

Interpretation of Esophageal pH Monitoring as part of Multichannel Pneumogram in Neonates: Limitations and Pitfalls - A Review Article

Charles G Njinimbam*

Department of Pediatrics, Indiana University School of Medicine, Indianapolis, USA

*Corresponding authors: Njinimbam CG, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, USA, Tel: + 3179628778; E-mail: cnjinimb@iu.edu

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Abstract

This review article discusses some of the challenges associated with the interpretation of esophageal pH monitoring as part of multichannel pneumogram in neonates with suspected gastroesophageal reflux and cardiorespiratory symptoms such as recurrent apnea, bradycardia and desaturations and chronic lung disease. Several of the early studies have suggested an association between GER and apnea in preterm and term infants and this has contributed to widespread use of antireflux medications in the treatment of apnea of prematurity and infants with chronic lung disease. Despite recent studies showing no temporal or causal relationship between GER and apnea or chronic lung disease referrals from pediatricians and neonatologists in community hospitals for esophageal pH monitoring as part of multichannel pneumogram remain relevant today in the Neonatal Intensive Care Units (NICU). Interpretation of esophageal pH monitoring is particularly challenging in preterm infants because of the lack of published normative data. The reflux index (RI), which represents the percentage of the total time esophageal pH<4 is the most widely used discriminator between acid and nonacid reflux. Several factors may influence the results and this article aims to highlight some of the limitations and pitfalls of this diagnostic technique.

Keywords: Gastroesophageal reflux (GER); Gastroesophageal reflux disease (GERD); Transient lower esophageal sphincter relaxation (TLESR); Electrocardiogram (EKG); Heart rate (HR); Pulse oximetry (SpO₂); Reflux index (RI)

Introduction

Esophageal pH monitoring as part of multichannel pneumogram in the evaluation of neonates with suspected gastroesophageal reflux (GER) and cardiorespiratory symptoms remains relevant today in the Neonatal Intensive Care Units (NICU). Gastroesophageal reflux is a common problem in both preterm and term infants [1]. It is not surprising that many pediatricians and neonatologists consider GER a clinical problem, as many infants are discharged on promotility and/or antacid therapy, the most common indications being feeding intolerance, recurrent apnea, bradycardia and desaturations and neonatal chronic lung disease. Unfortunately there is very little evidence to support the widely practiced approach [2]. While esophageal pH monitoring has been shown to be the gold standard in detecting GER in infants, there exist some issues with the methodology and the interpretation of the results. This article will attempt to address some of the issues in the methodology, interpretation as well as limitations and pitfalls of esophageal pH monitoring as part of multichannel pneumogram in neonates.

Definitions

GER is the passage of gastric contents into the esophagus with or without regurgitation or vomiting [3]. It is a normal physiologic process in healthy infants, children and adults. Gastroesophageal reflux disease (GERD) occurs when the reflux of gastric contents causes troublesome symptoms and/or complications [4].

Pathophysiology of GER and GERD in Preterm and Term Neonates

The physiology of GER in healthy preterm infants and all ages is related to transient lower esophageal sphincter relaxation (TLESR) as the predominant mechanism [5]. Increased frequency of TLESR and not delayed gastric emptying is the main factor in the pathophysiology of GERD in preterm and term infants [6,7]. Increased frequency of TLESRs results in frequent exposure of the esophageal mucosa to gastric acid. As a result of this excessive exposure, the protective barriers of the esophagus become overwhelmed, leading to mucosal injury. A vicious cycle then ensues where the injured esophageal mucosa leads to more GER and more GER leads to more injury and subsequently symptoms.

The Multichannel Pneumogram and Esophageal pH monitoring

The multichannel pneumogram and esophageal pH probe monitoring combined can be used to determine whether there is any temporal relationship between GER and any of the cardiorespiratory events recorded such as apnea, bradycardia and desaturations.

The multichannel pneumogram-5 channel (EKG, HR, Respiratory Effort, SpO₂) or 6 channel (EKG, HR, Respiratory Effort, Airflow, SpO₂) combined with esophageal pH monitoring is a modality used to identify apnea, bradycardia, O₂ desaturations and gastroesophageal reflux and to show whether or not a temporal relation exists in which an episode of reflux directly precedes an episode of apnea, bradycardia or O₂ desaturations [7].

pH electrodes

Two types of pH electrodes are available for pH monitoring, monocrystalline antimony electrodes and glass electrodes. The Glass electrodes, though the best for measurement of the pH of body fluids, are large and expensive. Antimony electrodes, on the other hand, are smaller, more flexible and less expensive and can be placed easily through the nostrils and esophagus in preterm and term infants [8]. Antimony electrodes are, therefore, more commonly used for pH probe studies in preterm and term infants.

Placement of the esophageal pH probe, electrode calibration and discontinuation of medications that can affect esophageal pH

The pH probe is passed through the nostril and positioned in the lower third of the esophagus between T7 and T9, with its position confirmed by chest x-ray. The Strobel formula ($0.252x$ length in cm of the baby +5 cm) can be used as a guide to determine the distance from the nostrils to the lower esophageal sphincter (LES) [9]. The Strobel formula has been shown to be inaccurate in premature infants. It can overestimate the distance from the nares to the lower esophageal sphincter and result in the probe being positioned in the stomach [10]. A modified Strobel formula is proposed for all age groups of children but regardless of which formula is used to determine pH probe placement, radiographic confirmation of the catheter tip position should still be considered [11].

The pH probes are calibrated in standard solutions of known pH that are compatible with the type of electrode. The standard solutions used include both acidic (pH 1 and 4) and neutral (pH 7) buffer. The probes are usually calibrated at room temperature. It is recommended that at the end of the 24-hr esophageal pH recording, the calibration is repeated to detect any pH drift or electrode failure.

All medications that affect the pH of the stomach or motility of the foregut should be stopped before the study when pharmacological intervention is being considered. Antacids may be used up until the night before the study. Motility-enhancing drugs should be discontinued at least 24 hours from the evening before and during the 24-hr pH monitoring. H_2 -receptor blockers should be discontinued 48 hours and proton pump inhibitors (PPIs) should be discontinued 7 days before the study [8].

Duration of monitoring

A 24-hour pH monitoring is the "gold standard". It allows study of the circadian patterns of reflux and monitoring of the effects of physiological activity over a 24-hour period. An 18-hour period of pH monitoring, including a day and night recording, has also been suggested by the ESPGHAN working group on GER [12]. Shorter duration pH monitoring such as 3hr postprandial period and 12hr or 16h overnight have been proposed, however, there are questions about the appropriateness of these shorter duration of monitoring.

Feeding during the study

During esophageal pH monitoring infants are given their regular milk feeds, breast milk or formula every 3 to 4 hours. Infant milk has a pH of around 7. Frequent milk feeds in exclusively milk fed preterm infants can cause greater buffering of the gastric pH and limit the usefulness of esophageal pH monitoring [13]. Apple juice (pH 3-4) has been used in some studies in older infants to overcome the problem of

buffering during esophageal pH monitoring [14], but its safety in preterm infants is not confirmed [15].

Use of nasogastric tubes during the study

The presence of a nasogastric tube during the study can significantly increase postprandial reflux by nearly 70% because of stenting of the LES [16]. This should be taken into consideration when interpreting the results of the study.

Interpretation

The threshold of $pH < 4$ is the most widely used discriminator between acid and nonacid GER [8]. The onset of the reflux episode is defined as the period when an esophageal $pH < 4$ is detected, and the end as a rise in pH across the predetermined threshold level. The reflux index, RI, which represents the percentage of the total time the esophageal pH is < 4.0 threshold is considered the most valid measure of abnormal reflux. The reflux index reflects the cumulative exposure of the esophagus to acid [12].

Normal values

There are no published normal values for GE reflux in preterm infants. Studies involving preterm infants are few, of small number of subjects and yield variable results due to inconsistencies in feeding methods, positioning and ventilation. This makes interpretation of esophageal pH monitoring in preterm infants difficult. In preterm infants, a reflux index $\geq 5\%$ is recommended by Ewer et al. to be indicative of pathologic GER [15]. In pH studies performed with antimony electrodes, an $RI < 3\%$ is considered normal, $RI > 7\%$ is abnormal and an RI between 3% and 7% is indeterminate [3]. Based on studies on the largest series of mature infants the recommended upper limit of normal of the reflux index is defined as up to 12% in the first year of life and up to 6% thereafter [17]. In other words in mature term infants an acid reflux index $> 12\%$ is considered clinically significant and should represent the level at which treatment would be considered [17].

Is there a relationship between GE reflux and apnea?

GER is usually suspected in premature infants with apnea, desaturation and bradycardia because of the observation that apneas are frequent in the postprandial period when GER is most likely to occur [18,19]. A survey of pediatric specialists in the USA showed that about 45-50% of neonatologists believed that it is very likely that there is causal relationship between GER disease and apnea [20]. This observation has raised the question as to whether there is a temporal relationship between acid GER and apnea. Di Fiore, et al. showed a lack of a temporal relationship between acid GER and apnea in preterm infants and no effect on apnea duration [21].

Their study also showed that GER episodes had no effect on the lowest oxygen desaturation or heart rate during apnea. Peter, et al. also showed, in a similar study of simultaneous recordings of multichannel intraluminal impedance and cardiorespiratory signals that there was no temporal relationship between acid GER and apnea [22]. The same was true for desaturations and bradycardia [23].

Is there a relationship between GER and Chronic lung disease (CLD)?

It is not surprising for pediatric caregivers to suspect an association between GER and CLD. It is possible that GER may predispose an infant to chronic aspiration and secondary lung damage but no clear association has been established between GER and bronchopulmonary dysplasia (BPD) [22], yet Fuloria, et al. showed that GER was treated more frequently in preterm infants with CLD than in those without [24]. The observed association of GER and CLD as it turned out was due to diagnostic suspicion and not based on esophageal pH monitoring [24]. Several other studies have failed to document a relationship between GER and CLD. Akinola, et al. in their study using esophageal pH monitoring of symptomatic infants showed no observed difference in the incidence of GER in infants who had BPD (defined as oxygen requirement at 28 days) compared with those without [25]. It is apparent that the current data do not show a clear relationship between GER and CLD in preterm infants; however it is possible that GER may be a contributing factor in some infants [26].

Limitations and Pitfalls

Interpretation of esophageal pH monitoring combined with multichannel pneumogram in neonates presents some challenges. Technical difficulties in the methodology, inconsistencies in feeding methods and positioning may be contributory to the variability in the results of the reflux index in preterm infants [15]. The probe position may also be a factor. Strobel's formulae aimed at placing the tip of the probe at the lower third of the esophagus is inaccurate for premature infants of body length less than 40 cm where it overestimates and for infants of body length 65.4 cm or less where it underestimates the distance from the nares to the lower third of the esophagus respectively [11,15].

There are no published normal values of reflux index in preterm infants. Some investigators recommend a threshold reflux index $\geq 5\%$ to be abnormal in preterm infants. [15]. The reflux index $> 12\%$ widely used as a threshold for pathologic GER in infants is based on a study in term infants [17].

Esophageal pH monitoring in preterm and term infants may not reliably detect acid reflux since the gastric pH may be >4 most of the time in milk fed infants [15]. Milk has a neutral pH 7 and a buffering effect on gastric contents and therefore esophageal pH monitoring using the criteria for GER cannot detect reflux nor correlate it with clinical events. This limitation to esophageal pH monitoring in milk fed infants may influence the results of the esophageal pH as a low reflux index may not be indicative of the absence of reflux but rather a prolonged buffering of gastric acidity. It may also impact on the temporal correlation between reflux episodes and clinical events [27].

Esophageal impedance - Will it replace esophageal pH monitoring?

Given the limitations and pitfalls of esophageal pH monitoring in preterm and term infants multichannel intraluminal impedance combined with pH monitoring (MII-pH) has become the preferred technique to measure acid and nonacid GER [28]. The basic principle of multichannel esophageal impedance-pH and pH alone monitoring are identical. The advantage of MII-pH is that it records simultaneously the impedance in at least 6 esophageal sites and pH in 1 or 2 sites. It provides information on the content, the direction and

localization of the reflux, independent of its pH level [28]. Using this impedance-based technology combined with cardiorespiratory monitoring Peter et al. failed to show a clear relationship between GE reflux and apnea [23].

Esophageal impedance has its limitations as well. It is costly and time-consuming to analyses. There are still questions regarding the clinical relevance of detection of weakly acid and nonacid reflux in preterm and term infants [28]. The impedance technique currently has no normative data and outcome measures are lacking and as such more research is needed with this technique [28,29].

Conclusions

Esophageal pH monitoring combined with a multichannel pneumogram study in premature and term infants remain a valuable tool for pediatricians and neonatologists needing answers to perplexing questions as to whether or not the convalescent preterm infant with recurrent apneas, bradycardias and desaturations or CLD and the term infant with either stridor or acute life threatening event (ALTE) have underlying GER.

Interpretation of esophageal pH monitoring as part of multichannel pneumogram faces great challenges in preterm and term neonates. The lack of normative data highlights the need for more research to establish age-related diagnostic reflux indices to identify infants affected by GERD.

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