Diagnosis and consequences of gastroesophageal reflux in otolaryngology

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Chapter 7

General Discussion
GENERAL DISCUSSION

Gastroesophageal reflux (GER) is the reflux of gastric juice into the esophagus that may result in gastroesophageal reflux disease, a well-known disease entity in gastroenterology. Although bile and pepsin are present in the refluxate, the attention has always been focused on the damaging effects of gastric acid. This gives rise to symptoms of which heartburn, retrosternal discomfort, dysphagia, and regurgitation are the most common. In approximately 50% of patients, complications occur such as esophagitis, stricture formation, or the development of Barrett’s esophagus. The movement of gastric contents beyond the esophagus is known as extraesophageal reflux. This reflux beyond the esophagus is also called gastropharyngeal reflux (GPR) or laryngopharyngeal reflux.

In otolaryngology, a variety of symptoms and diseases might be ascribed to GER as well as to GPR, such as globus pharyngeus, dysphonia, dysphagia, sore throat, chronic throat-clearing, subglottic stenosis, posterior laryngitis, otalgia, otitis media, sinusitis, dental injury, and carcinoma of the aerodigestive tract. Two mechanisms have been advocated as explanation for the symptomatology of reflux. On the one hand, laryngeal complaints may be caused by a vagally mediated reflex from an acid-sensitive distal esophagus, on the other hand they may be a consequence of direct acid injury by the acid gastric content in tissues beyond the esophagus, such as the larynx and pharynx. Furthermore, the mucosa of the esophagus is far more resistant to acid gastric juice than the laryngopharynx. This is reflected by the presence of a decreasing acid gradient towards the upper esophageal sphincter (UES) in the esophagus in healthy persons. Therefore, both GER and GPR have to be taken into consideration when investigating reflux related disorders.

GPR however, has been a controversial issue for some time: there was a lot of discussion concerning the technique of measurement and normal values for the amount of reflux to the upper esophageal sphincter were never seriously established. Furthermore, there was some doubt if, or to what extent, GPR might give rise to laryngological complaints and disorders.

This thesis mainly focuses on the relatively unknown phenomenon of GPR, which has been linked to otolaryngological symptoms and disorders since the end of the 20th century.

Monitoring protocol

Single probe ambulatory 24-hour pH monitoring has been established as the gold standard to demonstrate GER. A single probe located just proximal of the lower esophageal sphincter (LES) cannot detect the extent of the reflux up to the level of the UES. Therefore, 24-hour ambulatory double-probe pH monitoring appeared to be
more suitable in detecting changes at both the lower and the upper esophageal sphincter. Only a few studies have been published with the double-probe pH monitoring technique and only very limited data on GPR are available. Despite the appealing idea of a double-probe system, enabling to study the flow of acidity in the esophagus, which seemed mandatory for a correct GPR analysis, there was a lot of debate concerning proper positioning of the pH sensors and especially the positioning of the proximal probe, the normality of data, and the method of analysis, with or without dietary restrictions, the discarding of meals or postprandial periods, etc.

As to the placement, some authors placed the proximal probe just below the UES in the proximal esophagus, others above the UES in the hypopharynx. They did not realize the technical difficulties of the pH registrations in the hypopharynx. Acid exposure in the hypopharynx could be missed easily because of the relatively large space within the hypopharynx. Also, the physical requirements for intraluminal pH recording dictated a relatively constant maintenance of impedance between the intraluminal probe and the reference skin electrode. However, in the hypopharynx the proximal probe would be intermittently dry and moist, depending whether the probe is in contact with the mucosa or floating freely in the hypopharyngeal space. These changes alter the impedance of the circuit, resulting in artifacts called "pseudoreflux". The proximal probe then records isolated pH drops without a concomitant episode of esophageal acidity registered by the distal probe.

Theoretically, the best position for the proximal probe should be just inside the esophagus within the circumference of the UES. The probe is then as close as possible to the larynx with a more or less permanent contact with the mucosa during the 24-hour period. To standardize the positioning of such a probe within the area of the UES and to develop a method that made the use of manometry superfluous, a study was undertaken to investigate the positioning of the upper probe by plain view through a flexible laryngoscope (chapter 2). Firstly, both the positions of the LES and UES were assessed with the help of manometry. Then, the manometric findings were compared with the location of the UES, as observed with the flexible laryngoscope. The results showed that positioning of the proximal probe with a flexible laryngoscope was as reliable and consistent as positioning with the aid of manometry. Since manometry is expensive (equipment, extra staff, training) and not widely available in an ENT-department this was clearly cost-effective. However, the disadvantage of this technique was the unknown position of the distal probe. For correct GER analysis, the distal probe should be positioned 5 cm above the upper border of the LES. With the direct view technique and the fixed distance of 15 or 20 cm between both probes, the exact position of the distal probe might fluctuate over a distance of 5 cm. Therefore, we also used the pH step-up method to estimate the
position of the LES, which locates the pH transition point (introduction of the probe into the stomach where an acid pH is present and then pulling back the catheter into the esophagus until a more alkaline pH is noticed). However, this technique is not as accurate for localization of the lower sphincter as manometry. Should the length of the esophagus be calculated from a formula as is customary in children, positioning of the distal probe close to the ideal 5-cm above upper border LES would be feasible. Finding such a formula can only be achieved by measuring the length of the esophagus in the general population and relating these measurements to gender, height, race, etc. Notwithstanding this, the exact position of the distal probe for monitoring of GPR is not that crucial as it only served to study the flow of acidity in time.

After standardization of the positioning technique the next step was to determine normal values (chapter 2). Double-probe 24-hour pH-metry was performed in volunteers. In contrast to the physiologic reflux events at the distal probe, hardly any events were detected at the level of the UES in healthy persons. The mean reflux episode frequency during the 24-hour monitoring was 1.8, (95% CI: 0.06-3.54, range 0-17). For the percentage of total time of pH below 4, we found a mean of 0.01% (95% CI 0-0.02, range 0-0.1) and for the fractions of time upright and supine position a respective percentage of 0.02% (95% CI 0-0.04, range 0-0.2) and 0.0%. Our recording device measures times with pH below 4 in steps of 0.1% and in view of the ranges found in these 20 normal volunteers we considered the percentage of time more than 0.1% for the total time, 0.2% for the upright and 0% for the supine time of pH below 4 to be pathological. As to the number of reflux episodes, we considered more than 3 reflux episodes to be pathological. The few studies on normal values for GPR presented nearly the same results. Especially reflux in the supine position seems to be abnormal. When compared to the normal values established for GER, which are 5.5% for the total time, 8.2% for the time spent upright and 3.0% for the time spent supine, these GPR values are obviously much lower.

Since physiological reflux episodes at the proximal esophagus/hypopharynx region are almost absent, pH changes caused by artifacts may bias the outcome considerably and thus can easily lead to false positive GPR findings. As to the diagnosis of pathological GER, artifacts are less problematic because these are already accounted for in the so-called physiological reflux data. For a correct diagnosis of GPR to be made, the 24-hour pH data should be corrected for these artifacts necessitating meticulous analysis of the complete 24-hour data set. Artifacts are caused by the above-mentioned pseudoreflux but also by the intake of acidic foods and drinks. Acidity, first registered at the proximal probe and subsequently at the distal probe, signifies a normal passage of acidic foods.
However, a low pH, first seen at the distal probe followed by a low pH at the proximal probe, is compatible with acid reflux. The distinction between the two can only be made by a visual analysis of every minute of the pH-tracings on the computer screen. This analysis is quite elaborate and therefore we tried to find a method to reduce this work (chapter 6). Because a lot of artifacts were caused by the intake of food and beverages, we studied whether elimination of food and beverages and elimination of food and beverages together with a postprandial period of 2 hours would eliminate the artifacts. A much larger set of data was required which allowed us to update our normal values and to search for an easier analysis of GPR data.

The manually corrected data (by visual analysis of the tracings) agreed well with the data obtained by leaving out the intake time of meals and beverages. Many of the false positive, i.e. non-existing, reflux episodes could be removed. However, we found a chance of 9-18% that subjects are labeled as non-refluxers when meals are excluded from the analysis, who nevertheless suffer from GPR. This might implicate underdiagnosis and therefore we advise in cases with a negative test but with a high suspicion on reflux the meticulous study of the tracings by hand. Keeping this in mind, we think that in scientific reports the visual analysis should be employed, but in routine ENT practice the uncorrected data should be used for the LES and the meal period corrected data for the UES. Doing so, only a small part of the information will be lost. Ideally, a computerized analysis of the pH tracings, regarding the temporal relationship of both proximal and distal pH tracings, should become available.

As is shown. GPR monitoring requires a careful analysis of the data afterwards. Another problem might be the duration of the monitoring period. The quantification of GPR during 24 hours may suffer from a day-to-day variability. Although patients were stimulated to carry out normal daily activities without restrictions as to their diet, drinking, and smoking, reflux promoting factors such as certain activities or foods may not be present during this 24-hour monitoring period. Intermittent reflux episodes related for example to an occasional fatty and heavy meal might have been missed resulting in a negative pH test in a symptomatic patient. However, in practice repeated 24 hours measurements or a prolonged monitoring period might not be acceptable for a patient.

After having standardized our monitoring technique and having established normal values with the recognition that GPR data had to be manually corrected for artificial reflux, we studied patients with otolaryngological complaints and disorders suggestive for reflux.
EXTRAESOPHAGEAL MANIFESTATIONS OF REFLUX

Globus and hoarseness
Globus is a challenging but largely unresolved symptom in otolaryngology. Patients with a persisting sensation of a lump in the throat without dysphagia, odynophagia, or clear abnormalities on routine examination were diagnosed of having globus. We adhered strictly to this definition of globus but many studies evaluating the relationship between globus and reflux did not meet these strict criteria. Twenty-seven patients with complaints of only globus were selected and a pathological GER and GPR was present in about one-third of the cases, which is in agreement with other studies using the same strict definition of globus. Unfortunately, the number of patients was too low to enable us to study the influence of profound acid inhibition by proton pump inhibitors in a randomized, placebo-controlled, way.

Twenty-five patients had complaints of both globus and hoarseness. Surprisingly, we found a pathological reflux (GER and/or GPR) in 84% of these patients. Since the combination of globus and hoarseness showed a high prevalence of reflux, we investigated also patients with hoarseness in the absence of abnormalities of the larynx. To exclude abnormalities, we used flexible endoscopy but, as no stroboscopy was performed, one must realize that subtle abnormalities might have been missed. In only 9 out of 20 patients (45%) with hoarseness, we found a pathologic reflux (GER and/or GPR). Therefore, the complaint of hoarseness alone did not suffice to explain the high prevalence of reflux in patients with globus and hoarseness combined. Perhaps, a chance of finding abnormal reflux is higher in the presence of more disabilities. Here also, a randomized placebo-controlled acid inhibition might shed light on the role of acid.

Furthermore, one might question whether patients presenting with this combination of complaints should undergo an endoscopy of the esophagus anyway. In 65% of the patients with pathologic reflux values, we found abnormalities in the esophagus by endoscopy. To answer this question prospective studies are needed. Furthermore, it would be interesting to classify patients as to their degree of hoarseness by objective voice analysis as well as to different disorders, causing hoarseness, and to investigate the role of acid reflux and profound acid inhibition.

Head and neck cancer patients
Already more than two decades ago, a relation between acid reflux and cancer of the upper aerodigestive tract has been suggested. Since smoking and alcohol increase acid reflux, the observed reflux may only be due to this habit. However, also nonsmokers with laryngeal carcinoma demonstrated a high prevalence of pathological reflux, pointing towards the fact that reflux might be a co-factor, or
an etiological factor, in the development of laryngeal cancer. If so, acid gastric juice should pass the UES and reach the larynx and pharynx to induce precancerous lesions, finally leading to a carcinoma. Especially in these patients, the monitoring of GPR is of paramount interest. Until now, only Koufman investigated these patients with the double-probe pH monitoring technique. We also investigated head and neck cancer patients and found a high percentage of pathologic reflux as well. Unfortunately, head and neck cancer patients are a heterogeneous group of patients with laryngeal and hypopharyngeal carcinoma. Another point of criticism is that this was also a cross-sectional analysis. The ideal situation would have been to prospectively investigate patients. However, a prospective study in these patients can only be done when already precancerous lesions are diagnosed. Whether acid reflux is a factor in the development of head and neck carcinoma, remains therefore still unproven. So far, we can only conclude that reflux is a common event in these patients. Furthermore, it would be interesting to perform a well-designed pH study in nonsmokers with laryngeal carcinoma. We tried to find these patients but could not find any. With respect to radiotherapy, we could not find a difference in reflux between untreated and treated patients, but numbers are small. In laryngectomized patients, we did find a higher prevalence of GER and GPR. This observation might well be related to preexistent pathologic reflux, whereas extensive surgery might also compromise the reflux barrier. Ideally, a preoperative assessment of GPR and GER and prolonged follow-up after therapy should be performed. Simultaneously, any benefit of preventing or treating acid reflux postoperatively should be investigated, since some reports in the literature refer to its negative role in the healing process.

Conclusions

Based on the results of this study, the following can be concluded:

1. Endoscopic placement of the proximal probe in the UES is a reliable method for GPR monitoring. A distal pH probe is mandatory to assess the flow of acidity.
2. In healthy subjects, acid exposure is low at the level of the UES when awake, and no acid exposure is seen when asleep.
3. The intake-corrected 24-hr pH test might be the second best after the time-consuming visually corrected pH test of GPR. For scientific purposes and when in doubt, it remains necessary to manually review the computer-generated data of each episode of pH below 4 at the proximal probe to ensure the recording of true reflux events.
4. There is no distinct relation between pathologic reflux and globus or
hoarseness. A relationship between pathologic reflux and globus combined with hoarseness is more likely.

5. Pathologic reflux is a common event in head and neck cancer patients and laryngectomized patients. Presumably, all head and neck cancer patients should be investigated for reflux and, in the presence of pathologic reflux, be treated with reflux prophylaxis immediately after surgery, during radiotherapy and/or during follow-up.

Since GPR and GER may be important in otolaryngological disorders, further research as to its extent and treatment is mandatory. Suggestions for future research are on:
- the achievement of consensus on GPR monitoring, necessitating more studies in different centers on monitoring technique, normal values, on the highly debated issue of dietary restrictions, refraining from smoking, etc.
- the performance of placebo-controlled treatment studies together with prospective and repeated double-probe pH-metry in otolaryngological disorders found or assumed to be related to acid reflux.
- the investigation of the role of the different other components of gastric juice, for example pepsin and bile. Until now, a major drawback is the measurement technique, which is too complex to investigate properly the role of bile in laryngological disorders.
- the investigation of the role of reflux in head and neck cancer patients in relation to their smoking and drinking habits and in relation to their treatment (laryngectomy, radiotherapy or their combination).
REFERENCES
