Respiratory Physiology & Neurobiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Cough reflex sensitivity does not correlate with the esophageal sensitivity to acid in patients with gastroesophageal reflux disease

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ARTICLE INFO

Keywords:
Cough
Gastroesophageal reflux
Esophageal sensitivity
Cough reflex sensitivity
Vagus nerve

ABSTRACT

The sensitization of cough reflex observed in patients with gastroesophageal reflux disease (GERD) is attributed to activation of vagal C-fibers innervating the esophagus by acid, while the heartburn in GERD is mediated by esophageal acid sensitive C-fibers derived from (dorsal root ganglia) DRG. Here we explored the relationship between cough reflex sensitivity (CRS) and esophageal sensitivity to acid. We evaluated CRS to capsaicin inhalation and esophageal sensitivity to acid (intensity of heartburn evoked by esophageal infusions of acid pH = 3, 2 and 1) in patients with GERD and chronic heartburn before and 3 months after proton pump inhibitor (PPI) treatment. There was no correlation between CRS and esophageal sensitivity to acid at any pH tested. PPI treatment substantially reduced esophageal sensitivity to acid but did not affect CRS. We conclude that a simple direct relationship between CRS and esophageal sensitivity to acid is unlikely. The results indicate that spinal and vagal afferent pathways from the esophagus are probably influenced separately in subjects with GERD.

1. Introduction

It has been proposed previously that patients with GERD have sensitized cough reflex (Ferrari et al., 1995; O'Connell et al., 1994). This increased cough reflex sensitivity (CRS) can be demonstrated as lower dose of a defined irritant (most commonly capsaicin) required to evoke cough in patients with GERD compared to healthy subjects (Ferrari et al., 1995; O'Connell et al., 1994). This sensitization of cough reflex observed in patients with GERD is attributed to activation of vagal C-fibers innervating the esophagus by the acid reflux from the stomach (Hennel et al., 2015). The acid is also responsible for burning sensations from the esophagus (heartburn, retrosternal and epigastric burning). These sensations are thought to be mediated by stimulation of esophageal C-fibers derived from dorsal root ganglia by acid (Kollarik and Brozmanova, 2009). These burning sensations can be evoked in clinical settings by esophageal acid infusion (Bernstein test) (Bernstein and Baker, 1958; Fass et al., 1998).

The relationship between cough reflex sensitivity and esophageal sensitivity to acid has not been established yet. While the vast majority of patients with untreated GERD experience heartburn, and the patients with GERD as a group have reported increased cough reflex sensitivity (Benini et al., 2000), only a small proportion of these patients develop chronic cough (Hennel et al., 2015). This suggests that in patients with GERD the extent to which the nerve pathways influencing heartburn and cough reflex are affected is different.

In this study, we explored the relationship between the cough reflex sensitivity and esophageal sensitivity to acid in patients with GERD. In addition, we evaluated the effect of acid suppression therapy the cough reflex sensitivity and esophageal sensitivity to acid.

2. Methods

Consecutive patients with GERD and chronic heartburn were prospectively collected in the Gastroenterology Clinic, Jessenius Faculty of Medicine. A careful interview was conducted to assess for symptoms suggestive of gastroesophageal reflux disease (GERD). Personal, pharmacological and allergic history was obtained.

Inclusion criterion was chronic (> 6 months) burning sensation behind the sternum (heartburn), with frequency at least one day per week. Using the single-item questionnaire, patients were asked to mark the frequency of this sensation as follows: “Thinking about your symptoms over the past 7 days, how often did you have a burning feeling behind your breastbone (heartburn)?: never, one day, 2–3 days, 4–7 days." Answers were marked as 0, 1, 2, 3, respectively.

Exclusion criteria were chronic cough (persisting for > 8 weeks), age below 18 years old, infection of the upper or lower airways in last 6

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https://doi.org/10.1016/j.resp.2018.03.011
Received 13 November 2017; Received in revised form 17 March 2018; Accepted 21 March 2018

weeks, smoking, alcohol consumption > 40 g/d, history of thoracic or abdominal surgery, inability to cooperate in cough challenge, active malignancy, inflammatory bowel disease, significant renal, cardiac and interstitial lung disease. Some patients had medical comorbidities: arterial hypertension (2), treated hypothyreosis (2), bronchial asthma without exacerbation (2), type 2 diabetes mellitus (1), allergy to aeroallergens (2). Patients were instructed to withhold proton pump inhibitor therapy affecting gastric acid secretion for at least 30 days before undergoing the examinations. Written informed consent was obtained from all subjects and the protocol was approved by The Ethical Committee of the Jessenius Faculty of Medicine.

All patients completed capsaicin cough challenge and three esophageal acid infusions (pH 3, 2, 1) in this order.

Capsaicin cough challenge was determined using the standardized method of single breath capsaicin inhalation and is in detail described elsewhere (Fass et al., 1998). The challenge consists of single breath inhalations of the aerosols of the solutions with doubling concentrations of capsaicin. The challenge begins with the inhalation of the capsaicin vehicle (saline) and continues with capsaicin from 0.49 to 1000 µmol/l. The individual doses are separated by 60 s intervals. Aerosols are delivered through the mouth by the inspiration-triggered valve for 500 ms (nasal breathing is prevented by the nasal clip worn throughout the challenge). The coughs are counted during the first 15 s after each dose of capsaicin. Cough reflex sensitivity (cough threshold) is expressed as the lowest concentration of capsaicin causing two coughs (C2) and five coughs (C_5). The cough challenge was terminated when patients achieved C_5 or the highest concentration of capsaicin was reached (1000 µmol/l). Subjects were instructed to report any sensations and were unaware of the endpoint of the challenge (the number of coughs).

The following day after capsaicin cough challenge the subjects completed esophageal acid infusions. These were performed in the sitting position. Naso-esophageal catheter was inserted with the outlet positioned at approximately 10 cm above the upper margin of the lower esophageal sphincter. This was located using high resolution manometry. The catheter was secured and maintained in the same position. The infusion tube was connected to a peristaltic pump (flow rate 8 ml/min. resulting in total volume of 80 ml during 10 min of infusion, pump type PCD 21 M, Kouril, Czech Republic).

Acid solutions were infused into the distal esophagus as follows: infusion of HCl 0.001 mol/l (pH = 3), 0.01 mol/l (pH = 2) and 0.1 mol/l (pH = 1). Each infusion lasted for 10 min and after termination of one infusion the following infusion was initiated after 5 min interval. Patients were unaware of the composition of the acid infusions. They were asked to mark the severity of the burning sensation on the visual analogue scale (1–10, 1 = no heartburn, 10 = unbearable heartburn), in 2 min intervals (2., 4., 6., 8. and 10. min.) during the acid infusion. If the patient was unable to tolerate the infusion (mark 10 on visual analogue scale), the infusion was terminated.

After completion of cough challenge and esophageal acid infusions, patients were recommended proton pump inhibitors once daily (morning dose) for three months. After that symptoms were assessed using the same question regarding the frequency of the burning sensation as described above and capsaicin cough challenge and all esophageal acid infusions were completed.

Statistical analysis

Cough reflex sensitivity (CRS) was expressed as the $\log_{10}$ of the lowest concentration of capsaicin that evoked 2 coughs (C_2) and 5 coughs (C_5). Esophageal sensitivity to acid was expressed either as cumulative and maximal values. Cumulative esophageal sensitivity was defined as the summation of all 5 numbers marked during the 10 min esophageal acid infusion (2., 4., 6., 8. and 10. min.). For example, patients that marked the severity of the burning sensation in 2., 4., 6., 8. and 10. min. of the infusion as 1, 3, 3, 4, 6, respectively, had cumulative esophageal sensitivity = 17. Maximal esophageal sensitivity was defined as the highest number marked during the 10 min infusion. Cumulative and maximal esophageal sensitivity were obtained for each pH (pH 3, 2 and 1) of esophageal acid infusion.

Log_{10} capsaicin concentration (µmol/l), severity of heartburn and the frequency of heartburn determined by the single item questionnaire was expressed as average ± standard error of the mean. Correlations between CRS (expressed either as C_2 and C_5) and esophageal sensitivity to acid (either maximal and cumulative) for all esophageal acid infusions (pH 3, 2, 1) using Pearson correlation coefficient were performed. For evaluation of the CRS and esophageal acid sensitivity difference before and after treatment, a paired Student T-test was used.

Sample size calculation. Cough reflex sensitivity and esophageal sensitivity to acid as measured in this study are discrete (not continuous) values which increases the error of measurement. Therefore a rather liberal requirement of R2 = 0.6 was used as an estimate for a pathophysiologically meaningful correlation. With threshold probability for rejecting the null hypothesis $\alpha = 0.05$ (i.e. required significance level $P < 0.05$) and a stringent threshold probability of failing to reject the null hypothesis under the alternative hypothesis $\beta = 0.1$ (i.e. threshold for type II error), the sample size calculated by using UCSF Clinical and Translational Science Institute sample size calculator (http://www.sample-size.net/correlation-sample-size/) was 13.

3. Results

Thirteen patients (4M/9F) were enrolled into the study. The average age was 49.4 (± 13.6) years. None of the patients had acute, subacute or chronic cough as defined by (Irwin et al., 2006; Irwin et al., 2018). All patients completed capsaicin cough challenge and the esophageal acid infusions. We first evaluated the results of capsaicin cough challenge and esophageal acid infusions separately. The average $\log_{10}$ (µM) concentration of capsaicin that evoked 2 coughs (C_2) was 1.2 ± 0.11, and the average $\log_{10}$ (µM) concentration of capsaicin that evoked 5 coughs (C_5) was 2.42 ± 0.28.

As expected the infusion of acid evoked heartburn in all patients. The burning perception was linearly increasing during the 10 min duration of acid infusion resulting in approximately linear time course of acid-induced burning perception intensity (Fig. 1). Interestingly, we noted that the esophageal sensitivity to acid at pH 3 was essentially identical to that of acid at pH 2. In contrast, the perception of acid pH 1 was significantly stronger compared to those at pH 2 and 3 ($p < 0.01$)

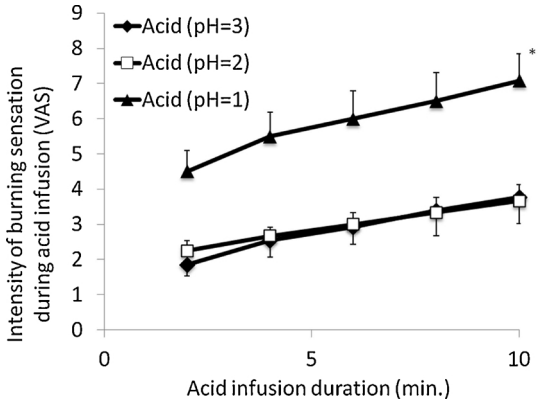

Fig. 1. Esophageal sensitivity to acid of pH 1 is significantly higher than to acid of pH 3 and 2. Sensitivity is expressed as heartburn sensation (the intensity of burning sensation) reported by a patient on visual analogue scale (VAS) ranging from 1 to 10 during infusion of acid (pH = 3, pH = 2 and pH = 1, 10 min each) into the distal esophagus (N = 13). There was no difference between the intensity of heartburn evoked by acid pH = 3 and pH = 2, but acid (pH = 1) evoked more intense heartburn ($P < 0.01$).