

Gastroesophageal reflux and chronic respiratory disease: past, present, and future

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Introduction

A very interesting case-control study published in this issue of *Jornal de Pediatria* concludes that nasopharyngeal pH is significantly lower in patients with respiratory symptoms and abnormal pH-metry in comparison to those children presenting with gastroenterological symptoms.¹ Children with respiratory symptoms and abnormal pH-metry have a more acid nasopharynx than the patients in the control group. Measurement of the nasopharyngeal pH can be considered a reliable test to indicate the likelihood of obtaining an abnormal esophageal pH-metry in patients with chronic respiratory disease.

There has been general consensus that investigations measuring reflux during the postprandial period (ultrasound, radiology, scintigraphy) are of limited value in the diagnosis of gastroesophageal reflux (GER) disease because of the high prevalence of GER in the postprandial period.² The percentage of non-acid reflux episodes as evaluated with esophageal impedance on the total number of GER-episodes varies between 40 and 89%, although the majority of publications report an incidence of about 50%.³ The different types of GER evaluated by impedance are listed in Table 1. Mattioli et al. reported in a series of 50 children with typical and atypical GER symptoms that the incidence of reflux detected by impedance was twice the incidence of reflux detected by pH monitoring.⁴

Diagnosis of GER in patients with respiratory symptoms

Questionnaires are the most simple and most child-friendly diagnostic investigation.⁵ A questionnaire is nothing more than the development of a scoring system based on the answers to validated questions that are asked during history taking. However, the correlation between the results of questionnaires and investigations such as endoscopy and pH monitoring is rather poor.⁶ Upper gastrointestinal series (UGIS) are of interest if anatomical abnormalities, such as malrotation, are suspected. Ultrasound has the advantage of being non-invasive, but the result depends on the experience of the investigator. Scintigraphy can demonstrate pulmonary aspiration, but this is so rare that it is not performed as a routine. Endoscopy and biopsy are invasive, but they are the only techniques that can diagnose esophagitis. Histology also allows the diagnosis of other conditions such as "eosinophilic esophagitis". A normal endoscopy and normal histology do not rule out GER disease. Manometry is a technique that demonstrates the pathophysiologic mechanism of GER, i.e., the relaxation of the lower esophageal sphincter.

Esophageal pH monitoring is today still considered the silver standard for the diagnosis of GER disease: with this technique, the number and duration of acid reflux episodes are measured during a 24-hour period.⁶ Attention has also been given to more sophisticated pH monitoring, by performing pH-metry in the lower and upper esophagus simultaneously.⁷ Impedance has the advantage of measuring not only the acid reflux, but also the non-acid one. There is also some literature suggesting that the continuous measurement of bile in the esophagus ("bilitec") might be useful.⁸

Finally, some other techniques have been proposed. The majority of the studies conclude that fat-laden macrophages

**See related article
on page 225**

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or their index have a too low sensitivity or specificity to be clinically useful.⁶ Some recent data suggest that determination of pepsin in bronchial aspirates may be more sensitive and specific. In preterm babies, the presence of acid in the oropharyngeal secretions may help in the prediction of acid GER.⁹ The method is simple, inexpensive cheap and involves minimal disturbance.

Correlation between GER and clinical symptoms

Chronic bronchitis, wheezing, chronic cough and infant apnea have been related to GER. Wenzl et al. suggested a strong relation between acid and non-acid GER and respiratory abnormalities: in a group of 22 children presenting with repetitive regurgitation and chronic respiratory symptoms, impedance recorded 364 reflux events, of which only 11.4% were acid.^{5,10} The analysis of the polysomnographic recording showed 165 episodes of apnea, of which 30% were associated with a reflux episode; the majority (78%) of reflux episodes were detected with impedance only.¹⁰ However, the association between pathological central, obstructive or mixed apnea has not been demonstrated (but this has not been well studied yet). Clear cutoff values discriminating normal from diseased children still need to be established. When compared with pH monitoring, impedance is a technique that

allows more accurate demonstration that apnea of short duration is likely to be a physiological phenomenon occurring more frequently than an episode of GER.¹¹ Nineteen preterm infants (gestational age of 30 weeks) presenting with apnea were studied at a mean age of 26 days (13-93 days)¹²: 2,039 episodes of apnea (median: 67; range: 10-346), 188 oxygen desaturations (median: 6; range: 0-25), 44 bradycardias (median: 0; range: 0-24) and 524 episodes of GER (median: 25; range: 8-62) were detected.¹² The frequency of apnea in a 20-second period before and after an episode of GER was not different from the frequency of apnea unrelated to a reflux episode [0.19/min (0.00-0.85) vs. 0.25/min (0.00-1.15)].¹² The analysis and conclusions were identical for oxygen desaturations and bradycardia.¹² Mousa analyzed the temporal relationship between apnea and GER in a group of 25 infants presenting with an apparent life-threatening event (ALTE) or pathological apnea.¹³ A time interval as long as 5 minutes between apnea and reflux was considered acceptable to demonstrate a "temporal link" between the two phenomena.¹³ In total, 527 apnea episodes were recorded, but only 80 (15.2%) were temporally linked to a reflux episode. Of these 80 episodes, 37 (7.0% of the total episodes of apneas) were related to acid reflux and 43 (8.2%) to non-acid reflux. Thus, even considering a time interval of as long as 5

Table 1 - Types of gastroesophageal reflux detected by intraluminal impedance

Liquid GER: drop in impedance to less than 50% of baseline values

Acid GER: pH falls below 4 for at least 4 seconds or, if pH was already below 4, as a decrease of at least 1 pH unit sustained for more than 4 seconds

Non-acid reflux: weakly acidic and weakly alkaline GER

Weakly acidic reflux: pH drop of at least 1 pH unit sustained for more than 4 seconds with basal pH remaining between 7 and 4

Weakly alkaline: pH did not drop below 7

Gas reflux: rapid and pronounced rise in impedance

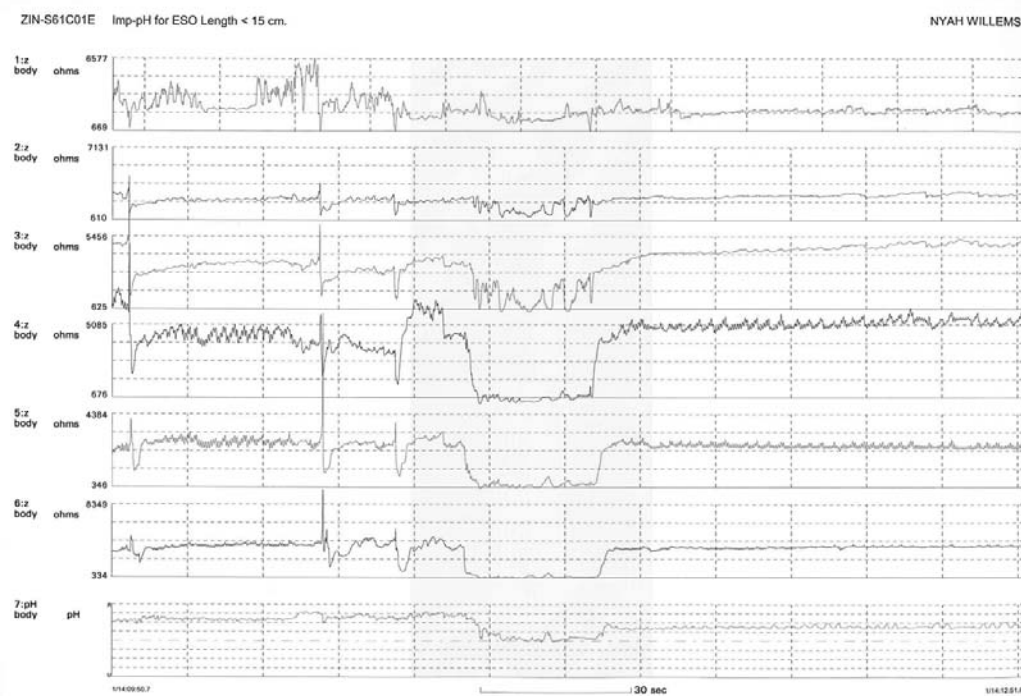


Figure 1 - A weakly acid reflux episode recorded by impedance (the drop in impedance is accompanied by a drop in esophageal pH, which does not decrease below pH 4.0)

minutes, one can conclude that the relation between reflux and apnea exists, but it is rare. The majority of the reflux events reach the proximal esophagus or the pharynx.¹³ The lack of difference between asymptomatic and diseased infants contravenes the hypothesis for macro- or microaspiration, but does not exclude hypersensitivity to reflux as a cause for respiratory symptoms.

Chronic respiratory manifestations such as coughing and wheezing are reported to occur in children with reflux disease. Rosen et al. reported their experience with 28 children (mean age: 6.5 ± 5.6 years) with chronic respiratory disease under antacid treatment.¹⁴ A total of 1,822 episodes of reflux were measured with impedance; 45% of them were non-acid. A multivariate analysis showed a stronger association between respiratory symptoms with non-acid reflux episodes than with acid reflux episodes.¹⁴ Also the height of the refluxate in the esophagus was associated with respiratory symptoms: the higher the reflux, the stronger the association.¹⁴ However, it seems obvious that pH monitoring detects less reflux during antacid treatment, and that such a pH monitoring score also has to be considered abnormal. In a selected group of 22 adults, a relation between chronic coughing and GER has been accurately studied by combined manometry

and impedance.¹⁵ Using a time frame of 2 minutes and symptom association probability, 69.4% of the coughing episodes were considered "independent" of a reflux episode. When a "reflux-cough" sequence occurred, the reflux was acid in 65% of the cases, weakly acid in 29% and weakly alkaline in 6%.¹⁵ In a series of 25 children (aged 6 months to 15 years) with unexplained chronic cough, wheeze or sputum production, the data support a relation between acid GER and chronic pulmonary symptoms, but do not support a role of non-acid reflux in children with respiratory symptoms not treated with antacid medications.¹⁶ Condino et al. studied 24 children with recurrent asthma and concluded that acid and non-acid reflux occurs with equal frequency in children with asthma and that most symptoms occur in the absence of a reflux event.¹⁷ The contradictions in the literature on the role of acid and non-acid GER in children with chronic respiratory symptoms may be explained, in part, by the fact that this literature does not consider whether reflux is primary (motility disorder) or secondary (to infection, allergy, respiratory efforts, etc.).

Conclusion

The measurement of the nasopharyngeal pH during a 24-hour pH-metry in children with chronic respiratory dis-

ease is an additional valuable parameter. However, this parameter does not inform us about the pathophysiological mechanism involved.

The diagnostic sensitivity of impedance may correspond to that of the pH probe in untreated patients, but it is superior to the pH probe in patients treated with antacid medications (Figure 1). Episodes detected only by pH monitoring are numerous in children; therefore, pH monitoring should be included in pH impedance analysis.¹⁸

Although impedance clearly records more GER events than pH monitoring, the advantage and/or the relevance to record “more” episodes of GER in daily clinical practice still needs to be demonstrated. Today, impedance should still be considered a (clinical) research tool. The clinical relevance of the detection of weakly acid and non-acid reflux is also still a matter of research because data are currently inconclusive and specific treatment is not available. Symptom correlation analysis, especially for extraesophageal symptoms, is likely to be more convincing with impedance than with pH monitoring.¹⁹ However, this evidence is still missing.

However, since pH monitoring is part of impedance recording, it is very likely that impedance will be more frequently performed in routine practice. From the above data, it emerges that it is currently difficult to draw conclusions on the advantage of the routine application of impedance in children to detect GER events because of the heterogeneity of the studies (in terms of population recruited and technical criteria such as time and symptom association), the lack of normal data and of outcome measures. The major advantage of impedance may be the demonstration of a better correlation in time between symptoms and reflux compared to pH monitoring rather than an improved diagnosis of GER disease as such. Clinical research on impedance should focus on “symptom index” (percent of reflux associated with symptom episodes), “symptom sensitivity index” (percent of symptoms associated with reflux episodes) and “symptom association probability” (calculation of the statistical relationship between symptoms and reflux episodes using Fisher’s exact test).²⁰ However, the simple fact that the parents have to push the “event marker” on the recorder and/or have to record the symptoms in a diary represents a major handicap. Adults have been shown to record only 39% of the cough episodes detected by simultaneous manometry.¹⁵ More homogeneous criteria of inclusion and analysis associated with complete baseline and prospective clinical features are mandatory. Impedance is a new, promising technical development offering unexplored possibilities to investigate GER. In the meantime, measurement of nasopharyngeal pH seems appropriate to

separate children with chronic respiratory disease related to GER from those in whom the respiratory symptoms are not related to reflux.¹

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