath-holding. *B*, inhalation of citric acid aerosol was started at arrow and continued for 20 s. *C*, the subject started voluntary coughing and continued it for 20 s. These experiments were conducted to see whether coughing or inhalation of citric acid aerosol can directly generate the sensation of air hunger.

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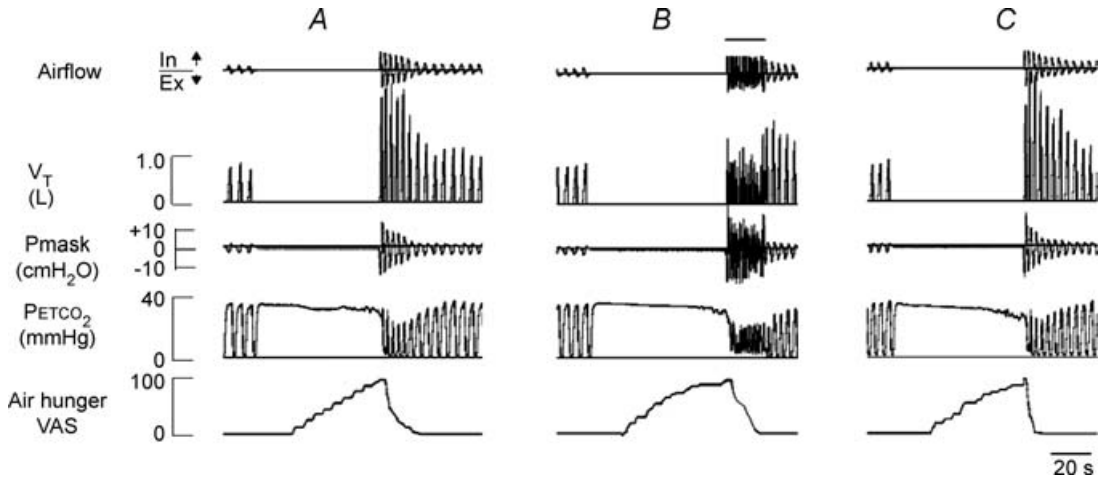


Figure 4. Experimental recordings illustrating changes in respiratory variables and the VAS score during the post-breath-holding period after airway anaesthesia
A, free breathing trial; *B*, voluntary coughing trial; *C*, citric acid inhalation trial. Horizontal bar indicates the duration of voluntary coughing. Note that coughing cannot be induced by inhalation of citric acid aerosol.

Figure 4 shows experimental records illustrating changes in respiratory variables and VAS score after airway anaesthesia during the free breathing trial (Fig. 4*A*), voluntary coughing trial (Fig. 4*B*), and acid inhalation trial (Fig. 4*C*) in a single subject. Changes in respiratory variables and air hunger VAS during the free breathing after airway anaesthesia (Fig. 4*A*) were almost identical to those observed during the free breathing before airway anaesthesia (Fig. 3*A*). The response of coughing was never observed in acid inhalation trial, indicating that airway anaesthesia by lidocaine completely abolished the cough response. Although a rapid relief of air hunger was evident in all three trials (Fig. 5), the values of air hunger VAS in the voluntary coughing trial at the 5 s point (79 (67–91)) were significantly higher ($P < 0.05$) than the corresponding values of free breathing (41 (16–48)) and citric acid inhalation trials (33 (21–45)). There were no significant differences in the values of air hunger VAS at 15 and 25 s points among the three different conditions. The values of AUC_{VAS} in the voluntary coughing (860 (815–1049)) were also greater than those in the acid inhalation trial (498 (405–614); $P < 0.01$).

Changes in respiratory variables after the resumption of breathing under airway anaesthesia condition are summarized in Table 2. There was no significant difference in the values of V_T and f in the first 30 s after the break-point of breath-holding between the free breathing trial and acid inhalation trial. Compared with these trials, the values of V_T were significantly smaller and the values of f were significantly higher in the first 20 s after the break-point of breath-holding in the voluntary coughing trial.

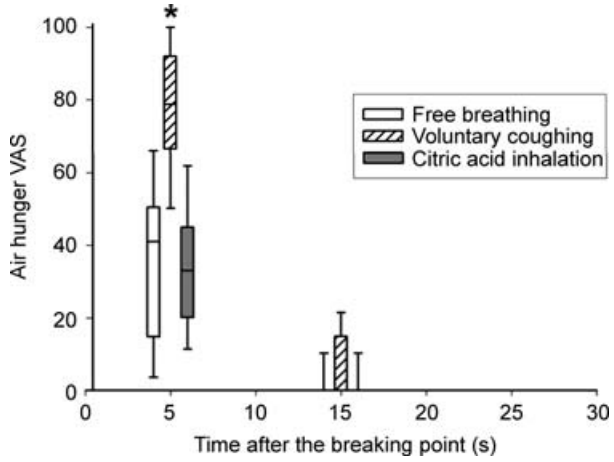


Figure 5. Changes in the air hunger VAS score after airway anaesthesia
*$P < 0.05$, significantly different from the corresponding values in the free breathing and voluntary coughing trials.

Experiment 3

Figures 6 and 7 show changes in respiratory variables and VAS score during free breathing, voluntary coughing, and panting before and after airway anaesthesia. Among these three trials, the decrease in air hunger VAS before airway anaesthesia was slower in the panting and voluntary coughing trials than that in the free breathing trial (Figs 6*A* and 7). The air hunger VAS at 5 s point (76 (66–85)) was not affected by airway anaesthesia (72 (65–79)) in voluntary coughing trial but the VAS at the 15 s point (20 (11–30)) decreased after airway anaesthesia (0 (0–15); $P < 0.05$). Accordingly, the values of AUC_{VAS} during voluntary coughing after airway anaesthesia (900 (779–982)) were significantly smaller than those before airway anaesthesia (1036 (917–1233); $P < 0.05$). By contrast, the changes in air hunger intensity in the panting trial were not affected by airway anaesthesia (VAS at 5, 15,

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Table 2. Changes in respiratory variables after breaking point under airway anaesthesia (Experiment 2: $n = 21$)

	Baseline	0–10 s	10–20 s	20–30 s
Free breathing				
V_T (l)	0.67 (0.64–0.74)	2.01 (1.48–2.56)	1.27 (1.07–1.61)	0.99 (0.81–1.23)
f (bpm)	13.5 (11.5–14.7)	18.0 (13.5–22.2)	15.7 (12.6–18.3)	14.9 (13.0–16.3)
$\dot{V}_I$ (l)	9.2 (7.7–10.0)	37.8 (25.6–48.7)	18.4 (16.6–26.1)	14.4 (10.8–18.0)
P_{ETCO_2} (mmHg)	38.3 (36.7–39.8)	43.7 (41.1–44.7)	38.1 (36.9–39.7)	38.0 (36.5–40.3)
Voluntary coughing				
V_T (l)	0.65 (0.62–0.74)	0.88 (0.67–1.05)*	0.80 (0.67–0.95)*	1.22 (1.02–1.36)*
f (bpm)	13.3 (11.4–15.3)	33.3 (2.92–43.3)*	32.3 (24.5–40.0)*	16.3 (13.1–17.8)
$\dot{V}_I$ (l min^{-1})	9.0 (7.4–10.5)	30.9 (20.5–40.3)	23.1 (17.7–37.1)	23.1 (17.7–37.0)*
P_{ETCO_2} (mmHg)	38.0 (37.0–39.3)	42.7 (38.7–45.9)	33.5 (32.0–37.7)*	35.0 (33.0–37.1)*
Citric acid inhalation				
V_T (l)	0.70 (0.64–0.75)	1.89 (1.43–2.30)	1.29 (1.08–1.59)	1.11 (0.78–1.31)
f (bpm)	13.5 (11.0–15.0)	19.8 (16.3–22.6)	16.4 (15.0–18.6)	15.0 (13.1–17.5)
$\dot{V}_I$ (l min^{-1})	9.1 (7.8–10.8)	36.8 (28.3–49.0)	20.6 (17.9–32.8)	18.6 (9.8–21.9)
P_{ETCO_2} (mmHg)	38.0 (37.0–39.6)	43.8 (42.0–45.3)	37.7 (35.3.-38.6)	37.7 (36.0–40.5)

*$P < 0.05$, compared with the corresponding values of free breathing trial.

25 s point before *versus* after airway anaesthesia: 73 (65–75) *versus* 67 (61–79), 18 (9–30) *versus* 15 (9–23), 0 (0–0) *versus* 0 (0–0); AUC_{VAS} before *versus* after airway anaesthesia: 923 (859–1155) *versus* 888 (857–1064); $P > 0.1$).

Changes in respiratory variables after the resumption of breathing are summarized in Table 3. The breathing pattern in the voluntary coughing trial and the panting trial was characterized by a high respiratory frequency with

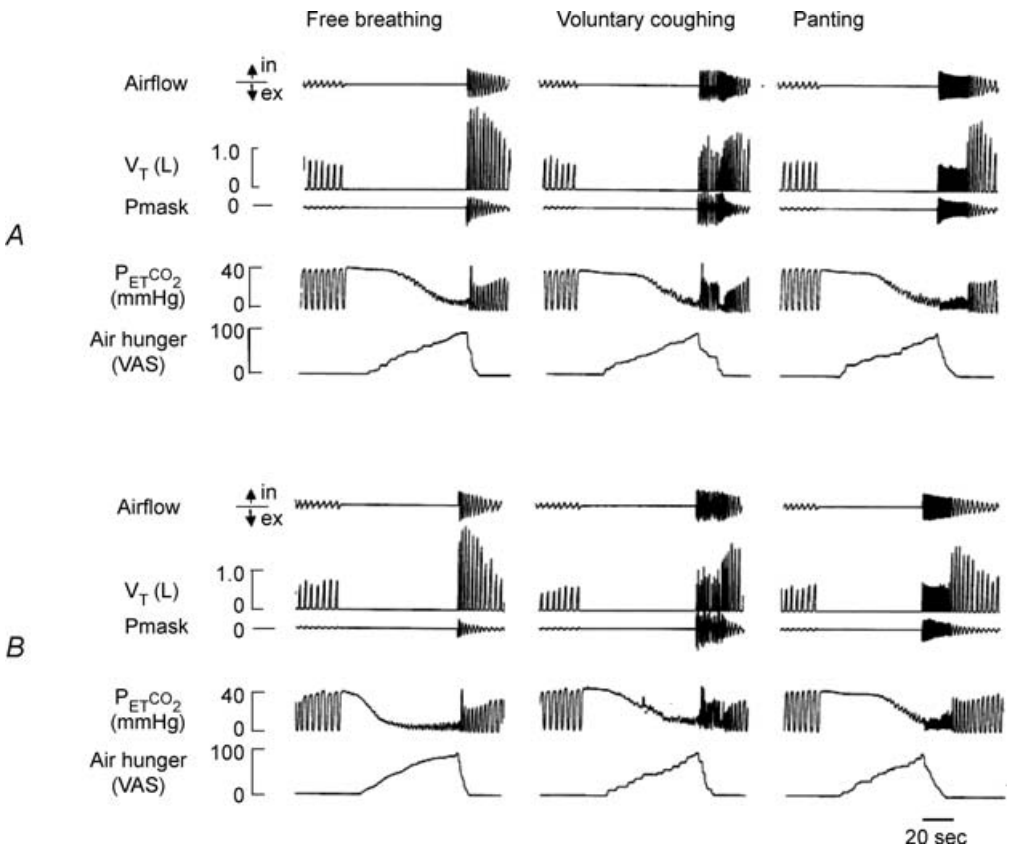


Figure 6. Experimental recordings illustrating changes in respiratory variables and VAS score during free breathing, voluntary coughing, and panting before and after airway anaesthesia
A, before airway anaesthesia; *B*, after airway anaesthesia

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Table 3. Changes in respiratory variables after breaking point before and after airway anaesthesia (Protocol 3: $n = 15$)

	Before airway anaesthesia			After airway anaesthesia		
	0–10 s	10–20 s	20–30 s	0–10 s	10–20 s	20–30 s
Free breathing						
V_T (l)	1.80 (1.53–2.20)	1.40 (1.00–1.58)	0.97 (0.77–1.20)	1.70 (1.38–2.14)	1.19 (1.00–1.85)	0.97 (0.77–1.28)
f (bpm)	20.8 (14.4–21.8)	17.0 (14.6–18.9)	14.0 (13.5–15.8)	21.0 (14.3–22.4)	17.0 (14.7–18.5)	14.5 (13.5–16.0)
$\dot{V}_I$ (l)	37.8 (23.8–47.6)	19.0 (15.4–36.4)	12.8 (10.2–17.3)	35.7 (20.7–53.4)	18.2 (14.4–36.4)	12.8 (10.2–17.9)
P_{ETCO_2} (mmHg)	43.0 (38.5–47.5)	33.1 (31.9–42.2)	36.5 (34.7–39.3)	42.5 (38.5–45.9)	34.7 (33.1–40.4)	36.5 (34.7–39.3)
Voluntary coughing						
V_T (l)	0.68 (0.50–0.95)*	0.69 (0.54–0.80)*	1.05 (0.80–1.20)*	0.74 (0.51–0.88)*	0.80 (0.48–0.86)*	1.15 (0.79–1.30)
f (bpm)	32.0 (29.5–35.0)*	32.5 (27.0–37.6)*	18.7 (16.5–25.1)	34.4 (30.0–42.9)*	33.0 (24.0–40.0)*	18.2 (16.5–24.0)
$\dot{V}_I$ (l min^{-1})	22.5 (18.5–26.8)*	20.9 (16.8–26.5)	19.7 (14.9–27.6)	24.8 (17.8–35.5)	22.8 (16.8–29.8)*	16.8 (13.1–33.4)*
P_{ETCO_2} (mmHg)	40.0 (35.9–42.3)	32.3 (30.0–37.4)*	34.6 (31.8–36.8)	40.7 (38.0–46.1)	33.0 (27.4–36.2)	34.2 (29.5–36.5)
Panting						
V_T (l)	0.40 (0.38–0.59)*	0.39 (0.31–0.55)*	1.01 (0.85–1.37)	0.41 (0.33–0.60)*	0.38 (0.35–0.60)*	1.15 (0.94–1.40)
f (bpm)	96.4 (86.0–120)*	93.5 (74.0–110)*	18.0 (15.0–21.9)	98.0 (85.0–120)*	87.8 (80.0–100)*	18.0 (15.4–20.2)
$\dot{V}_I$ (l min^{-1})	48.6 (38.4–54.9)*	37.5 (34.1–43.2)*	18.1 (14.1–27.0)	45.3 (38.4–50.4)*	37.3 (35.0–48.8)*	21.7 (14.2–25.9)*
P_{ETCO_2} (mmHg)	nd	nd	32.0 (30.0–39.9)	nd	nd	32.0 (30.6–40.4)

*$P < 0.05$, compared with the corresponding values of free breathing trial. nd: not determined.

a relatively small V_T. This characteristic breathing pattern was more evident in the panting. During the panting, the accurate measurement of P_{ETCO_2} was not practical since the respiratory frequency was too high to detect the accurate levels of end-tidal P_{CO_2}.

Discussion

This study demonstrated that the resumption of free breathing after the breaking point of a breath-hold immediately causes the relief of air hunger whereas coughing can cause a delay in the relief of air hunger after the breaking point of breath-holding, regardless of whether it is a voluntary coughing or a citric acid-induced coughing. Furthermore, we also demonstrated that the delay in the relief of air hunger is more prominent with the citric acid-induced coughing than with the voluntary coughing. Our results are in agreement with the common clinical observation that coughing aggravates dyspnoea when coughing and dyspnoea coexist. Our findings that neither voluntary coughing nor citric acid-induced coughing without the preceding breath-holding generates any sensation of air hunger suggests that stimulation of mechanoreceptors from the chest wall and the lungs alone may not be associated with generation of air hunger although the stimulation of these receptors can modulate

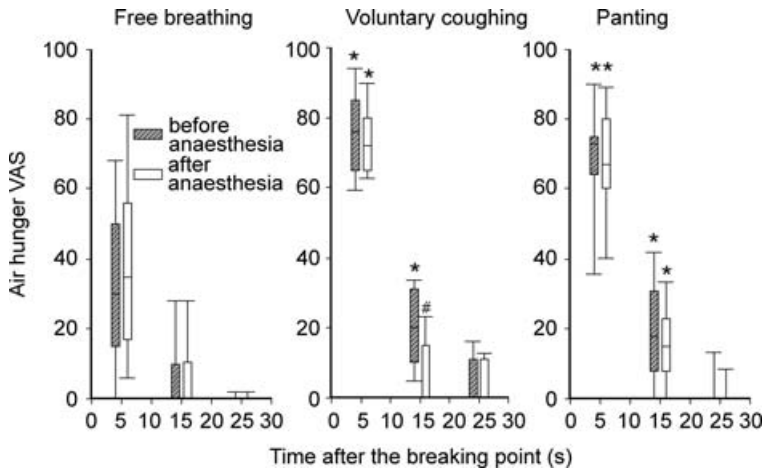


Figure 7. Changes in air hunger VAS during free breathing, voluntary coughing and panting before and after airway anaesthesia

*$P < 0.05$, significantly different from the corresponding values in the free breathing; #$P < 0.05$, significantly different from the corresponding values before airway anaesthesia.

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the sensation of air hunger only in the presence of air hunger.

There are several possible mechanisms that may explain why the presence of cough can modulate the sensation of air hunger in the immediate post-breath-holding period. First, coughing may cause a delay in improvement of blood gases, particularly hypercapnia which has been known to cause air hunger (Banzett *et al.* 1989; Banzett *et al.* 1990), for it is possible that the act of coughing may disturb adequate ventilation, causing a slow recovery from hypercapnia developed during breath-holding. Our results showed no sign of relative hypoventilation during the period of coughing immediately after the breakpoint of breath-holding. In addition, considering the delays to circulatory times from lung to chemoreceptors and CO_2 equilibration at chemoreceptor sites (Gelfand & Lambertsen, 1973), it is quite unlikely that the slow recovery from hypercapnia is the main mechanism responsible for the delay in the relief of air hunger during coughing. In fact, Banzett (1996) studied the time course of air hunger ratings in response to step changes in P_{ETCO_2} and demonstrated that the median best half-time during hyperoxia was 52 s, suggesting that the speed with which air hunger changes following a sudden change in P_{ETCO_2} is quite slow. Second, coughing was characterized by irregular breathing patterns consisting of a relatively small tidal volume with high respiratory frequency. The relatively small V_T in the immediate post breath-holding period may contribute to the less rapid and smaller relief of air hunger, since the small V_T may cause less excitation of pulmonary stretch receptors which probably play the most important role in alleviation of air hunger immediately after the breakpoint of breath-holding (Flume *et al.* 1994). Third, the act of coughing, particularly the explosive flows associated with coughing may cause excitation of chest wall mechanoreceptors, which in turn may contribute to the delay in the relief of air hunger after the breaking point of breath-holding. In this connection, it has been shown that mechanical vibration of the chest wall reduces the sensation of dyspnoea when the vibration is applied in phase with the respiratory cycle whereas out of phase vibration increases the dyspnoeic sensation (Homma *et al.* 1984). However, a recent study by Bloch-Salisbury *et al.* (2003) demonstrated that chest wall vibration does not relieve air hunger during breath-holding or mechanical ventilation, suggesting that mechanoreceptors from the chest wall may not modify the sensation of air hunger. In addition, Banzett *et al.* (1990) studied changes in the respiratory sensation during total neuromuscular block in mechanically ventilated subjects and concluded that respiratory muscle contraction is not important in the genesis of air hunger evoked by hypercapnia. Fourth, some airway receptors stimulated directly by irritants or indirectly by the act of coughing may modulate the sensation of air hunger. Among several airway receptors that transmit information to the central nervous system, vagal irritant receptors and vagal C-fibre receptors are known to respond to a variety of mechanical and chemical stimuli, causing coughing and bronchoconstriction (Widdicombe, 1995, 2001). Considering that pulmonary vagal afferents project to the sensorimotor cortex (Balzamo *et al.* 1990), it is not surprising that afferent information from these receptors can modulate the sensation of air hunger which is generated as a result of the cortical procession of respiratory afferent signals. Citric acid inhalation can induce coughing probably due to excitation of both the vagal irritant receptors and C-fibre receptors (Morice *et al.* 1992), but voluntary coughing may also stimulate these receptors due to mechanical stimulation. Therefore, it is possible that the act of coughing by itself may stimulate the vagal irritant receptors and/or C-fibre receptors, which counteract the dyspnoea-relieving effect of pulmonary stretch receptors and cause the delay in the relief of air hunger. In accordance with this notion, our results demonstrate that airway anaesthesia not only abolishes the cough response to citric acid inhalation but also nearly eliminates the delay in the relief of air hunger associated with coughing. In contrast, we found that the rapid and substantial relief in air hunger after breakpoint of breath-holding during free breathing is not affected by airway anaesthesia, suggesting the intact activity of pulmonary stretch receptors after airway anaesthesia. Since vagal irritant receptors lie in the epithelial layer of airway wall while pulmonary stretch receptors are believed to lie deeper in the airway wall, and probably within the bronchial smooth muscle layer (Sant'Ambrogio, 1982), it may be possible to speculate that vagal irritant receptors can be more easily blocked than pulmonary stretch receptors by airway anaesthesia. This possibility is compatible with the findings that the air hunger sensation during the panting was not affected by airway anaesthesia whereas the air hunger sensation during the voluntary coughing was reduced by airway anaesthesia. However, there is no clear evidence to show that in humans nebulized local anaesthetics can exert an effect of differential blockade on different types of vagal receptors. Thus we are not sure whether the activity of pulmonary stretch receptors remains intact after the application of nebulized lidocaine.

The results of additional experiments (Experiment 3) not only confirmed the effect of airway anaesthesia on the air hunger during the coughing but also showed that the panting similarly caused a slight delay in the relief of air hunger with or without airway anaesthesia. These findings support the idea that the small V_T does contribute to the maintenance of unrelieved sensation of air hunger immediately after the breakpoint of breath-holding.

Our finding that the delay in the relief of air hunger is more prominent during the citric acid-induced coughing than during the voluntary coughing may not be explained

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by the difference in coughing patterns between the two different types of coughing since both types of coughing consisted of a surprisingly similar breathing pattern characterized by a rapid breathing frequency with a relatively small V_T. The most plausible explanation for the difference in air hunger ratings between the two types of coughing is that citric acid can activate the vagal afferents which voluntary coughing does not. A recent study by Canning *et al.* (2004) showed the presence of a subpopulation of myelinated, capsaicin-insensitive polymodal afferent neurons that are not readily classified as either a vagal irritant or C-fibre receptor in guinea pig airways. These nervous receptors are relatively insensitive to mechanical stimulation and smooth muscle constriction but are easily activated by acid in a rapidly adapting manner. However, in human airways the presence of such vagal afferents remains to be elucidated. An alternative explanation for the difference in air hunger ratings between the citric acid-induced coughing and voluntary coughing is that the vagal irritant receptors and C-fibre receptors may be activated more during citric acid-induced coughing than during voluntary coughing.

Finally, the role of central respiratory motor behaviour in the relief of air hunger has to be considered. Since the sensation of air hunger was sustained when the act of coughing or panting was present, one might speculate that the act of coughing or panting produced by descending respiratory motor behaviour sustains a sensation of air hunger after breath-holding. In other words, the sustained sensation of air hunger during coughing or panting may be a central effect rather than peripheral. Our findings showed that both the voluntary coughing and panting had a rapid, shallow type of breathing pattern and similarly caused a slight delay in relief of air hunger immediately after breakpoint of breath-holding. Although the sustained air hunger may be explained by the lack of pulmonary stretch receptor activity due to the absence of deep breaths during voluntary coughing and panting, it is also possible to assume that neural behaviours that sustain the rapid, shallow breathing may cause the subject to have a sensation of unrelieved air hunger.

In conclusion, our results show that coughing induced by airway irritation can aggravate the sensation of air hunger. This aggravation of air hunger might be brought about by vagally mediated mechanisms but central mechanisms cannot be ruled out.

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