

# Sex difference in the inhaled tartaric acid cough threshold in non-atopic healthy subjects

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## Abstract

**The threshold for cough induced by inhaled tartaric acid was measured in 71 non-atopic healthy volunteers. The cough threshold was lower in women than in men, which may be relevant to previous reports that angiotensin converting enzyme inhibitors induce cough more frequently in women than in men.**

Cough is one of the most common respiratory symptoms. Angiotensin converting enzyme inhibitors have been shown to cause cough in 5-20% of patients with hypertension receiving the drugs, more commonly in women than in men.<sup>1</sup> Irritant receptors and C fibre receptors are generally recognised as cough receptors in the airways.<sup>2</sup> Tartaric acid and citric acid are chemostimulants and induce cough by stimulating cough receptors. We have measured the threshold for cough induced by inhaled tartaric acid in non-atopic men and women to examine whether the cough reflex is more sensitive in women than in men.

## Methods

### SUBJECTS

Seventy one healthy, non-atopic volunteers, 48 men and 23 women, participated in this study. None of them had allergic disease or a past or family history of allergic disease. Twenty eight men were non-smokers (mean age 25 years) and 20 were smokers (mean age 24 years). All the women were non-smokers, with a mean age of 20 years. The study was approved by the ethics committee of our university, and informed consent was obtained from all subjects after the purpose of the test had been explained.

### MEASUREMENT OF COUGH THRESHOLD

Tartaric acid (Wako Pure Chemical Industries, Tokyo) was dissolved in physiological saline to make solutions with percentage concentrations of 0.156, 0.312, 0.625, 1.25, 2.5, 5, 10, 20, 40, and 80. Each subject inhaled a control solution of physiological saline followed by progressively increasing concentrations of tartaric acid. Solutions were inhaled for 15 seconds by tidal breathing at one minute intervals from a Bennett Twin nebuliser (3012-60 cc, Puritan-Bennett Company, Carlsbad, California) with the subject wearing a nose clip. Increasing concentrations were inhaled until five or more coughs were produced. The nebuliser output was 0.21 ml/

min. Cough threshold was defined as the lowest concentration of tartaric acid that elicited five or more coughs.

### STATISTICAL ANALYSIS

Cough threshold values were expressed as geometric mean values with the geometric standard error of the mean (GSEM) expressed as a factor. Geometric mean values for cough threshold were compared by Student's unpaired *t* test. A *p* value of 0.05 or less was taken as significant.

## Results

A cough threshold was obtained in 67 subjects. No cough was elicited in three men and one woman with the final concentration of tartaric acid (80%); a cough threshold value of 100% was assumed for statistical analysis.

Individual values for the cough threshold are shown in the figure. The geometric mean value of cough threshold in non-smoking women was 10.3% (GSEM 1.27%), which was significantly lower than that in non-smoking men, 26.2% (GSEM 1.24%) (*p* < 0.01). Cough threshold values in smoking men, 9.0% (GSEM 1.31%), were significantly lower than those in non-smoking men (*p* < 0.01).

There was no significant correlation between cough threshold and height in non-smoking men (correlation coefficient (*r*) = 0.29), smoking men (*r* = 0.03), or women (*r* = 0.25).

## Discussion

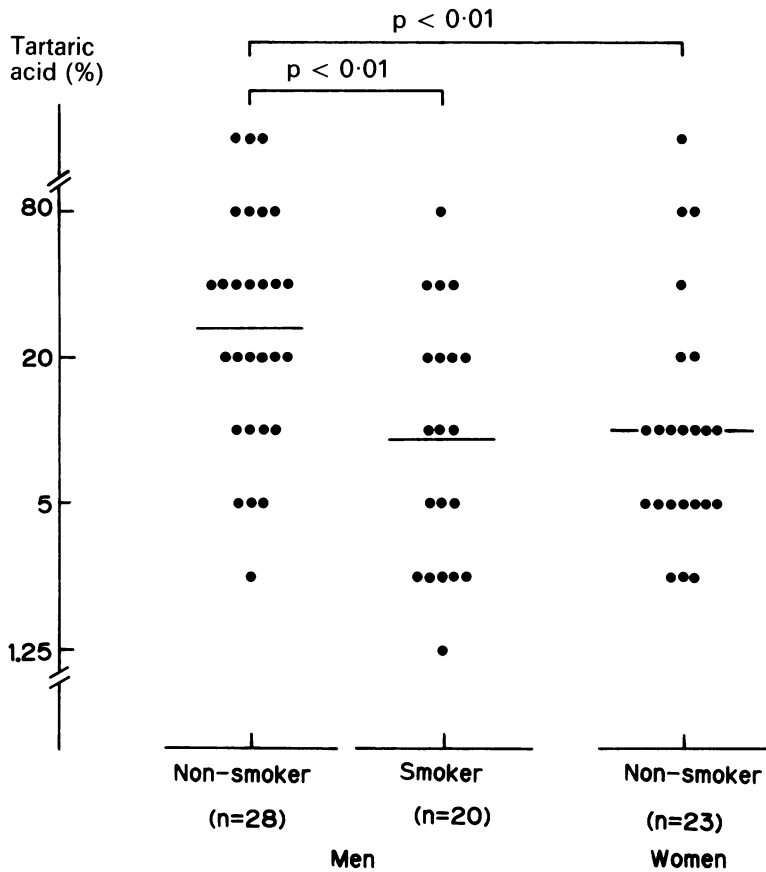
This study showed that the cough reflex is more sensitive to inhaled tartaric acid in healthy women than in healthy men who were non-allergic and non-smokers. The cough provocation test in this study was performed with a tidal breathing method, and this might influence the cough threshold by delivering a relatively higher dose of tartaric acid to women. There was, however, no correlation between the cough threshold and body height in women, non-smoking men, or smoking men; so we think that the cough reflex is more sensitive in women than in men. Of the various airway sensory receptors, irritant and C fibre receptors<sup>2</sup> can elicit cough; inhaled tartaric acid is thought to induce cough by stimulating irritant receptors. Our results may indicate that airway irritant receptors are more sensitive in women than in men. Angiotensin converting enzyme inhibitors

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Threshold of cough induced by tartaric acid aerosol in non-smoking and smoking men and non-smoking women (geometric means shown as horizontal bars).

induce cough more frequently in women than in men with hypertension.<sup>1</sup> Cough induced by these drugs has been attributed to increased concentrations of bradykinin, which elicits cough<sup>3</sup>; increased release of neuropeptides—for example, substance P and enkephalin—from C fibre endings in the respiratory tract as a result of an axon reflex<sup>4</sup>; or alternatively enhanced prostaglandin E<sub>2</sub> production, which

stimulates irritant receptors and C fibre receptors.<sup>5</sup> The increase in cough induced by angiotensin converting enzyme inhibitors in women may be due to increased concentrations of bradykinin, neuropeptides, or prostaglandin E<sub>2</sub> (or some combination of these) in the respiratory tract, or increased sensitivity of irritant or C fibre receptors (or both) in the airways. This study supports the latter possibility, but further studies are needed.

The association between cigarette smoking and cough is well established,<sup>6</sup> moderate smokers tending to cough more than non-smokers after inhalation of citric acid.<sup>7</sup> With citric acid the cough threshold is related to cigarette consumption and depth of inhalation.<sup>8</sup> In our study the tartaric acid cough threshold was lower in smokers than in non-smokers. Cigarette smoking could influence sensitivity of airway cough receptors by inducing chronic airway inflammation<sup>9</sup> or increasing airway mucosal permeability,<sup>10</sup> or both.

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