Gastroesophageal reflux in children: the use of pH-impedance measurements and new insights in treatment
Loots, C.M.

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Addition of pH-impedance monitoring to standard pH-monitoring increases the yield of symptom association analysis in infants and children with gastroesophageal reflux.

Clara Loots
Marc Benninga
Geoffrey Davidson
Taher Omari

ABSTRACT

Objective: To assess the additional yield of combined multichannel intraluminal pH-impedance (pH-MII) monitoring compared with standard pH-metry on gastroesophageal reflux (GER) symptom associations in infants and children.

Study design: In 80 patients, 24-hr ambulatory pH-MII monitoring was performed. Tracings were analysed using established pH-MII criteria. Symptoms of regurgitation and belching were excluded from analysis, as these were considered a direct consequence of GER. Standard GER-symptom correlation indices were calculated using (1) standard pH-metry; (2) MII detection of liquid and mixed bolus GER; (3) MII detection of all bolus GER (liquid, mixed and gas); (4) pH-MII detection of all GER, including pH-only GER.

Results: Fifty pediatric patients (29 infants) were included. MII detection of all bolus GER yielded a significantly greater number of symptom-positive patients, 36 (72%) compared to 25 (50%) with standard pH-metry, p=0.04. A positive symptom association was observed in 8 of 10 (80%) patients with pathological esophageal acid exposure and 28 of 40 (70%) patients with negative pH-findings.

Conclusions: A high proportion of patients with normal esophageal acid exposure, had a positive symptom association on pH-MII monitoring. Including all MII-detected bolus GER and excluding pH-only GER for analysis, optimizes the yield of GER-symptom associations in infants and children.
INTRODUCTION

Twenty four hour multichannel intraluminal pH-impedance (pH-MII) monitoring has been used to detect bolus gastro-esophageal reflux (GER) in infants and children for over 15 year.\textsuperscript{1-5} This technique allows to detect liquid, mixed and gas bolus flow in the oesophagus. The diagnostic use of pH-MII in GER disease has been limited by the absence of diagnostic criteria that quantify levels of pH-MII detected bolus GER in the normal pediatric population. In this respect standard pH-metry is more useful because normative values for esophageal acid exposure (% time pH<4) have been defined across the age spectrum.\textsuperscript{6} Standard pH-metry also has the advantages of being more cost effective and less time consuming to perform.

Standard pH-metry is however a poor detector of weakly acidic (pH>4) bolus GER and of ‘superimposed’ acid GER (pH already <4). Furthermore, pH-metry records a large number of ‘pH-only’ GER which are not detected by impedance.\textsuperscript{7, 8} In infants and children, weakly acidic and pH-only GER are more prevalent than in adults,\textsuperscript{9-11} potentially diminishing the accuracy of pH-metry for detection of GER.

Studies in adults show that including liquid, mixed and gas GER in pH-MII monitoring significantly improves detection of GER-symptom associations,\textsuperscript{12} particularly in patients on PPI therapy with increased weakly acidic GER.\textsuperscript{13} Although similar results are likely to be found in the pediatric population, little data exists on the impact of pH-MII monitoring on GER-symptom associations.\textsuperscript{14} In children with respiratory symptoms refractory to PPI therapy, Rosen and Nurko reported that MII significantly increased the number of patients with a positive symptom association compared to pH-metry.\textsuperscript{15} In a later study, the sensitivity of pH-MII was found to be superior to pH-metry in children on therapy compared to children off therapy.\textsuperscript{8}

The aim of this study was to characterise the impact of GER detection by pH-MII monitoring on diagnosis of GER-symptom associations in the pediatric population. This is the first study to evaluate the impact of incorporating gas-GER and pH-only GER in determining a statistical association between GER and a range of common symptom types using SI, SSI and SAP.

METHODS

Between November 2006 and January 2008, 80 children and infants referred for investigation of GER symptoms underwent ambulatory 24hour pH-MII monitoring. Anti-reflux medication was ceased 48 hours prior to the study. Parents and patients were instructed to maintain normal daily routines and diet with the exception of acidic foods and beverages.
Procedure, inclusion and exclusion

Retrospectively, the pH-MII tracings were manually analysed by two independent investigators to identify pH drops to below pH 4 and episodes of liquid (retrograde drop in impedance to 50% of baseline in at least the two distal channels), gas (retrograde or simultaneous increase in impedance to >5000 Ohm in two or more channels sustained for at least 5 seconds) and mixed (meeting both gas and liquid criteria) bolus GER. The acidity of each bolus GER episode was defined by the nadir pH recorded during the GER episode. Reflux index (%time pH<4 in distal esophagus) was calculated (Sandhill Scientific, Colorado, USA). A reflux index of >4.1% in children and >11.7% in infants (0 – 12 months) was considered pathological.6

Symptoms of cough, pain irritability/crying, sneeze, nausea, choking, back arching, heartburn, hiccups, stridor and bad breath were included for analysis. Symptoms of regurgitation, vomiting and belching were not included as these were considered to be a consequence of GER and therefore could be a confounding factor in assessment of GER-symptom associations. Patients with <5 symptoms during the 24hr monitoring period were excluded from further analysis for two reasons. The symptom recording seemed to be inaccurate rather than a reflection of a low number of symptoms because the low number was inconsistent with the symptom severity reported before the study. Furthermore, more obvious events, such as meal times, remained unmarked suggesting that the person charged with event marking was not sufficiently attentive.

Equipment

A multi-channel intraluminal impedance ambulatory data logger (Sleuth™, Sandhill Scientific, Colorado, USA) was used to perform esophageal pH-MII monitoring studies. Symptoms were recorded by either the parent(s) or the patients using pre-set marker buttons on the data logger or a symptom diary. After calibration and intubation, correct position (between T6 and T8) of the pH-MII catheter was confirmed by a lateral chest X-ray. Three different catheter configurations were used for patients <75cm (ComforTech Infant catheter), 75-150cm (ComforTech Pediatric Catheter) and >150 cm (ComforTech Adult catheter) (Sandhill Scientific, Colorado, USA).

Analysis

For the purposes of symptom association analysis, pH-MII detected GER events were grouped into one of four GER types as defined below:

1. Standard pH-metry detected GER; all GER episodes with a pH drop to below 4 for >2sec. This includes both acid bolus GER and pH-only GER.
2. MII detected liquid and mixed bolus GER; liquid and mixed (acid and weakly acidic) bolus GER episodes.
3. All MII detected bolus GER; all bolus GER including liquid, mixed AND gas (acid and weakly acidic) bolus GER episodes.
4. All GER; all pH-metry and/or MII detected GER episodes including pH-only GER.
GER episodes were considered ‘symptomatic’ if a symptom event occurred within 2 min of the onset of the GER episode. The SI, SSI and the SAP were manually calculated as previously described. Briefly, the SI is the percentage of symptoms that were GER related, the SSI is the percentage of GER episodes that were symptomatic and the SAP is the statistical relationship between symptoms and GER episodes as determined by Fisher exact test calculation. A positive symptom association was defined by a SI ≥50% and SSI ≥10% or a SAP ≥95%.

SigmaStat® 3.0 (SPSS Science, Chicago, IL, USA) was used for statistical analysis. The SAP was calculated manually using http://www.exactoid.com/fisher/index.php. Agreement between the reflux index and the SI, SSI and SAP was calculated with Cohen’s kappa test. The data was not normally distributed and accordingly presented as median (interquartile range). Median values were compared using a Mann Whitney Rank test. Proportions were compared using a z-test. Differences were considered statistically significant when p<0.05.

RESULTS

Of the 80 patient pH-MII studies evaluated, 30 were excluded from further analysis due to either insufficient (<5) symptoms during the study period (n=15 studies), or technical failure including loss of reference electrode, pH sensor failure and impedance ring failure over two or more segments (n=15). Twenty-nine infants (median age 147 [64 – 200] days) and 21 children (median age 3.4 [1.5 - 9.8] years) were included.

A median of 107 GER episodes in total were detected per study analysed. Infants had more GER episodes overall than older children (119 [83, 194] vs 85 [45, 128], p=0.068). A total of 2489 symptomatic events and 5977 GER episodes were recorded. Of GER episodes, 882 (14.8%) were defined as symptomatic based upon the 2min criteria. Of these symptomatic episodes, 134 (15%) were preceded by pH-only GER, 367 (42%) by weakly acidic bolus GER, 381 (43%) by acid bolus GER, 0 (0%) by weakly alkaline GER, 845 (96%) by liquid and/or mixed bolus GER and 37 (4%) by gas GER.

GER-symptom associations

The smallest number of symptom positive patients were detected by standard pH-metry (25 patients with positive SAP). Thirty five patients with a positive SAP were identified by MII detection of liquid/mixed bolus GER only and when gas bolus GER was included the number of patients with positive symptom findings increased to 36 patients. The further addition of pH-only GER to all MII detected bolus GER (i.e. All GER episodes detected by pH-metry and MII combined) decreased the likelihood of a positive symptom finding (30 patients). Hence, the improvement in SAP related to MII detected bolus GER was not merely a function of greater numbers of GER episodes detected. This pattern of SAP-positive findings based upon the method of GER detection, was consistent for both infants
and children (Table 1). For all indices infants were more frequently symptom positive than children (Table 1).

**Pathological acid exposure vs. positive SAP**

The median [IQR] reflux index in the patients was 5.0% [2.5%, 9.6%] for infants and 1.5% [0.9%, 3.6%] for children. Ten out of 50 patients (20%, 5 infants and 5 children) had pathological levels of esophageal acid exposure (a positive reflux index as defined by standard pH-metry), eight of whom also had a positive SAP to all MII detected bolus GER. Including all GER (pH-only & bolus) in the analysis, demonstrated a positive SAP in only four out of 10 (40%) patients who had pathological levels of oesophageal acid exposure. Of the 40 patients with normal esophageal acid exposure 28 (70%) nevertheless had a positive SAP to all MII detected bolus GER (Figure 1). Over the whole cohort the agreement between pathological acid exposure and a positive SAP to all MII detected bolus GER was poor ($\kappa = 0.05$).

![Figure 1. Agreement between reflux index and SAP.](image)

The percentage of patients with a negative reflux index (RI) and a positive SAP is high. In 60% of patients the RI and SAP did not agree.
DISCUSSION

The additional diagnostic yield of pH-MII monitoring for determining GER-symptom associations has been previously reported in adults on and off therapy as well as children with respiratory symptoms refractory to acid suppression therapy. The current study confirms these findings in infants and children off therapy with a wide range of symptom types. In addition, this study demonstrates the importance of including gas-bolus GER and excluding pH-only GER in determining a symptom association with GER.

Like patients on-therapy, infants have a predominance of weakly acidic bolus GER due to pH buffering by more frequent milk feedings. Paradoxically, the frequency of pH-only GER and the acid reflux index are also higher in infants than older children and adults. This is due to a higher proportion of time spent sleeping, which reduces acid clearance by swallowing and primary peristalsis, and more time spent in the supine position. This impairs clearance of acid refluxate reducing the baseline intraesophageal pH to approximately 4 and therefore increasing likelihood that pH will drop below 4 at any given time or during a GER episode. Currently, there is a debate about whether pH-only GER episodes, of insufficient volume to be detected by MII, are important in the aetiology of symptoms and should be included in the pH-MII analysis. Rosen et al suggested that pH-only GER should be included in pH-MII analysis because it represented 25% of all reflux episodes, however they did not investigate the impact of including pH-only GER on GER-symptom associations. The current study clearly shows that the inclusion of pH-only GER diminishes the ability of pH-MII to demonstrate a positive symptom association. This important finding suggests that symptoms are more likely to result when refluxate is of sufficient volume to fill and distend the entire esophagus. pH-only GER may well be artefactual, therefore the ability of pH-MII monitoring to distinguish between acid bolus GER and pH-only GER is further evidence of its superiority over pH-metry alone.

As previously shown in adults, the current study shows that the inclusion of gas-bolus GER, in addition to liquid and mixed-bolus GER, improves the GER-symptom association. Moreover, including gas-bolus GER detected a significantly higher number of symptom positive patients compared to pH-metry alone, whereas including liquid and mixed-bolus GER only did not reach the cut-off value for significance. Our data therefore supports inclusion of gas-GER in the symptom association analysis.

It is important to recognise that symptom indices are a statistical reflection. A positive symptom association suggests causality between GER and symptoms, but does not conclusively prove the association. Symptom association is based on the balance of probability and therefore subject to the vagaries of a 2min association time window which, despite widespread acceptance and use, is arbitrary for children. Furthermore,
the outcomes of GER-symptom association analysis are heavily dependent upon accurate symptom recording by diligent parents or co-operative patients. The indices calculated also have limitations inherent to their characteristics; SI does not take the total number of GER episodes into account and therefore is more likely to be positive when GER is very frequent (as is the case when all pH-only GER episodes are added to the total number of GER episodes); the SSI does not take the total number of symptoms into account and therefore is more likely to be positive when symptoms are very frequent. The SAP is superior as it takes both the number of symptoms and the number of GER episodes into account and will only increase when GER-symptom association is increased, or decrease with decreasing symptom association. \textsuperscript{20, 21}

An important secondary finding of this study was the high proportion of patients with normal esophageal acid exposure time (reflux index), who nevertheless exhibited a positive GER-symptom association. In adults, Watson et al\textsuperscript{22} performed a placebo controlled study of the effect of omeprazole in patients with a normal reflux index and found that omeprazole significantly reduced GER symptoms, especially in patients with a positive SI to acid GER on standard pH-metry. While no equivalent data are available for infants and children, it is clear that symptoms can persist on PPI therapy and can be temporally associated with weakly acidic GER. Children and infants who are symptom positive, but with a normal reflux index might respond to PPI therapy as was shown in adults \textsuperscript{(22)} however patients are more likely to respond to therapeutic strategies designed to reduce bolus GER. These strategies attempt to decrease the number of transient lower esophageal sphincter relaxations, the mechanism that allows reflux to occur. \textsuperscript{23} Possible interventions include GABA (B) agonist therapy \textsuperscript{24} and left side body positioning. \textsuperscript{25} Studies evaluating the therapeutic efficacy of these measures are yet to be reported.

In conclusion, in infants and children, combined pH-MII monitoring increases the likelihood of demonstrating a positive GER-symptom association compared to standard pH-metry alone. Specifically, the addition of gas-GER increases diagnostic yield while the inclusion of pH-only GER decreases this yield. These findings support the use of pH-MII monitoring in pediatric patients in whom symptoms require further investigation, particularly those on acid suppression therapy or with symptoms refractory to therapy. Prospective studies examining the efficacy of therapeutic interventions based on positive symptom associations, are needed to investigate the diagnostic value of pH-MII.
REFERENCES