

Gastroesophageal reflux disease and chronic sinusitis: In search of an esophageal–nasal reflex

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ABSTRACT

Background: This study was performed to explore whether or not a neural reflex linking the esophagus and the nasal airway exists, as a pathogenic mechanism accounting for the association between gastroesophageal reflux (GER) disease and chronic rhinosinusitis (CRS). A prospective trial of healthy human volunteers was performed.

Methods: Ten healthy volunteers without GER or sinonasal disease were investigated using an acid infusion challenge test. Normal saline and hydrochloric acid were infused into the lower esophagus through an esophageal manometry catheter. Nasal responses in symptom score, nasal inspiratory peak flow, and mucus production were analyzed after the esophageal challenge.

Results: A tendency for an increase in nasal mucus production was observed after esophageal stimulation with both normal saline and HCl. This returned to baseline level 45 minutes after the acid infusion. A similar trend was also observed with the measurements of nasal symptom scores and, to a lesser extent, nasal inspiratory peak flow.

Conclusion: These results support the possibility that a neural reflex exists between the esophagus and the paranasal sinuses via the vagus nerve. If indeed present, the reflex-mediated rhinitis derived from this neuropathic inflammation may contribute to the development of CRS in patients with GER. Further study is required to define the relationship between GER and CRS.

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Key words: Chronic rhinosinusitis, esophageal–nasal reflex, gastroesophageal reflux, neural reflex, neuropathic inflammation, reflex-mediated rhinitis, vagus

Chronic rhinosinusitis (CRS) is a complex condition with a multitude of etiologic factors. Gastroesophageal reflux (GER) has recently been implicated as one of these factors contributing to the development of CRS, and the association between these two conditions is now well documented.^{1–3} The exact pathogenic mechanism responsible for this association is, however, still not understood. The prevailing theory in the literature at the present time is that direct reflux of acid from the stomach to the nasal cavity leads to injury of the paranasal sinus mucosa.^{4–6} The evidence for which this theory is based centers around only a handful of studies, with the majority of them conducted in the pediatric population.

Our department previously reported data from 24-hour pH studies using a novel sensor that can be sited above the esophagus without any artifactual interference.⁷ We found that in patients with GER and CRS, reflux of acid from the stomach to the nasopharynx is an extremely rare event. This finding contradicts the current theory of direct nasopharyngeal acid reflux, but supports an alternative mode of pathogenesis that we proposed. We hypothesized that a pathogenic increase in nasal mucus production and congestion occurs in the paranasal sinuses of patients with GER, which results *via* a vagal reflex when acid comes into contact with the esophagus. Such a neural reflex between the esophagus and the nasal cavity has never been documented in the literature previously. The aim of the current study is to show such an esophageal–nasal reflex, which will further support our theory for the association between GER and CRS.

MATERIALS AND METHODS

The protocol for this study was approved by the Ethics Committee of the Royal Adelaide Hospital (Adelaide, South Australia). Healthy volunteers recruited by advertisements were selected for the purpose of this investigation. Subjects with a history of CRS, reflux, asthma, eczema, or allergic rhinitis were excluded from the study. Smokers and patients with previous sinonasal surgery were also excluded from the study. Potential subjects underwent further screening with anterior rhinoscopy and nasendoscopy. Those subjects with clinical evidence of allergic rhinitis or a grossly deviated nasal septum were excluded from the study. Subjects with nasal polyposis or with presence of mucopus in the nasal cavities were also excluded.

Volunteers who were deemed to be appropriate for the study after the screening clinical evaluation were given a trial run of the experimental procedure. This allowed the subjects to familiarize themselves with the sampling technique to prevent any inadvertent loss of critical samples during the actual study. Informed consent was obtained from each subject. A radioallergosorbent test was organized for the subject and the results were negative; the subjects proceeded with the experiment at the Esophageal Function Laboratory of the Royal Adelaide Hospital.

All subjects fasted for 6 hours before the commencement of the experiment on the day of testing. All subjects were tested at the same time in the afternoon. After arriving at the laboratory all subjects underwent routine manometry using a multichannel catheter. This manometry catheter has eight channels that are connected to pressure sensors, with an infusion channel that expels infused solutions at 15 cm above the distal tip. The location of the lower and upper esophageal sphincters was identified through the manometry study. Once the location of the lower esophageal sphincter was identified the catheter was then positioned such that the tip of the catheter was just proximal to the gastroesophageal junction. This was to standardize the site of solution infusion in all study subjects relative to the lower esophageal sphincter. The catheter was then secured in place with adhesive tape.

When the patient was set up as described, a series of nasal lavages

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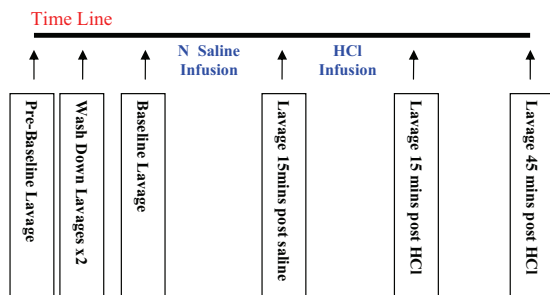


Figure 1. Summary of nasal lavage protocol.

were then collected using the nasal pool device.⁸ Preexisting nasal secretions were removed with the initial prebaseline lavage. This was followed by two washdown lavages (which were discarded). A baseline lavage was then collected after a 30-minute period of quiescence. Lavages were then collected 15 minutes after infusion of saline through the manometry catheter and also at 15 and 45 minutes after the infusion of HCl. A schema showing the timing of these lavages is presented in Fig. 1.

Fifteen milliliters of normal saline was instilled in the pool device for each lavage during this experiment. Each lavage was of 5-minute duration except for the two washdowns, which were 2.5 minutes each. The saline and HCl solutions were both infused at identical rates of 100 mL over 15 minutes; 0.1 N HCl was chosen as the concentration of the acid infused.

Nasal inspiratory peak flow (best of three) was measured at baseline, 15 minutes post-saline infusion, and at 15, 30, and 45 minutes after the infusion of HCl. At these same times the subjects were also asked to rate their overall sinonasal symptom score using a visual analog scale of 0–10.

Once all of the sampling procedures were complete, the manometry catheter was removed. A specially designed four-channel pH probe was then inserted and the subject underwent 24 hours of pH monitoring as described in our previous study.⁷

The nasal lavage fluids collected during the experiment were rushed to the clinical biochemistry laboratory of the Institute of Medical and Veterinary Science adjacent to the Royal Adelaide Hospital. Each sample was centrifuged at $105 \times g$ for 10 minutes at a temperature of 4°C. The supernatant was then pipetted away and separated into two identical 5-mL sample tubes. Both samples were marked with the same identification number, with one designated for Lund in Sweden and the other remaining in storage in Adelaide. Both specimens were then stored at –20°C. Once testing of all the subjects was completed, the specimens designated for Lund were sent frozen via a medical courier for biochemical analysis. The fucose levels of each specimen were then determined, because it is a marker of nasal mucus secretion.⁹ The laboratory in Sweden was blinded to the details of the samples as they were labeled by only a number. The results were then returned to Adelaide, where interpretation and statistical analyses were performed. These were performed using the software SPSS Version 11.0 (SPSS, Inc., Chicago, IL).

RESULTS

Subjects

The first 10 volunteers to meet the inclusion and exclusion criteria were entered into the study. Radioallergosorbent testing on all subjects was negative. Of the 10 subjects, 9 were women and 1 was a man. The mean age of the subjects was 27.4 years (range, 18–52 years).

Diagnosis of GER

The median reflux index (percent time pH of <4) was 1.6% (interquartile range, 0.4–4.4%). One of the 10 studies was judged abnormal

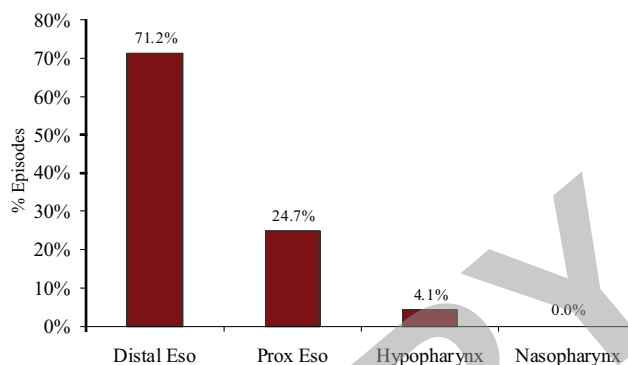


Figure 2. Proximal extent of all recorded reflux episodes. Eso, esophagus.

with a reflux index of 8.9% (normal reflux index, $\leq 4\%$). Therefore, 10% of the study sample returned a 24-hour pH study that was consistent with a diagnosis of GER.

Profile of Reflux Episodes

A total of 267 reflux episodes were recorded during the 10 studies. Of these, 71.2% were detected only in the distal esophageal probe, whereas 24.7% reached as high as the proximal esophagus. Only 4.1% of all the recorded reflux episodes were registered in the supra-esophageal probes. All of these 11 episodes were recorded at the hypopharyngeal probe, with none of the reflux episodes reaching the nasopharynx. Figure 2 is a graphic representation of the distribution of the reflux episodes in terms of their proximal extent.

Effect on Sinonasal Symptom Score

There was a rise in mean symptom score from baseline with the infusion of saline and HCl. There was a trend for the symptom scores to return to baseline levels at 45 minutes after the infusion of HCl. However, because of the small magnitude and sample size, this difference was not statistically significant (Friedman test; $p = 0.443$). The mean symptom scores are presented in Fig. 3.

Effect on Gastrointestinal Symptoms

No subjects reported any heartburn during the infusion of either saline or acid. However, a significant proportion of the subjects reported that they could detect a sensation of a fluid being infused into their esophagus. Most subjects reported this sensation as a “cold feeling.”

Effect on Nasal Inspiratory Peak Flow

There appeared to be a reduction in nasal patency after infusion of saline in the esophagus when compared with baseline. However, this difference was also not statistically significant. A smaller reduction was detected 15 minutes after the infusion of HCl. There was significant improvement of nasal patency at 30 minutes after HCl infusion. At 45 minutes post-HCl infusion, nasal inspiratory peak flow measurements appeared to return to baseline levels. The nasal inspiratory peak flow measurements are summarized in Fig. 4.

Effect on Nasal Lavage Fucose Levels

There was a measurable, but statistically nonsignificant, rise in fucose level in the nasal cavities when saline was infused into the esophagus. This effect seemed to be less prominent 15 minutes after the infusion of HCl into the esophagus. By 45 minutes after the infusion of HCl, the fucose levels appeared to return to baseline levels. Although this trend is clearly evident from the graphic representation of the results (Fig. 5), the differences measured in this parameter did not reach statistical signifi-

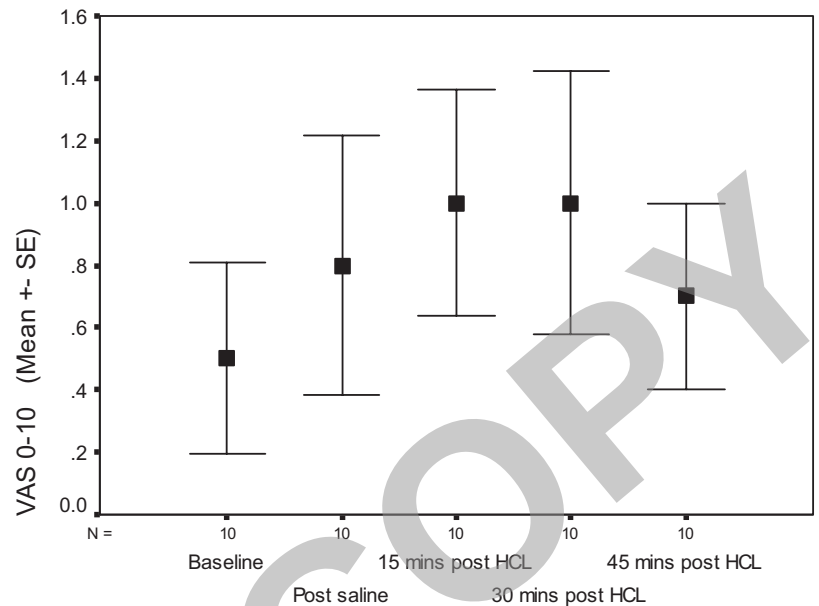


Figure 3. Effect of esophageal infusion of normal saline and acid on mean sinonasal symptom score.

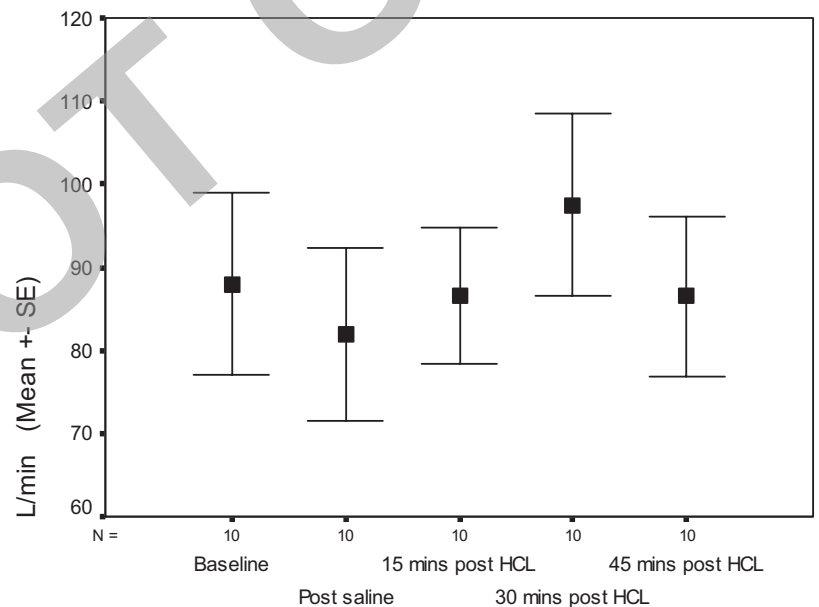


Figure 4. Nasal inspiratory peak flow measurements.

cance (lowest value of $p = 0.11$ between baseline and 15 minutes post-saline; Wilcoxon signed-rank test).

DISCUSSION

The aim of this study was to test our hypothesis that a vagally mediated neural reflex exists between the esophagus and the respiratory mucosa of the nose and the paranasal sinuses. Our rationale for this theory is because of a similar reflex that had already been established between the esophagus and the respiratory epithelium of the bronchopulmonary system. Schan *et al.*¹⁰ was able to show a reduction in peak expiratory flow rate with an esophageal acid infusion challenge. Similar changes in airway hyperresponsiveness was documented by Wu *et al.*¹¹ These and other confirmatory studies followed the initial work by Mansfield, who was able to show reduced airway conductance when the esophagus was infused with HCl in both humans and dogs.¹² During the canine experiment, Mansfield was also able to document an identical reflex with distension of the

esophagus alone. Hence, it would appear that the reflex induced by the esophagus on the airway is indiscriminate of the type of sensory afferent that is triggered by the initiating event.

To our knowledge, no other research group had endeavored to establish such an esophagobronchial reflex in the past. Hence, there are no studies in the literature for comparison of our results. The protocol that we used to show the proposed reflex is based on an acid infusion challenge test is similar to the method used by respiratory researchers to elicit the reflex between the bronchial airways and the esophagus. We chose healthy volunteers without CRS or GER symptoms for this experiment because these subjects will be least likely to have any preexisting reactivity in either their nasal cavity or their esophagus. Thus, any change that was observed in the outcome measures used in this experiment can be unequivocally attributed to a simulated reflex, rather than any concurrent disease states. We were meticulous in our screening of the volunteers for any sinonasal comorbidities.

In relation to the 24-hour pH studies, we chose a threshold level of

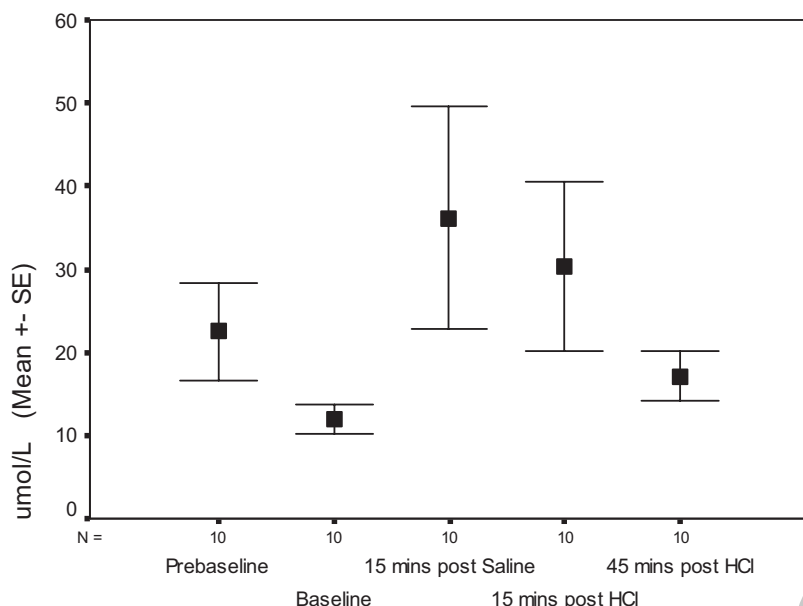


Figure 5. Nasal lavage fucose levels.

pH <4 because this remains the most conventional and accurate level for the detection of an acid event. There are currently no universally accepted normative values for pH studies >5 cm above the distal esophageal sphincter.¹³ Some recent studies have reduced the threshold of an acid event based on the reactivity of pepsin but this has led to results that are confusing and difficult to interpret. For example Pawar *et al.*,¹⁴ using a threshold value of pH <5, found no difference in reflux symptoms or laryngoscopic findings between those patients with either positive or negative 24-hour pH tests, even though there were significant improvements after the administration of a proton pump inhibitor.

The important finding in the current study is that there appears to be some response in the nasal mucosa from esophageal stimulation. Although the same trend can be seen in all three of the parameters, these changes did not quite reach statistical significance because of the small sample size in our series. However, the fact that a similar pattern is seen in all three parameters raises the possibility that the observations are secondary to a measurable effect. The authors of this article would like to emphasize once again that statistical significance was not reached in this study.

With regard to the results obtained specifically for nasal inspiratory peak flow (NIPF), it is unclear as to the reason behind the significant increase in nasal patency at 30 minutes after the infusion of acid. One possibility is that a certain amount of variability would be expected on account of the physiological nasal cycle. There is also debate in the literature about the accuracy of NIPF. Although some studies show that it is a reliable measurement of nasal patency, its sensitivity is questioned by others.¹⁵ An alternative to NIPF may have been acoustic rhinometry, which has been shown to be a more sensitive test of nasal patency.¹⁶ It is, however, a much more cumbersome test, requiring more sophisticated equipment than the Youlten meter.

Our results, interestingly, seem to suggest that the esophagus could be stimulated with saline as well as acid, which was not expected by the authors. The protocol of the present study was designed to show a response to esophageal stimulation with acid, with the infusion of normal saline beforehand intended as a control. However, this response to esophageal stimulation with saline is not unique and had already been previously documented. Wright *et al.*¹⁷ studied 136 subjects using a similar infusion challenge and observed a pulmonary as well as a cardiac response to both normal saline and acid infusion. They offered no explanation for their finding but the response to normal saline could conceivably be caused by the temperature of the

solution. Although none of our subjects reported any discomfort with either of the infusions, most of our subjects were able to detect a "cold" sensation when the infusions commenced. This sensation would disappear as the esophagus is cooled to room temperature by the infusion and the subjects became accustomed to the sensation.

There are a number of different sensory afferents that have been identified to arise from the esophagus.¹⁸ These may respond to a range of stimuli including electrical, mechanical, and chemical as well as thermal inputs. Recent research has mapped the location of these sensory nerve endings in relation to their position in the esophageal wall. It is of interest to note that the thermal receptors are preferentially located closest to the luminal surface whereas the chemical receptors are further away within the mucosa.¹⁹ Some authors, in fact, are of the opinion that chemical responses from the esophagus can only be detected if there had been some preceding erosion or deficiency in the epithelium of the mucosa, thereby allowing the nerve endings to come into contact with the chemicals.¹²

For the purposes of the current study, however, the unexpected response to normal saline does not jeopardize the theory for the association between GER and chronic sinusitis, which we have postulated. Clearly, what is important is that there appears to be a reflex response linking the esophagus and the nasal cavity, which would support our hypothesis for an esophagoneasal reflex. We could reasonably expect that a similar, possibly even stronger, reflex response would be present in patients who actually have erosive esophagitis.

CONCLUSION

In conclusion, the results of the present study appear to show a nasal response to esophageal stimulation. This is the first study in the literature to search for such an esophagoneasal reflex. If indeed present, such a reflex could contribute to the pathogenesis of CRS in patients with GER. However, given the limited power of this study, additional research is required to fully determine the relationship between GER and CRS.

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