An Increase in the Threshold of Citric Acid–Induced Cough during Chest Wall Vibration in Healthy Humans

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Abstract: This study tested the hypothesis that the afferent input from the respiratory muscles may be involved in the neural mechanisms inducing cough responses. Coughing was evoked in conscious healthy humans by the inhalation of citric acid aerosol of several concentrations either during or not during chest wall vibration (100 Hz) at the right second intercostal space or during vibration of the right thigh. The mean threshold citric acid concentration to induce coughing was significantly higher during chest wall vibration (geometric mean, 131.8 mg/ml)

than without vibration (75.9 mg/ml). Vibration after topical anesthesia of the chest wall skin did not significantly change the threshold concentration of citric acid. The threshold citric acid concentration during vibration of the right thigh did not significantly differ from that without vibration. We concluded that inputs from the chest wall afferent, presumably from the intercostal muscle or costovertebral joint, may have an inhibitory effect on the initiation of coughing at the higher neural structure in conscious humans. [Japanese Journal of Physiology, 48, 341–345, 1998]

Key words: muscle spindle, control of respiration, defense reflex.

Coughing is a major symptom of respiratory diseases; thus a self-excitation mechanism of cough response has been speculated. In the previous animal study [1], we evoked the cough response by mechanical stimulation of the tracheal bifurcation in a decerebrated dog and found that the intensity of cough decreased after muscular paralysis. From this finding, we suspected that input from the muscles, presumably from the respiratory muscles, may facilitate the cough response. However, since the muscular paralysis profoundly changed the respiratory pattern of the experimental animal, the cough evoked after muscular paralysis was also altered. Furthermore, general anesthesia or decerebration in animal studies had a strong influence on the intensity and probability of occurrence of cough responses. Therefore it was very hard to study the role of muscular input in the cough response. In contrast, in the clinical investigations [2, 3] a determination of cough threshold to inhaled citric acid aerosol has been widely accepted. With these reasons, we investigated the role of input from the respiratory muscles on citric acid–induced cough by modulating muscular input by vibration in conscious human subjects.

SUBJECTS AND METHOD

Subjects were 24 conscious healthy males and females. Their ages ranged from 22 to 31, except for 2 subjects who were 35 and 45. Nine were smokers, but none reported productive cough or expectoration. None had suffered from a common cold at least 1 week before the study. They were asked to be enrolled in the study after being given a detailed explanation of the study design, but none were informed of the expected results.

The experiment was conducted on four separated days, and each session was actually conducted as a randomized cross-over study design. Coughing was induced by inhalation of citric acid aerosol of several concentrations either during or not during chest wall vibration. On the first test day ($n=20$), the subjects deeply inhaled physiological saline 10 times from a jet nebulizer (Pari-boy, Germany). Then they inhaled aerosol of citric acid solved in physiological saline (10 mg/ml) under the same procedure. The concentration was increased twofold, each time, that is, 20 mg/ml, 40 mg/ml, and so on. There were 3 min of in-

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interval between the inhalation tests of either concentration. If one cough developed during inhalation, the concentration was regarded as a threshold of coughing [2]. Once a threshold had been determined, the subject was encouraged to try inhaling twofold of the threshold concentration. With this "above threshold" test we were able to avoid erroneous determination of the threshold because of an accidental development of a cough. If a cough did not develop, the inhalation test was repeated with double the concentration of aerosol until the maximum concentration was reached (640 mg/ml).

On the second test day ($n=11$), the threshold of citric acid-induced cough was again determined during chest wall vibration. Vibratory stimulus (frequency 100 Hz, amplitude 3 mm; Power Panavibrator EV226, Panasonic) was continuously applied during the inhalation at the right second intercostal space in the parasternal region. In this region, Homma *et al.* [4] and Homma [5] reported that sustained vibration (100 Hz) increased electromyographic activity of the underlying intercostal muscles in the conscious human subject while phase-limited vibration shortened inspiratory duration. The vibrator was always held by another person.

On the third test day ($n=7$; two subjects were the same as in the second test day), the threshold of citric acid-induced cough was determined during the chest wall vibration at least 30 min after topical anesthesia of the chest wall skin by using lidocaine tape (Penles, Lederle). All the subjects reported that they felt no sensations of light touch and pain over the area of skin anesthesia.

On the fourth test day ($n=8$), the threshold of citric acid-induced cough was determined during continuous vibration on the right quadriceps femoralis muscle, that is, the nonrespiratory muscle.

The threshold was expressed as logarithmic concentration [2]. The logarithmic thresholds were analyzed by a Wilcoxon's single-rank nonparametric test for paired results. A $p<0.05$ was considered significant.

RESULTS

Figure 1 shows the threshold of citric acid-induced cough (log scale) before and during upper chest wall vibration. In 6 of the 11 subjects, the threshold of cough increased, and in the remaining 5 it did not increase during chest wall vibration. The geometric mean of the cough threshold during chest wall vibration (131.8 mg/ml) was significantly higher than without vibration (75.9 mg/ml).

Figure 2 shows the threshold of cough during chest

Fig. 1. Threshold citric acid concentration to induce cough before (CONTROL) and during chest wall vibration (VIBRATION). The geometric mean ($\pm$ SD) of the threshold during vibration was significantly higher than without vibration.

Fig. 2. Threshold citric acid concentration to induce cough during chest wall vibration before (VIBRATION) and after topical anesthesia of the skin (ANESTHESIA + VIBRATION). The geometric means ($\pm$ SD) of the thresholds in both conditions were exactly the same.

wall vibration before and after topical anesthesia of the skin of vibrated portion. The threshold did not change in three subjects, decreased in two, and increased in two. However, in these three subjects, the changes of the threshold concentration were not twice or half of those before anesthesia. The geometric means of the threshold during vibration before and after skin anesthesia were the same (144.5 mg/ml). Thus the threshold during chest wall vibration was still high even after skin anesthesia. This finding sug-

Fig. 3. Threshold citric acid concentration to induce cough before (CONTROL) and during vibration of the right quadriceps muscle (LEG VIBRATION). The geometric mean ($\pm$ SD) of the threshold during vibration was not significantly different from that without vibration.

gested that the vibration-induced elevation in cough threshold may not be caused by input from the cutaneous receptors.

Figure 3 shows the threshold of cough before and during vibration of the right quadriceps muscle. The threshold increased by thigh vibration in three subjects, decreased in three, and did not change in two. The geometric mean of the threshold during leg vibration (63.1 mg/ml) was not significantly different from that without vibration (69.2 mg/ml).

Although each pair of the sessions was conducted as a randomized cross-over method on the same subjects, we were unable to apply each session to all the subjects. However, the mean thresholds of the control data in two independent sessions (that is, 75.9 mg/ml in the chest wall vibration and 63.1 mg/ml in the leg vibration) were not significantly different. The mean thresholds during the chest wall vibration in two independent sessions (that is, 131.8 mg/ml in the chest wall vibration and 144.5 mg/ml in topical anesthesia of the skin) were also not significantly different.

DISCUSSION

We found that the threshold of citric acid-induced cough increased during upper chest wall vibration but not during leg vibration. This finding suggested that upper chest wall vibration had an inhibitory effect on cough initiation. In contrast, the threshold of cough during the chest wall vibration was not changed by topical anesthesia of the skin. This finding further

suggested that receptors in the skin have no effect on the inhibitory mechanism of chest wall vibration. Coughing is a nonrespiratory response, but it shares many of the neural and other structures concerned with respiration [6]. An intimate relationship between the control of coughing and that of respiration has been reported [7]. Since the depth and rhythms of respiration are strongly influenced by input from the receptors in the respiratory muscles [8], it is reasonable to expect that coughing is also influenced by input from the respiratory muscles.

It is speculated that a facilitation of coughing may occur in the interaction between the airway receptors and airway smooth muscle [9]. However, only a few investigators [10, 11] have explored involvement of the respiratory muscles in the facilitation mechanism of coughing. In our previous study [1], we evoked a cough by mechanical stimulation of the tracheal bifurcation in decerebrated and tracheostomized dogs and found that the strength of fictive cough estimated by phrenic neurogram decreased after muscular paralysis. However, we failed quantitative analysis of this observation because the animals' respiratory patterns had been profoundly changed after muscular paralysis. In contrast, in the clinical investigations [2, 3] a determination of cough threshold to inhaled citric acid aerosol has been widely accepted. Citric acid stimulates bronchial C-fiber endings [12] or rapidly adapting receptors [13] via changes in extracellular pH. The citric acid-induced cough has a good reproducibility in the threshold [14]. In this study we applied this method to conscious human subjects and altered the input from muscular afferent by sustained vibration of the respiratory muscles.

Vibration of the respiratory muscles has significant effects on activity of the respiratory neurons [5, 15]. Vibration stimulates several neural receptors. For example, input from muscle spindles augments activity of the stimulated respiratory muscle as a tonic vibration reflex [4], and it also changes the duration of inspiration presumably via supraspinal mechanism [15]. Input from the costovertebral joint either augments or inhibits inspiration, depending on the vagus nerve input [16]. Cutaneous receptors also have an excitatory response on the respiratory muscle activity [17]. Among these inputs, involvement of the cutaneous receptors may be excluded by the experiment of topical anesthesia on the vibrated skin. However, we did not discriminate whether afferent inputs from muscle receptors or joint receptors decreased the threshold of cough response.

In animal studies, the respiratory rate increased during sustained intercostal muscle vibration [18], but

it decreased when the animals had been vagotomized [8, 16]. The latter finding suggests that sustained intercostal muscle vibration inhibits inspiration in a vagotomized animal. Since the vagus nerve plays little role in the control of quiet respiration in humans [19], sustained chest wall vibration may have inhibited inspiration in our study. As we have reported previously, there is an intimate relationship between the phase of respiration and that of coughing [7], and such synchronizing mechanism must exist in the brain stem neural network [7]. Although this study gave no precise mechanism of inhibitory effect of chest wall vibration on coughing, we speculate that inspiratory inhibition induced by chest wall vibration may suppress cough response.

Vibration of the nonrespiratory muscle did not change the mean threshold of cough. However, this result does not deny any influence of afferent inputs from the leg muscles on cough threshold. In Fig. 3, we can see that the threshold extremely increased, that is, by two steps of the citric acid concentration, in one subject and decreased in the other. Such a large change may not be an accidental phenomenon. It has been reported that input from leg muscle receptors changes the activities of respiratory neurons [20] and the autonomic nervous system [21]. However, since our study was conducted on only a few subjects and with a simple experimental setup, we were unable to analyze the role of input from the nonrespiratory muscles on cough threshold in conscious human subjects.

Chest wall vibration is frequently used as a physiotherapy in patients complaining of sputum production. Frequency of vibration is ideally around 30 Hz, but a higher frequency, near 100 Hz, is commonly used in clinical practices. Many physicians have requested physiological bases of this therapy because an enhancement of mucus clearance with this therapy is almost denied [22]. In this study we showed that chest wall vibration increases the threshold of cough response. This mechanism, together with other mechanisms modifying the sense of dyspneic sensation [5], may explain how chest wall vibration relieves respiratory symptoms. Whether these effects are sustained for a long time after removal of the chest wall vibration is very important, but it remains to be investigated.

In conclusion, inputs from the chest wall afferent, presumably from the intercostal muscle or costovertebral joints, may have an inhibitory effect in the initiation of coughing at the higher neural structure in humans.

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