Cough induction by high-frequency chest percussion in healthy volunteers and patients with common cold

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Summary

Background: In patients with chronic obstructive pulmonary disease, chest percussion is often used to facilitate the drainage of respiratory secretions which may be removed from the airway by coughing. The cough reflex is believed to be mediated by mechanically sensitive rapidly adapting receptors (RARs). Chest percussion stimulation may stimulate RAR cough receptors, but there is no evidence that mechanical airway stimulation in man induces cough. The aim of this study was to determine if cough can be induced by high-frequency chest percussion in healthy subjects and in patients with acute upper respiratory tract infection (URTI).

Methods: Two groups were studied: 15 healthy subjects and 29 subjects with URTI, mean age 22 years. Percussion stimulation (70 Hz) was applied to the chest. Cough frequency and latency were recorded. All subjects were asked to complete a questionnaire about how they felt after the chest percussion by questionnaires.

Results: The results demonstrate that high-frequency chest percussion causes cough in human subjects with a recent history of URTI, but induces relatively little cough in healthy subjects. In URTI subjects there was a significant increase in the number of coughs after three periods of airway vibration, whereas in healthy subjects there was no change in cough. Furthermore, analysis of the questionnaires showed that more of the subjects with URTI felt an urge to cough compared to the healthy subjects in the subjective questionnaires.

Conclusions: This study demonstrates that cough can be induced in subjects with URTI by chest percussion. This method of inducing cough in subjects with URTI may be useful for studies on the mechanism of cough and for studies on antitussive medicines.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) and patients with conditions such as cystic fibrosis are often treated with chest percussion in order to facilitate the drainage of respiratory secretions. The benefits of chest percussion in clearing mucus from the airway would be facilitated by cough, but there is no evidence in the literature that mechanical stimulation of the airway in man induces cough.

Chest wall vibration in healthy volunteers and patients with asthma has been reported to create a sensation of breathlessness but these studies have not reported any cough associated with the chest wall vibration.1,2 Similarly, studies in anaesthetised...
dogs have reported an increase clearance of tracheal mucus on chest wall vibration, but no cough was reported.3,4

Preliminary studies in man in our laboratory have indicated that it may be possible to induce cough in patients with acute upper respiratory tract infection (URTI) by mechanical vibration of the trachea.5 Mechanical induction of cough has also been achieved in anaesthetised animals by stimulation of the airway with intratracheal stimulation with bristles or iron slugs,6,7 but to our knowledge cough has not been previously induced in man with a mechanical stimulus to the airway. Studies on cough induced by inhalation of citric acid aerosol in healthy volunteers have shown that chest vibration causes an increased threshold to citric acid, i.e. an inhibition of the cough reflex and the authors have speculated 'that inputs from the chest wall afferents, 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'.8 The cough reflex is reported to be mediated by rapidly adapting airway receptors (RARs) and these sensory receptors have been described as 'particularly sensitive to mechanical stimuli'.9 Therefore, one would predict that airway vibration by chest percussion would facilitate rather than inhibit cough.

The aim of the present study was to determine if cough could be induced by high-frequency chest percussion in healthy volunteers and in patients with acute URTI. The increase in cough associated with acute URTI is believed to be due to sensitisation of RARs by the presence of inflammatory mediators10 and therefore one would predict that this group would have an enhanced cough reflex compared to healthy volunteers.

Materials and methods

Subjects

Two groups of subjects were recruited from the student and staff population of Cardiff University: (a) healthy subjects, with no history of acute URTI in the previous 4 weeks, and no history of any clinically significant disease as judged by the medical history (b) subjects who were otherwise healthy apart from a history of acute URTI in the previous week. Subjects with a history of URTI had to have at least two of the following symptoms in order to qualify for the study—runny nose, sore throat, cough, blocked nose, with a score of at least 2 (moderate) on a four-point box scale of symptom severity (0—not present, 1—mild, 2—moderate, 3—severe) for one of the symptoms, and a total score of equal to or greater than 4. The number of spontaneous coughs 5 min prior to the vibration application was also documented.

Subjects were excluded from the study if they were under 18 years or over 60 years of age, they had taken any medication that was deemed by the clinician to be contraindicated for this study, e.g. multi-symptom common cold medicine with antitussive, they were unwilling to sign the consent form, they had a history of disease or current disease that was deemed clinically significant for this pilot study, e.g. asthma, significant neurological and endocrinological disease, they were pregnant or lactating, they were smokers.

Forty-four subjects (13 males 31 females; mean age 21.8 years; range 18–41 years) were included. Fifteen were healthy and 29 had a history of acute URTI in the previous week.

Apparatus

A G5 Variko percussor (Physiotherapie Generale France S.A., B.P. 18—Z.I. Bello—47700 Casteljaloux, France/Stimulation frequency 70 cycles/s) was used in this trial to produce the percussion stimulation on the airways (Fig. 1). The G5 respiratory percussors are used to facilitate pulmonary drainage procedures, in conditions such as cystic fibrosis, bronchiectasis, asthma, chronic bronchitis, chronic emphysema, etc. The percussor was used with a polyurethane sponge applicator (applicator no. 212; diameter 100 mm and thickness 30 mm, Physiotherapie Generale France S.A., B.P. 18—Z.I. Bello—47700 Casteljaloux, France).

Figure 1 A G5 Variko percussor (Physiotherapie Generale France S.A., B.P. 18—Z.I. Bello—47700 Casteljaloux, France) was used in this trial to produce the percussion stimulation on the chest.
Laboratory and recording phase

Subjects were informed about the nature of the study, and shown the respiratory percussor to be used to stimulate the upper airway. The subjects were told to sit with their back supported by a chair. During a 5 min period of instruction prior to applying the percussor, the number of spontaneous coughs made by the subject was documented by the investigator.

1. The percussion applicator was positioned above the manubrium sternum by the investigator.
2. The percussor was turned on and the stimulation on the manubrium was applied for a maximum of 1 min.
3. The percussor was switched off if the volunteer coughed within the 1-min period.
4. The number of coughs were counted by the investigator for 2 min from the start of percussion stimulation by using a tally counter while listening to the volunteer, and the time of the first cough was recorded as cough latency (in seconds). Any sounds that were not related to cough, such as speech, throat clearing, and sneezes, and sounds associated with gagging, were discarded in the cough count.
5. Steps 1–4 were repeated 3 times with a 2-min rest period between each period of airway percussion stimulation.

Patient questionnaires

At the end of the recording period, all subjects were asked what they felt after the percussion stimulation of the chest. Subjects were asked if they felt they wanted to; sneeze, laugh, cough, breathe deeply, stop breathing or breathe rapidly. They were also asked if the chest percussion stimulation was: pleasant, unpleasant or did not bother them.

Statistical analysis

This was a pilot study and there were no pre-designated outcome measures. The aim of the study was to determine if cough can be induced by high-frequency chest percussion in healthy volunteers and in patients with acute URTI. Summary measures of mean cough were calculated for the different categories, and appropriate statistical tests were applied to make comparisons between and within the two subject groups. The parametric independent sample t-test and paired sample t-test were used in significance testing. Mean values of cough frequency are given with the standard deviation.

Ethical approval

The study was conducted according to the ICH guidelines (1997) for good clinical practice and all volunteers provided signed informed consent to participate. The study was approved by the Bro Taf Local Research Ethics Committee, Cardiff.

Results

Spontaneous symptoms

The mean symptom severity score in the healthy group was 0.00 ± 0.00, whereas in the URTI group the mean was 6.72 ± 1.62 (minimum 4, maximum 10).

The mean cough score in the healthy group was 0.00 ± 0.00, whereas the mean cough score in the URTI group was 1.52 ± 0.911 (minimum 0, maximum 3).

The mean number of coughs 5 min prior to the vibration application in the healthy group was 0.00 ± 0.00, whereas in the URTI group the mean was 0.48 ± 0.74 (minimum 0, maximum 2).

No adverse events were reported in the study.

Cough induced with chest percussion

Chest percussion caused very little cough in the healthy subjects with 13 out of 15 subjects having no cough at all. One healthy subject coughed only once on the first application of the percussor and another healthy subject coughed twice on each application of the percussor. In comparison, nearly all of the URTI subjects coughed on application of the percussor with only four out of 29 subjects having no cough at all. Any cough present in the subjects with URTI was a dry unproductive type of cough.

The mean number of coughs for subjects in each of the three stimulation episodes is shown in Fig. 2. In the healthy subjects, the mean cough counts were 0.20 ± 0.561, 0.13 ± 0.516 and 0.13 ± 0.516 whereas in the URTI subjects the mean cough counts were 1.97 ± 2.934, 1.59 ± 2.486 and 3.93 ± 4.598.

In terms of the mean cough count for the total three stimulation episodes, the healthy group (mean 0.47 ± 1.55) and the URTI group (mean 7.48 ± 9.75) are significantly different (P < 0.01).
In the URTI subjects, the figure illustrates that there was a significant increase ($P \leq 0.001$) in the mean number of coughs from the first to the third stimulation episodes. In healthy subjects there was no significant change in mean cough throughout the three episodes of airway vibration ($P = 0.334$).

In the URTI subjects, cough occurred after around 60 s after the start of percussion. The mean latency to the first cough after commencement of percussion was $57.12 \pm 27.59$, $78.29 \pm 35.37$ and $65.83 \pm 23.21$ s for the three periods of chest percussion.

**Subjective effects of chest percussion**

A chart showing how all the subjects felt about the sensation of chest percussion stimulation is shown in Fig. 3. The figure shows that a greater percentage of URTI subjects felt an urge to cough (52%) compared to the healthy subjects (7%). In general, most subjects scored that the percussion ‘did not bother me’ (URTI 62%, healthy 60%), but more subjects in the URTI group (31%) felt the percussion was unpleasant compared to the healthy group (13%).

**Discussion**

The results of the present study demonstrate that high-frequency chest percussion causes cough in human subjects with a recent history of URTI but induces relatively little cough in healthy subjects. The frequency of cough in the URTI subjects was greatly increased with repeated chest percussion to a mean of 3.93 coughs/2 min (7.86/min) following the third period of chest percussion. Only 2/15 healthy subjects coughed on chest percussion whereas 25/29 subjects with URTI coughed. The absence of cough response in the great majority of healthy subjects (13/15) is consistent with previous studies that have not reported any cough in response to airway vibration in healthy subjects.$^{1,2}$ The subjects with URTI were not selected on the basis that they were suffering from cough, and they had very little cough prior to chest percussion with a mean of only 0.48 coughs/5 min (0.096/min). In studies recruiting patients with cough associated with URTI, the cough frequency has been mentioned around 4–5/min.$^{11}$

The percussion stimulus used in the present study may induce cough by stimulation of RARs in the trachea and bronchi. RARs occur throughout the respiratory tract from nose to bronchi and they respond to both chemical and mechanical stimuli and to many inflammatory mediators.$^{12}$ RARs have been described as very sensitive to mechanical stimulation,$^{9,12}$ and sensitisation of RARs on exposure to inflammatory mediators has been put forward as a mechanism of cough hyper-sensitivity associated with URTI.$^{10}$ An enhanced cough response in subjects with URTI compared to healthy subjects has been previously demonstrated for cough induced on inhalation of citric acid$^{10}$ and
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...capsaicin, and this hyper-reactivity of the cough reflex in subjects with URTI is supported by the results of the present study. The mechanism of this cough hyper-reactivity may be related to the presence of inflammatory mediators around the RARs that mediate cough.

A previous study by Kondo et al. on the effects of chest wall vibration on cough induced by inhalation of citric acid aerosol in healthy subjects has reported that chest wall vibration increased the threshold for cough induction, i.e. inhibited cough. The inhibition of cough was proposed to occur via stimulation of sensory receptors in the intercostal muscles or costovertebral joints and the authors did not mention any possibility of stimulation of airway receptors such as RARs. The chest wall vibration that inhibited citric acid induced cough was provided at a frequency of 100 Hz and amplitude of 3 mm whereas in the present study the percussion frequency was 70 Hz. It is possible that chest vibration may cause either inhibition or facilitation of cough according to differences in the physical parameters of chest vibration. It is not possible to determine the nature of any change in the sensitivity of the cough reflex in either the present study or the previous study by Kondo et al. but it seems more likely that any change in cough sensitivity will be due to some change in the airway RARs that are known to mediate the cough reflex. The fact that in the present study cough was not induced by chest percussion in the healthy subjects but was induced in subjects with URTI indicates that chest percussion is stimulating airway rather than chest wall receptors as one would not expect any changes in the chest wall receptors with URTI.

The results of the present study indicate that in subjects with URTI there were significantly more coughs after three periods of percussion compared to the first period. The increase in cough with repeated stimulation may be due to cough traumatizing the airway and triggering the release of inflammatory mediators or it could be related to a central recruitment of cough pathways in the brainstem rather than a peripheral mechanism.

The data collected from the questionnaire regarding airway sensations indicate that both healthy subjects and those with URTI did not find that the percussion 'bothered them', but more subjects in the URTI group found the percussion unpleasant. More of the URTI subjects felt an urge to cough compared to the healthy subjects and this mirrors the objective results on cough counts. However, our data show that this way of percussion is well tolerated and harmless.

Previous studies have reported that chest wall vibration may cause a sensation of breathlessness in healthy subjects and asthmatics, and the authors have speculated that this may be due to stimulation of sensory receptors in chest wall muscles. Chest wall vibration has also been reported to decrease the sensation of breathlessness in healthy subjects associated with a hyper-capnic ventilatory response, and the authors speculate that this could be due to 'decreased central motor command and/or modification in breathlessness-related afferent activity from the respiratory system'.

In the present study, chest wall vibration will have stimulated chest wall muscles and deeper structures in the airway. However, it seems unlikely that stimulation of chest wall muscles is responsible for the induction of cough, and airway receptors such as RARs are more likely to be involved in the cough response.

It is interesting that in a study on chest wall vibration in five asthmatics, the subjects reported a sensation of breathlessness similar to an asthma attack but no cough was reported in the study. There are no reports in the literature to our knowledge that have previously investigated the induction of cough in patients with COPD receiving therapy with chest percussion for mobilisation of secretions. It is reasonable to expect that percussion would also induce in cough in these patients but this must form the basis of a future investigation.

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