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

Citation for published version (APA):
Outcomes of endoscopy and pH-Impedance in children with GERD: impedance baselines correlate with endoscopic outcomes

Rachel van der Pol
Clara Loots
Laura Peeters
Yvan Vandenplas
Taher Omari
Marc Benninga
Michiel van Wijk

Submitted
ABSTRACT

Introduction
Discordance exists between outcomes of endoscopy, pH-metry, multichannel intraluminal impedance monitoring (pH-MII) and gastroesophageal reflux (GER) symptoms. MII baseline values have been suggested to be a marker for mucosal damage.

Objective
To determine the association between endoscopy, pH-MII and MII baselines, in children with symptoms of GER.

Methods
Patients who underwent endoscopy and pH-MII were studied retrospectively. Endoscopies were graded according to the Los Angeles classification. Biopsies of the distal esophagus were assessed on signs suggestive of esophagitis. Reflux index (RI), symptom association probability (SAP), number of bolus reflux episodes and mean baseline values were calculated. pH-MII was considered positive when RI was \( \geq 7\% \) and/or SAP was \( \geq 95\% \). For the purpose of comparing MII baselines, patients were divided in three groups: 1. Normal endoscopy and normal pH-MII; 2. Normal endoscopy and positive pH-MII; and 3. Reflux esophagitis (RE).

Results
40 children were included, median age: 26.5 months (2 months-16.2 years). Thirteen (32.5%) children had macroscopic evidence of esophagitis. No associations were observed between outcome of macroscopic and histologic results compared to a positive pH-MII or number of reflux episodes. Moreover, microscopic and macroscopic findings did not correlate. Baseline values were significantly higher in group 1 compared to 2 and 3 (\( p=0.011 \) and \( p=0.004 \), respectively).

Conclusion
A significant association between endoscopy and pH-MII baseline values was observed whereas endoscopy and conventional pH-MII parameters are not associated.
INTRODUCTION

Gastroesophageal reflux disease (GERD) is common in infants and small children. Reflux esophagitis (RE) is a complication of GERD in infants and children, and diagnosis is based on endoscopically visible mucosal breaks.\(^1\) Several scoring systems for these macroscopic abnormalities are available, of which the Los Angeles classification is the most commonly used. Histology findings are quite non-specific, but biopsies are nevertheless routinely performed to confirm or rule out other pathologies, such as eosinophilic esophagitis.\(^1\) Adult GERD patients without macroscopic evidence of RE are classified to suffer from non-erosive reflux disease (NERD).\(^2\) It is, however, largely unclear which of the GERD patients are at risk for RE. Reliable patient selections or predictions of endoscopic findings cannot be made based on symptoms nor pH-metry.\(^3\)-\(^7\) In addition, a recent study using combined pH and multichannel intraluminal impedance monitoring (pH-MII), showed similar numbers of acid reflux, weakly acid reflux and alkaline reflux episodes, similar numbers of liquid and gas reflux episodes and similar reflux indices (% of time that pH is below 4 in the esophagus) in children with and without histologic evidence of esophagitis.\(^8\) Symptom association probability scores (SAP) based on pH-MII results are commonly used to establish a causal relationship between reflux episodes and symptoms.\(^9\)-\(^12\) Only recently, MII baseline values have been reported to be indicative of esophageal wall conductance and potentially a novel marker for esophageal integrity.\(^13,14\) This new paradigm is based on the fact that MII measures the resistance against alternating current. When the esophagus is at rest MII electrodes are in contact with the esophageal wall and this impedance baseline is thought to be a marker of mucosal integrity. MII baselines could potentially contribute to select patients at risk for RE.

In this study, we aimed to determine any association between SAP and MII baselines as well as conventional pH-MII results on the one hand and macroscopic endoscopy findings and histology on the other in children with GERD.

METHODS

Patients

All Infants and children (aged 0-18 years) with symptoms of GERD who underwent endoscopy (including biopsies) and pH-MII in the Academic Centre of the Free University in Brussels, Belgium between 2007 and 2009 were studied retrospectively. Patients were excluded when endoscopy and pH-MII were performed more than 3 months apart, when using anti-reflux medication during endoscopy and not during pH-MII or vice versa or when recording errors occurred during pH-MII. In addition, children with eosinophilic esophagitis, cow’s milk allergy, cystic fibrosis, anatomic malformations of the gastrointestinal tract, and neurologic or metabolic disease, were excluded. For baseline values,
patients using proton pump inhibitors (PPI) were excluded for the analysis of MII baselines, since PPIs can increase baseline values in impedance measurements.\textsuperscript{14}

**Endoscopy**

During endoscopy, macroscopy was described using the Los Angeles classification and considered positive when esophagitis grade A or more was present.\textsuperscript{15} Biopsies were taken as per standard operating procedure at approximately 3 cm proximal to the cardia and assessed by a pathologist specialized in pediatric gastroenterology. Histology was considered suggestive for esophagitis, and hence positive, when basal zone hyperplasia, papillar lengthening or an increased number of neutrophils and/or lymphocytes were found.\textsuperscript{16}

**Combined pH-MII**

All patients were intubated with an age appropriate (infant/pediatric/adult) combined MII-pH catheter (Unisensor, Attikon, Switzerland). pH-MII was monitored for 24-hours and symptoms were recorded with an Ohmega data logger (MMS, Enschede, The Netherlands). All tracings were manually scanned for artifacts, which were excluded before analysis. Subsequently, tracings were analyzed by MMS automated analysis, software version 8.18 (MMS, Enschede, The Netherlands).

**Conventional ph-MII**

The reflux index (RI), the percentage of total time esophageal pH was below 4, number of acid (pH <4), weakly acid (4<=pH<7) and weakly alkaline (pH >= 7) episodes were extracted from the software.\textsuperscript{11} The RI, according to the NASPHGAN/ ESPGHAN guideline in 2009, was considered normal when smaller than 3%, intermediate when between 3 and 7%, and positive if higher than 7%.\textsuperscript{17} The number of weakly acid and weakly alkaline reflux events were combined and are described as the number of non-acid reflux episodes. Because no reference values are available in children, the number of acid and non-acid reflux episodes were used as a continuous variable. The SAP was calculated by the automated software, based on the Fisher’s exact test. SAP was considered positive when 95% or higher.\textsuperscript{9,10} The overall pH-MII result was considered positive when RI\geq7% and/or SAP\geq95%. All other patients are referred to as having a normal pH-MII result.

**MII Baselines**

For the first 10 patients, we analyzed MII baselines in two manners. First, we analyzed the data with a purposely designed Matlab\textsuperscript{TM} based algorithm. This algorithm automatically excludes sudden drops and rises in impedance values and has been used and described previously by us. In short, this algorithm excludes all data samples higher than 5000 Ω, and calculates the nadir impedance point per 10 seconds. Mean and standard deviation of these points are calculated for every 10-minute interval and samples below or above
one standard deviation of the mean are excluded. Again, the mean is calculated of the remaining samples. Of all the means of every 10-minute interval the median is calculated giving an estimation of the baseline value of the complete measurement.

Secondly, we tested the accuracy of this algorithm by exporting raw MII data of the most distal MII segment, with a frequency of 1 Hz, into a Microsoft Excel 2010 file. We manually excluded all data-points that were part of a previously detected reflux episode. In addition we excluded all data-points with a value of more than 5000 $\Omega$ and those during meals. The median value of the remaining data-points was calculated. Based on an excellent correlation (pearson $r = 1$, $p=0.000$, intra class correlation coefficient = 0.988, $p=0.000$), all remaining analyses were performed by the Matlab algorithm only. We report the baseline values as calculated by this automated algorithm.

For the purpose of comparing baselines with endoscopy, patients were divided in three different groups: 1. Patients with normal macroscopy and normal conventional pH-MII; 2. Patients with normal macroscopy and with abnormal conventional pH-MII; and 3. Patients with RE. Finally, baselines were compared between patient with and without histologic abnormalities.

**Statistical analysis**

All statistical analyses were performed with SPSS 18. Normally distributed data are shown as mean ± SD. Medians (range) are given when normal distribution could not be assumed. Logistic regression analysis was performed to find relationships between MII results and endoscopy. Outcomes of endoscopy (macroscopy and histology), RI and SAP were entered into the model as dichotomous and separately as continuous variables. Number of reflux episodes was entered as a continuous variable. Outcomes of endoscopy (macroscopy and histology) were considered dependent variables, outcomes of pH-MII as independent variables (positive pH-MII, RI, SAP, number of acid and non-acid reflux episodes). For comparing baseline values, Kruskal Wallis and Mann-Whitney-U tests were used. A p value smaller than 0.05 was considered statistically significant.

**RESULTS**

**Patients**

One hundred and three children underwent endoscopy as well as pH-MII during the study period. Of these, 63 children were excluded because time frame between endoscopy and pH-MII was longer than 3 months in 24 patients; 9 patients because of recording errors of pH-MII, 23 patients because of inconsistent use of medication and 7 because of co-morbidities. The remaining 40 children had a median age of 26.5 months (2 months-16.2 years). Median time between endoscopy and pH-MII was 0 (0-34) days. Eight children used PPI during both endoscopy and pH-MII measurement and were consequently excluded from baseline analysis.
Figure 1. pH-impedance outcomes compared to endoscopy (macroscopy).
In Figure 1A dichotomous results for pH-MII compared to macroscopy are presented. In Figure 1B reflux index (RI) result is compared to macroscopic outcomes according to the Los Angeles classification. Figure 1C represents SAP outcomes compared to macroscopic outcomes.

Figure 2. pH-impedance outcomes compared to endoscopic biopsies (histology).
In Figure 2A dichotomous results for overall pH-MII compared to histology are presented. In Figure 2B reflux index (RI) result is compared to histology outcomes (normal vs aberrant). Figure 2C represents SAP outcomes compared to histology.
Endoscopy

RE was diagnosed in 13 (32.5%) children based on macroscopic findings (grade A, B or C esophagitis). Histology was suggestive for esophagitis in 20 (50%) patients. Of these 9 patients (45%) had macroscopic evidence of esophagitis. No correlation was found between histologic and macroscopic outcome (p=0.098, OR=3.273).

Combined pH-MII

Median RI was 3.9% (0-19.8). Sixteen patients had a normal RI, 16 patients intermediate, and 8 patients an abnormal RI. A total of 5 patients had a SAP above the cutoff of 95% of whom two had a RI>7%.

The median number of acid and non-acid reflux episodes was 22 (1-129) and 79 (5-237) respectively. A positive overall pH-MII result was found in 11 patients. Of these 6 patients (54.5%) had RE based on macroscopy, while 8 (72.7%) had abnormal histology.

Associations between endoscopic findings and pH-MII results are shown in Table 1 and Figures 1 and 2. Stratifying for age or the use of anti-reflux medication immediately prior to diagnostic investigations did not significantly change these associations.

<table>
<thead>
<tr>
<th>Presence of RE</th>
<th>Histology suggestive for esophagitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td># Acid GER episodes</td>
<td>0.640</td>
</tr>
<tr>
<td># non-acid GER episodes</td>
<td>0.570</td>
</tr>
<tr>
<td>RI (dichotomous)</td>
<td>0.712</td>
</tr>
<tr>
<td>RI (continuous)</td>
<td>0.277</td>
</tr>
<tr>
<td>SAP (dichotomous)</td>
<td>0.823</td>
</tr>
<tr>
<td>SAP (continuous)</td>
<td>0.056</td>
</tr>
<tr>
<td>RI and SAP (dichotomous)</td>
<td>0.967</td>
</tr>
<tr>
<td></td>
<td>0.849</td>
</tr>
<tr>
<td></td>
<td>0.841</td>
</tr>
<tr>
<td></td>
<td>0.164</td>
</tr>
<tr>
<td></td>
<td>0.897</td>
</tr>
<tr>
<td></td>
<td>0.171</td>
</tr>
<tr>
<td></td>
<td>0.186</td>
</tr>
<tr>
<td></td>
<td>0.036*</td>
</tr>
</tbody>
</table>

Table 1. Associations between pH-MII parameters and endoscopic findings.

A positive association was found between overall outcome of pH-MII and histology findings (*OR=6.285, CI=1.123-35.192). All other parameters did not show a relation. RE: reflux esophagitis, defined as macroscopic visible mucosal breaks as classified Los Angeles A or higher. GER: gastroesophageal reflux; RI: reflux index; SAP: symptom association probability score.

MII Baselines

For the 32 patients who did not receive PPI treatment during endoscopy and pH-MII monitoring, the mean baseline of the most distal channel was 2812±920 Ω. Baselines were 33678 Ω (3154-4411) in group 1 (n=6), 2332 Ω (1341-4567) in group 2 (n=14), and 2778 Ω (767-3570) in group 3 (n=12), for the most distal channel. The most significant p values were found in the most distal channel. In the proximal channels p values varied, as presented in Table 2. MII baseline results per group are shown in Figure 3. No difference was found between the baselines in patients with normal histology and those with histologic evidence of esophagitis (p=0.327).
This is the first study to assess the relation between novel pH-MII parameters and endoscopy findings in children with GERD. We found MII baselines to be significantly higher in patients with normal pH-MII and normal macroscopy compared to patients with abnormal pH-MII and/or patients with RE.

MII baselines have been suggested indicative of mucosal integrity. In adult RE patients the visible disruption of the mucosa and inflammatory exudate result in lower baselines. In this study it was demonstrated that infants and children with RE have lower baselines than patients without RE and with normal pH-MII outcomes. Furthermore, as was shown in adults, we also observed lower baselines in children with a positive pH-MII study compared to children with a negative pH-MII study. This may suggest that impedance baselines detect subtle changes in esophageal mucosal integrity. In adult NERD patients, esophageal integrity is disturbed by dilated intercellular spaces (DIS), which has been shown to result in lower baselines. In contrast to adults, we did not demonstrate
a significant difference between children with normal endoscopy and abnormal pH-MII outcome and those with RE. In our data, there is little overlap in baselines between children with RE and the group of patients with normal macroscopy and normal pH-MII, indicating that MII baselines could possibly play a role in selecting those patients who should undergo additional endoscopic testing. The need for such a selection is urgent as infants and children are not only prone to more complications following endoscopy, but also need to undergo general anesthesia. Larger prospective studies are, however, needed to establish the exact diagnostic role and potential cut-off values of MII baselines in infants and children with and without RE.

PPI therapy, both in children and adults have been shown to increase MII baseline. In light of this, it would be very interesting to test MII-baselines and perform endoscopy in RE patients before PPI therapy and after treatment to evaluate whether healing of RE coincides with an increase in baseline and could also be used to monitor treatment effect. MII baselines have been calculated differently by different groups. This is the first study to employ an algorithmic analysis method. This method was a perfect correlate of a manual sub-analysis, and had the significant advantage of being far less time consuming and not subject to observer variability and bias.

SAP scores that describe a temporal relation between GER based on pH-MII and symptoms results showed no relation with endoscopy findings in this study. This result, although never tested before in children, is not entirely surprising as many studies have tried and failed to reliably correlate endoscopy findings with clinical symptoms. In concurrence with previous studies, we did not demonstrate any association between conventional pH-MII parameters and RE and histology. Previous pH-metry studies have reported inconsistent associations and the one study using pH-MII in children, found no association as well. The value of histology, specifically DIS and inflammatory markers, for the diagnosis of GER will need to be established in the pediatric population.

There are some drawbacks of our study. First, it was retrospectively designed. We have tried, however to prevent selection biases as much as possible by including all children who underwent endoscopy and pH-MII. Another limitation, that limits all studies using MII, is the absence of normal values for MII parameters. Cut-off points were therefore chosen based on established best practise guidelines (ESPGHAN/NASPGHAN). In addition, the use of automated analysis to analyze MII data is thought by some to be inferior to manual readings. However, we have recently demonstrated large inter and intra-observer variability amongst pH-MII analyses performed by experts in the field and this suggests that automated analysis may in fact be more reliable.

In conclusion, we have shown that MII baselines could potentially be valuable to select patients at increased risk for RE. Large prospective studies should be performed to establish the exact role of MII-baselines in the diagnosis of RE. None of the other pH-MII parameters was found to be associated with the macroscopy of the esophagus.
REFERENCES


