Cough Reflex Sensitivity in Cigarette Smokers*

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Study objectives: To evaluate cough reflex sensitivity in a population of young, healthy, male cigarette smokers.

Design: Cross-sectional comparison.

Setting: Academic medical center.

Participants: Twenty healthy, male current-smokers (mean ± SEM age, 32.2 ± 1.2 years).

Measurements: Subjects underwent baseline spirometry followed by capsaicin cough challenge testing, which involved the inhalation of capsaicin in ascending, doubling concentrations until the concentrations inducing two or more coughs (C₂) and those inducing five or more coughs (C₅) were reached. The data were compared to those from a group of 50 healthy, male nonsmokers who had undergone identical cough challenge testing.

Results: The two groups did not differ in terms of age or baseline pulmonary function. Cough sensitivity was significantly diminished in the current-smokers compared to control subjects. The mean (± SEM) log C₂ values in smokers and nonsmokers were 1.26 ± 0.13 and 0.81 ± 0.08, respectively (p = 0.004). The mean log C₅ values in smokers and nonsmokers were 2.03 ± 0.10 and 1.20 ± 0.08, respectively (p < 0.000001).

Conclusions: Cough reflex sensitivity is significantly diminished in young, healthy, male current-smokers compared to a similar population of nonsmokers. The mechanism of cough suppression in smokers remains speculative but may involve long-term tobacco smoke-induced desensitization of the cough receptors within the airway epithelium.

Key words: capsaicin; cough; pulmonary function tests; smoking

Abbreviations: C₂ = concentration of capsaicin inducing two or more coughs; C₅ = concentration of capsaicin inducing five or more coughs; RAR = rapidly adapting pulmonary stretch receptor

Cough results from the stimulation of sensory receptors within the respiratory tract the afferent impulses of which activate a brainstem cough center. The following two types of receptors are involved in cough production: rapidly adapting pulmonary stretch receptors (RARs) with thin, myelinated, afferent fibers; as well as pulmonary and bronchial C-fiber receptors with unmyelinated afferent fibers. RARs are believed to induce cough via a primary sensory pathway, whereas C fibers, the central pathways of which inhibit cough, may stimulate cough peripherally by causing the release of sensory neuropeptides that activate RARs.¹

The cough reflex serves a protective function by preventing foreign material from entering the respiratory tract and by facilitating the expulsion of mucus from the airways. To date, relatively little attention has been paid to the effect of cigarette smoking on cough reflex sensitivity. Animal studies have suggested that long-term exposure to tobacco smoke enhances the sensitivity of the cough reflex, perhaps by stimulating tachykinin synthesis and release within the airways.²⁻⁴ However, two small studies in humans have demonstrated higher cough thresholds (ie, diminished cough sensitivity) in smokers compared to nonsmokers.⁵,⁶

To further investigate the effect of long-term cigarette smoking on cough reflex sensitivity, we prospectively performed capsaicin cough challenge testing in a group of healthy, male current-smokers...

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and compared the data with those of healthy, male nonsmokers. The tussive agent capsaicin has been shown in humans to induce cough in a safe, reproducible, and dose-dependent manner, thereby rendering it an excellent tool for the measurement of cough reflex sensitivity. Unlike previous studies, only subjects of one gender (male) were compared because of the well-documented gender differences in cough reflex sensitivity.⁸ ⁹

**Materials and Methods**

**Subjects**

Twenty healthy, asymptomatic, male, current-smokers were recruited for the study, which was approved by the Institutional Review Board of Albert Einstein Hospital/Montefiore Medical Center. The amount and duration of cigarette smoking required for study entry was arbitrarily defined as at least five cigarettes daily for 1 year. Subjects had no history of pulmonary disease for study entry was defined as at least five cigarettes daily for 1 year. Subjects had no history of pulmonary disease (including asthma or previous history of chronic cough) or recent (≤4 weeks) symptoms suggestive of respiratory tract infection, seasonal allergies, or postnasal drip syndrome. Participants denied a history of, and symptoms consistent with, gastroesophageal reflux. Subjects were not receiving any medications known to affect cough reflex sensitivity. The data, including subject age, amount and duration of smoking, and baseline pulmonary function, are provided in Table 1.

**Capsaicin Cough Challenge**

Cough challenge testing was performed as previously described.¹⁰ Briefly, solutions of capsaicin (Sigma Chemical Co; St. Louis, MO) were prepared to make a stock solution of 0.01 mol/L. Fresh dilutions were prepared on each day of testing. Concentrations were titrated to achieve a single cough. Subjects inhaled single breaths (from FRC to TLC) of capsaicin aerosol administered via a nebulizer (model 646; DeVilbiss Health Care Inc; Somerset, PA) controlled by a dosimeter (KoKo DigiDoser; Pulmonary Data Service Instrumentation Inc; Louisville, CO). The nebulizers used in these studies were modified in two ways. First, an inspiratory flow regulator valve (RIFR; Pulmonary Data Service Instrumentation, Inc) was added, which limited the inspiratory flow rate to 0.5 L/s regardless of inspiratory force, thereby guaranteeing a consistent and reproducible inspiratory effort with each breath. Second, the straw and baffle assembly of each nebulizer was welded in place, thereby eliminating the variations in nebulizer output that occur when these components are detached for washing and then reattached with resulting variable distances between the jet orifice and the straw. The nebulizers were chosen, historical control group of 50 healthy, male nonsmokers who had previously undergone identical cough challenge testing during the period between January 2, 1996, and July 15, 1999. All cough challenge studies were performed by the author.

**Data Analysis**

Mean (±SEM) values for age, FVC (in liters and percent predicted), FEV₁ (in liters and percent predicted), log C₂, and log C₅ were calculated and compared by an unpaired Student t test for independent samples with those from a consecutively chosen, historical control group of 50 healthy, male nonsmokers who had previously undergone identical cough challenge testing during the period between January 2, 1996, and July 15, 1999. All cough challenge studies were performed by the author.

**Results**

The induction of five or more coughs was achieved in all subjects and nonsmoking control subjects. Subjects and control subjects did not differ in terms of age and baseline pulmonary function (Table 1). The mean (±SEM) log C₂ and log C₅ values for subjects and control subjects are displayed in Figure 1. Cough reflex sensitivity was significantly diminished in current-smokers relative to nonsmokers.

**Discussion**

This study has demonstrated that asymptomatic current cigarette smokers have a significantly diminished cough reflex relative to that of healthy nonsmokers. The inhibition of cough sensitivity due to long-term exposure to tobacco smoke contrasts with the previously documented enhancement of bronchial reactivity caused by cigarette smoking.¹¹ ¹² These observations are an excellent illustration of the concept that cough and bronchoconstriction are separate entities that are controlled by distinct afferent neural pathways.¹³

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**Table 1—Subject Data**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Smokers (n = 20)</th>
<th>Nonsmokers (n = 50)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of smoking, yr</td>
<td>10.8 ± 1.3</td>
<td>31.0 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Pack-years, No.</td>
<td>6.1 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes/d, No.</td>
<td>10.6 ± 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>32.2 ± 1.2</td>
<td>31.0 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁ L</td>
<td>3.59 ± 0.1</td>
<td>3.81 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>% predicted</td>
<td>85.4 ± 2.3</td>
<td>88.4 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>FVC L</td>
<td>4.34 ± 0.1</td>
<td>4.58 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>% predicted</td>
<td>85.9 ± 1.9</td>
<td>88.0 ± 1.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values given as mean ± SEM, unless otherwise indicated. NS = not significant.
†p < 0.05 considered significant.
The results of this investigation confirm those of previous, smaller studies employing capsaicin and citric acid as tussive stimuli. To the best of my knowledge, the present study provides the largest and only gender-specific comparison of cough reflex sensitivity between healthy, asymptomatic, current-smokers and nonsmokers. When analyzing cough sensitivity measurements among different populations, it is essential that the comparison be gender-specific, since the cough reflex is significantly more sensitive in women. A potential limitation of this study is the use of historical rather than contemporaneous control subjects.

The mechanism of diminished cough reflex sensitivity in smokers remains speculative. Perhaps long-term exposure to tobacco smoke desensitizes the cough receptors residing within the airway epithelium. Cough receptor desensitization may explain the lower incidence of angiotensin-converting enzyme inhibitor-induced cough in smokers relative to nonsmokers. This hypothesis also may explain the interesting observation that cough often transiently increases after smoking cessation.

Alternatively, long-term tobacco smoke-induced changes in the character of airway mucus may play a role in modulating cough reflex sensitivity. Previous studies have shown both a quantitative as well as a qualitative difference in the composition of mucus from asymptomatic smokers, with increased volume and increased mucociliary clearability compared to the mucus of nonsmokers. Enhanced mucus volume may provide a barrier shielding the superficial airway cough receptors from tussive stimuli.

It has been suggested that the nicotine-induced inhibition of C fibers, or the depletion of neuropeptides, within the airways may explain the diminished cough reflex sensitivity in smokers. However, earlier work showed that, in humans, inhaled nicotine induces concentration-dependent cough and, in animals, electrophysiologic studies have demonstrated that nicotine excites cough-inducing RARs.

Another possible explanation of our results is that smokers comprise a select group of individuals with naturally diminished cough reflex sensitivity. Although this theory may seem unlikely, it is quite interesting to note that multiple studies have demonstrated diminished cough sensitivity in persons who enjoy smoking occasionally, compared to regular smokers and nonsmokers.

The significance of diminished cough reflex sensitivity in current-smokers is unknown at this time. However, previous studies in different populations have suggested that the suppression of the cough reflex may indeed have important clinical ramifications. For example, a diminished cough reflex has been associated with an increased risk of developing aspiration pneumonia in stroke patients and in the elderly. Conversely, hypertensive stroke patients treated with angiotensin-converting enzyme inhibitors, drugs that enhance cough reflex sensitivity, have a lower incidence of pneumonia compared with stroke patients treated with other antihypertensive agents.

In addition to the diminished cough reflex sensitivity demonstrated herein, other factors may contribute to further compromise the effectiveness of cough in current-smokers. For example, studies using radiolabeled aerosols have shown that young, healthy smokers with normal pulmonary function are unable to enhance their rate of mucus clearance by coughing, suggesting an alteration in the mucociliary apparatus. The clinical spectrum and significance of long-term tobacco smoke-induced changes in the cough reflex await further elucidation in future studies.

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