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A Review of Esophageal pH Monitoring for the Diagnosis of Gastroesophageal Reflux in Children

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Abstract Gastroesophageal reflux (GER) is a common disease found in early childhood. It commonly presents with vomiting and feeding problems. However, it may involve other systems like respiratory system, growth failure. Twenty-four hours esophageal pH monitoring is a useful technique in diagnosis of gastroesophageal reflux. Results of 24 hours esophageal pH monitoring should be correlated with clinical features before and during the procedure. As the conventional esophageal pH monitoring only detects reflux into the distal esophagus, reflux that reach beyond upper esophageal sphincter would not be detected. This so-called extra-esophageal reflux could cause a myriad of upper and lower airway symptoms. To address this problem, a special technique called dual probe esophageal pH monitoring of both distal esophagus and hypopharynx was reported to be useful.

Key words Children; Gastroesophageal reflux; Esophageal pH monitor

Introduction

Intraesophageal pH monitoring was first introduced by Spencer almost three decades ago.[1] In 1974, Johnson and Demeester reported their pioneering studies of 24 hours pH monitoring of distal esophagus in adult patients.[2] Subsequently, there have been numerous studies documenting the usefulness of 24-hour pH study, both in adult and paediatric patients. Over the past ten years, 24 hours lower esophageal pH monitoring has been established as the gold standard for documenting gastroesophageal reflux (GER).

Pathophysiology of GER

At birth, the esophagus measures about 8-10 cm in length. This length doubles during the first two to three years of life and eventually reaches a length of approximately 25 cm in adults.[3] The normal gastroesophageal function depends on effective esophageal motility, basal contractility and synchronous relaxation of the lower esophageal sphincter, mean intraluminal pressure in the stomach, effectiveness of gastric emptying, and ease of gastric outflow.[4]

Gastroesophageal reflux is defined as involuntary passage of gastric contents into the esophagus. This can be a normal physiological event that occurs mainly after meals during daytime in healthy people. It becomes pathologic when it is frequent, prolonged and/or causing symptoms. It is a common cause of morbidity in childhood.[5,6] The extra-esophageal reflux or laryngopharyngeal reflux is defined as gastric acid reflux to the more proximal level of the pharynx. This is an entity that is becoming more well recognized in the past decade as a cause of so-called atypical symptoms in GER.[7]

There are several mechanisms responsible for gastroesophageal reflux. The most important one is the transient lower esophageal sphincter relaxation (TLESR). It is a 3-35 seconds abrupt period of complete sphincter relaxation usually against a background of normal sphincter tone. It may occur independent of swallowing and is considered as a major mechanism for GER in both infants and adults.[8,9]

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The "defective basal contraction of the lower esophageal sphincter" or low basal sphincter tone permits retrograde escape of gastric content. This accounts for a minority of reflux episodes and usually occurs in patients with severe GER.[10] A transient increase in intra-abdominal or gastric pressure will also cause reflux. In most normal individuals, some degree of GER occurs post-prandially due to rise in intra-gastric pressure with relaxation of lower esophageal sphincter when synchronized with swallowing.[10] In newborn infants, the increase in intra-abdominal pressure during crying or straining causes increased frequency of GER. However this problem may improve over time.[4] Delayed gastric emptying is an important factor causing reflux in cerebral palsy patient with autonomic neuropathy. It causes gastric distension with increased gastric pressure and increases the number of TLESR as well.[3,4]

The presence or absence of an intra-abdominal esophagus also contributes to the frequency of GER. In infants, the intra-abdominal part of the esophagus is under-developed and this favors escape of the gastric content into the esophagus. The angle of indentation of the esophagus into the gastric fundus also contributes to the competence of sphincter. The blunting of the angle results in inefficient protective mechanism and promotes reflux. Patient with hiatus hernia, the intra-abdominal part of the esophagus is virtually absent. It results in a negative intrathoracic pressure surrounding the sphincter with an abolished angle.

In normal individual, all acid that enters the esophagus is emptied by one to two peristaltic waves. If the primary and secondary peristalses are disturbed, the esophageal acid clearance is impaired and leaves the esophagus exposed to noxious refluxate.[3] The clearance of refluxed material from the esophagus is particularly delayed during the night because of multiple reasons. These include elimination of effect of gravity on esophageal content at supine position, decrease in saliva production and decrease in peristalsis secondary to swallowing. It is observed that supine reflux is particularly important in the development of esophagitis.[11]

The constituents of refluxate include saliva, ingested foods and drinks, gastric, pancreatic or biliary secretions. Saliva increases the pH of the esophagus up to 6.8. It is considered as a defense mechanism against the development of esophagitis.[12] Other protective factors are esophageal mucus, increased mucosal blood flow and capillary epithelial growth factors.[3] Concerning the constituents of gastric juice, pepsin is more noxious for the esophageal mucosa than acid. Trypsin and deconjugated bile salts may induce esophageal injury at neutral pH, whereas conjugated bile salts may cause injury at acid pH.[3] The recently recognized phenomenon of duodenogastroesophageal reflux with duodenal secretion reflux into esophagus may cause significant esophagitis.[13]

Clinical Features of Gastroesophageal Reflux

(Table 1)[14]

Children with gastroesophageal reflux commonly have more refluxing episodes when in supine position. Common GER symptoms are vomiting, feeding problems, dysphagia, heartburn, and failure to thrive. Barrett's columnar mucosal changes in the lower esophagus are not infrequent in adolescent children with chronic GER, particularly when Helicobacter pylori is present in the gastric mucosa.[4]

Concerning the extra-esophageal complication of GER, the intermittent acid reflux into the nasal cavity, pharynx, larynx and pulmonary tree do not have the classic symptoms of heartburn or acid regurgitation and are seldom associated with esophagits.[15] However, it contributes to the so-called extra-esophageal symptoms. The more well known symptoms are acute airway obstruction with laryngospasm or bronchospasm causing ALTE, choking, recurrent cough, wheezing, exacerbation of bronchopulmonary dysplasia, worsening of asthma, and recurrent aspiration pneumonia.[9] Other rarer otolaryngologic presentation includes reflux rhinitis, chronic sinusitis, reflux laryngitis with hoarseness, globus pharyngeus (the sensation of having a lump in the throat), otalgia, laryngeal or vocal cord contact ulcers and granuloma, laryngomalacia, and subglottic stenosis.[16]

Although 24 hours lower esophageal pH monitoring has been established as the gold standard for documenting GER, the lower esophageal pH monitoring is not useful in detection of extra-esopharyngeal reflux (or pharyngeal reflux). The use of proximal pH monitoring or dual probe pH monitoring can document GER in patients with upper airway disorders or extra-esophageal symptoms.

Investigations for Suspected GER

Several investigations are available for diagnosis of GER.[17] These include pH probe, endoscopic examination, radio-isotope milk scan, barium radiography. It is beyond the scope of this paper to discuss all except pH probe in details. Endoscopic examination is an invasive procedure that requires sedation or general anaesthesia. Its advantage over pH probe is availability of esophageal biopsy specimen for documentation of esophagitis, concomitant examination

Table 1 Symptoms of GER

1) esophageal symptoms	2) Neurobehavioural symptoms
• regurgitation and vomiting	• Sandifer-Sutcliffe syndrome
• haematemesis and melaena	• seizure-like events in infants
• epigastric or retrosternal pain	
• heartburn	
• anaemia	
• irritability	
• feeding problem	
• esophageal stricture	
• failure to thrive	
• Barrett's esophagus in adolescent	
3) extra-esophageal symptom (may be more acutely dangerous in VLBW infants)	4) Otolaryngologic symptoms
• aspiration pneumonia	• Rhinitis
• ALTE	• Sinusitis
• Apnoea	• reflux laryngitis
• Stridor	• globus pharyngeus
• cyanotic episodes	• otalgia
• recurrent cough	• laryngomalacia
• wheeze	• subglottic stenosis
• intractable asthma	• contact ulcers and granuloma in vocal cord
• worsening of existing respiratory condition e.g. cystic fibrosis, BPD	

of laryngeal inlet and anatomy of upper gastrointestinal tract. Radio-isotope milk scan is a non-invasive physiological procedure. When compared with pH probe, its main problem is the short sampling time with associated decrease in sensitivity of the test. Barium radiography entails unphysiological drinking, i.e. milk thickened with barium and radiation exposure. Its advantage lies with ability to delineate structural anomalies of the upper gastrointestinal tract. Hence, use of these diagnostic tests depends on availability and exactly what questions need to be answered.

Intraesophageal pH Monitoring

Patients with symptom listed in Table 1 would raise the question whether the symptoms are associated with GER. The pH probe would then be an appropriate study to answer this question. For patients who present with otolaryngologic symptoms, special technique such as 'dual probe' or pharyngeal pH monitoring should be considered instead.

The technique of performing the study and the choice of pH recording equipment will influence the accuracy of results. Standardized protocol has been proposed by a working group of the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN).[18] The recording device is a small box that allow high portability so as to include as much normal activity as possible. During the 24 hours of the study, the patients are allowed normal diet and unrestricted activity.[19] Data are collected in the recorder for 24 hours. The data are downloaded into a computer at the end of recording. Then graphic and numerical displays can be presented. The patients are instructed to record activities and events like eating, drinking, change of position and occurrence of symptoms. In the authors' experience, it is preferable to use a detailed diary to mark the events instead of pressing the button of the recorder by parents. Glass or monocrystalline antimony electrodes are being used. Calibration is necessary for standardization and is fundamental for the reliability of the measurement. Calibration is done before the procedure and the system ideally should also be calibrated after the procedure is completed. The reference electrode is placed on the skin of the patient as close as possible to the esophagus.

For standard recording, the pH electrode is placed in adult 5 cm above the manometry determined lower esophageal sphincter. The Strobel formula allowed

estimation of the lower esophageal sphincter in paediatric patients. Fluoroscopy is considered the most appropriate method to check the exact location of the electrode. The location of the tip of the probe should be at the third vertebra above the diaphragm. Prokinetic agent should be discontinued at least 48 hours before the procedure, H-2 antagonist at least 3 to 4 days and antacids at least 24 hours before the investigation.

Dual Probe Esophageal Monitoring

In the 1970s, Fearon and Brama recognized reflux as a cause of various respiratory symptoms in children. Subsequently, there has been increasingly more awareness on this aspect. During the past decade, reports of extra-esophageal reflux have appeared more frequently. The reflux episodes occur through the upper esophageal sphincter into the nasal cavity, pharynx, larynx and tracheobronchial tree. These was not documented by the traditional esophageal monitoring until 1986, when Koufman and Wiener et al demonstrated that pharyngeal reflux could be detected in adults by placing a pH sensor in the pharynx.[7] The use of dual system determine whether events recorded proximally are associated with distal acidification. No consensus exists for the placement of the proximal probe. In adult, it may be placed 20 cm above the lower esophagus, just below the upper esophageal sphincter or in the hypopharynx. Anti-reflux treatment is indicated in the presence of proximal reflux and this is associated with improvement of symptom in adult patients.[20] Matthews et al reported a prospective study of 222 children underwent 24-hour dual probe (i.e. simultaneous esophageal and pharyngeal) pH monitoring. The data suggested that extra-esophageal reflux may be underestimated by single-probe intraesopharyngeal monitoring alone and laryngopharyngeal reflux or proximal reflux may play a role in the pathogenesis of airway symptom.[7] Dual probe is mainly useful for atypical cases with extraesophageal presentation and normal pH monitoring of the distal esophagus.

Short Duration pH Monitoring

Prolonged esophageal pH monitoring of at least 18 hours is the most accurate method for detecting abnormal GER. However, the child's discomfort and the cost of overnight hospitalization are major disadvantage of prolonged esophageal pH monitoring.[21] Recent efforts have been directed at further simplifying pH monitoring by decreasing its duration. Some investigators have found that short-duration post-prandial pH monitoring in the up-right position is also useful. However, there has been no consistant data suggest its routine use in diagnosis of GER. The choice of postprandial period is based on observation that both patient and normal subjects experience more reflux during this period. Friesen et al evaluated the three different scoring methods for diagnosis of GER in children. The late post-prandial method is most sensitive in detection of GER-induced ALTEs. However, the correlation among the methods were suboptimal.[22] Further study is needed to determine the predictive value, sensitivity and specificity of these methods.

Interpretation

A pH of 4 is regarded as the cut off level for acid GER. The standard parameters calculated are the total number of episodes with a pH less than 4.00, the number of episodes lasting more than 5 min with a pH less than 4.0, the percentage of time related to the total duration of the investigation with a pH less than 4.00 (reflux index). The reflux index is now the most important criterion for measurement of refluxes. GER is a naturally occurring event, the 'normal' and 'abnormal' value will be overlapped inevitably. Percentile curves proposed by Vandenlpas et al may be used to define whether a result deviated from normal ranges or not. The working group of ESPGAN also recommend to relate 'events' to pH changes to diagnosed GER.[6,18] The relatively new parameter, 'area under pH 4.0', provides additional information on acid exposure, which is considered as a major contribution in the development of reflux esophagitis. The specificity in the prediction of esophagitis was 88% compare to 50% with the use of reflux index. The sensitivity of both parameters were comparable, which is 96% and 93% respectively.[23] Results of pH study are best interpreted by a person who is experienced in the procedure and with understanding of the clinical problem. It is important to study the whole tracing and not just the summary data alone. Artifact such as disconnection of the probe or electrodes may pass undetected unless the whole tracing is examined carefully.[6] Interpretation of the data is further complicated by the fact that there is no threshold value of esophageal acid exposure that directly predicts esophagitis. Other than acid exposure time, esophageal mucosal acid sensitivity, mucosal resistance to inflammation, the extent of mucosal acidification or the

constituents of the refluxate other than acid may cause GERD and esophagitis.[24]

Artifact Related to Technical Problem

Glass electrodes are generally more accurate than antimony electrodes. They have a very small linear drift (an intrinsic problem of the electrode that result in deviation of reading form actual value). Antimony electrodes are more susceptible to drift. The electrodes may not be H+ selective and tend to read up to 1.0 pH higher than actual value.[13] The accuracy of antimony electrodes could be improved if the buffer solution were heated to body temperature during calibration, but even with this, an error of up to 0.5 pH unit was noted. The consumption of hot or chilled beverages and foods may affect the results when antimony electrodes are used. Cold will decrease the reactivity of the electrode for a prolonged period whereas heat will increase the sensitivity of the electrode.[18] The position of electrode may have an important impact on the detection of pH changes. Manometry is the most accurate method to define the lower esophageal sphincter. However, it requires special equipment and particular expertise that is not readily available. Strobel formula is less accurate in determining the LES in children over 1 m in height. Fluoroscopy is recommended to position the electrode, this method is widely available. The tip should be positioned so that it lies over the third vertebral body above the diaphragm throughout the whole respiratory cycle.

The recording should be started at least 30 min after insertion of electrode because saliva secretion is stimulated by the presence of foreign object in the pharynx. The saliva neutrolizes the acid inside the esophageal lumen and raises the intraesophageal pH up to 6.8.

Specificity, Sensitivity and Reproducibility

The use of 24-hour esophageal monitoring for detection and quantification of GER is found to be sensitive and specific. The sensitivity and specificity was quoted as 87-93% and 93-97% respectively. In adult group of patient, the reproducibility of the test varies from 77-85%. Limited information is available regarding the reproducibility of 24-hour intraesophageal pH monitoring in paediatric patient. Vandenplas et al studied 30 paediatric patients and found that the reproducibility of 24-hour esophageal monitoring was satisfactory for routine clinical application.[24] Mahajan et al prospectively investigated 26 patient with suspected GER. The patients underwent extended intraesophageal pH monitoring over two consecutive 24-hour periods. The data analysis revealed that the overall reproducibility is only 69%.[17] There are two possible contributing factors. Firstly, the underlying variability in GER as there is considerable day-to-day variation in our amount of acid reflux.[20] Maneuvers that increase intra-abdominal pressure such as bending over may increase episodes of reflux. Physical exercise, change in posture, diet and number of hours spent sleeping may result in intrasubject variability of reflux. Secondly, the increase in the flow of bicarbonate-containing saliva after insertion of esophageal probe is different on day 1 and day 2 of the procedure. It is observed that the normal result on day 1 may be due to excessive secretion of saliva after the introduction of foreign object. The patient may adapt to the procedure with decreased saliva secretion on day 2. Therefore, typical pattern of reflux would be more likely to occur on day 2 of study. Hence a single normal 24-hour esophageal pH study in a child with symptom of GER may not be sufficient to exclude the diagnosis.[20] It is recommended that the intraesophageal pH investigation be repeated if the result does not correlate with the patient's clinical symptom.

Conclusion

GER is a common phenomenon affecting all ages. Esophageal pH monitoring is a useful diagnostic tool that should be considered as a standard investigation for diagnosis of pathologic GER. However, there are problems in interpretation of data and technical aspect that need to address to.

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