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Outcomes of endoscopy and novel pH-impedance parameters in children; is there a correlation?

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Abbreviations used:

GERD: gastroesophageal reflux disease
NERD: non erosive reflux disease
pH-MII: combined pH and multichannel intraluminal impedance monitoring
PPI: proton pump inhibitors
RE: reflux esophagitis
RI: reflux index (% time that esophageal pH <4)

SAP: symptom association probability score Corresponding author
ABSTRACT

Objectives: 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. Aim: 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 for reflux esophagitis (RE) according to the Los Angeles classification. Biopsies of the distal esophagus were assessed for signs suggestive of esophagitis. Reflux index (RI), symptom association probability (SAP), number of bolus reflux episodes and mean baseline values were calculated. Conventional pH-MII was considered positive in children when RI was ≥3% and/or SAP was ≥95% and for infants when RI was ≥10% and/or SAP was ≥95%. For the purpose of comparing MII baselines, patients were divided in three groups: 1. Normal endoscopy and negative overall pH-MII; 2. Normal endoscopy and an overall positive pH-MII result; and 3. RE.

Results: 26 children and 14 infants were included, median age: 26.5 months (2 months-16.2 years). Thirteen (32.5%) children had RE. RE and histology suggestive of esophagitis did not correlate. A positive association was found for RI and MII baselines (p=.009) and between SAP and presence of RE (p=.039, OR=1.018). MII baseline values were not predictive for conventional pH-MII parameters nor for RE. Distal MII baselines were significantly lower in children and infants with a positive overall pH-MII outcome compared to the proximal esophagus (p=.049). No significant changes were found in baselines between the different groups 1-3.

Conclusion: No significant associations of clinical relevance were found between endoscopy, conventional pH-MII parameters and pH-MII baseline values. Acid related parameters are significantly related to MII baselines. Large prospective studies are needed to confirm the exact role of endoscopy and MII baselines.

Keywords: endoscopy, GERD, children, pH impedance, baselines
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 used most commonly. 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 pediatric 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 in children 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). MII baseline values have been reported to be indicative of esophageal wall conductance and are potentially a novel marker for esophageal mucosal 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 the impedance measured is consequently a result of the integrity of the mucosa. It is hypothesized that MII baselines are lowered in the case of esophagitis because of a lower
resistance of the inflamed mucosal wall. Therefore, 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. Children with eosinophilic esophagitis, cow’s milk allergy, cystic fibrosis, anatomic malformations of the gastro-intestinal tract, and neurologic or metabolic disease, were excluded. In addition, patients were excluded when endoscopy and pH-MII were performed more than 3 months apart, when they used anti-reflux medication during one of the two diagnostic tests or when recording errors occurred during pH-MII. If patients used anti reflux medication during both endoscopy and pH-MII they were included for all analyses but those regarding MII baseline values, because PPIs are known to increase these baselines (14).

**Endoscopy**

During endoscopy, macroscopy was described using the Los Angeles classification and considered positive when esophagitis grade A or more was present (15). Throughout this paper these patients will be referred to as having reflux esophagitis (RE).
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, papillary lengthening or an increased number of neutrophils and/or lymphocytes were found (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 parameters**

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 (17). In infants, RI was considered positive when above 10%(17). For older children, according to the NASPGHAN/ESPGHAN guidelines, RI was considered normal when smaller than 3%, intermediate when between 3 and 7%, and positive if higher than 7% (18). 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 relation between symptoms and all the reflux episodes. Also, a different SAP was calculated
solely based on acid reflux episodes, since it has been shown that histology suggestive for esophagitis is associated with acid reflux (4). We termed this acid-SAP. SAP and acid-SAP were considered positive when 95% or higher (9,10). In infants, overall pH-MII result was considered positive when RI≥10% and/or SAP≥95%. In older children, overall pH-MII was positive when RI≥3% and/or SAP≥95%. All other patients are referred to as having a normal (negative) pH-MII result.

*MII Baselines*

For the first 10 patients, we analyzed MII baselines in two ways. First, we analyzed the data with a purposely designed Matlab™ based algorithm. This algorithm automatically excludes sudden drops and rises in impedance values and has been used previously by us (19). 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 1Hz, 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 Ω and those during meals. The median value of the remaining data-points was calculated.

Based on an excellent correlation (pearson r>0.999, p<0.001, intra class correlation coefficient = 0.988, p<0.001), all remaining analyses were performed by the Matlab algorithm only. We report the baseline values as calculated by this algorithm.
For the purpose of comparing baselines with endoscopy, patients were divided in three different groups: 1. Patients with normal macroscopy and negative overall pH-MII; 2. Patients with normal macroscopy and with positive overall pH-MII; and 3. Patients with RE.

**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. For the association between macroscopic and histologic outcome (dichotomous), odds ratio (OR) and confidence interval (CI) were determined.

For associations between MII baselines and conventional pH-MII parameters, a linear regression model was used with MII baselines as dependent variable. For associations between endoscopy and conventional pH-MII parameters as well as MII baselines, logistic regression analysis was performed. Outcomes of endoscopy (macroscopy and histology), were entered as dependent variables, outcome of pH-MII, RI and SAP, number of reflux episodes, and MII baseline values as independent variables. pH-MII, RI and SAP were entered as dichotomous variables, the latter two also as continuous variables. All the other parameters were entered as continuous variables. For comparing MII baseline values between group 1 to 3, Kruskal Wallis test was used. For comparisons of MII baselines of different segments throughout the esophagus Wilcoxon signed rank test was 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 of the time frame between endoscopy and pH-MII being longer than 3 months (n=24), technical problems with pH-MII recordings (n=9), inconsistent use of medication (n=23) and co-morbidities (n=7). The remaining 40 children had a median age of 26.5 months (2 months-16.2 years). Fourteen (35%) were infants (12 twelve months old or younger). 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 only from the analyses regarding MII baselines.

Endoscopy

RE was diagnosed in 13 out of 40 (32.5%) patients. Two (15%) of these were infants. Of the patients with RE, nine (69%) patients also had histology findings suggestive for esophagitis. Yet another 11 patients (5 infants) had histology findings suggestive of esophagitis, however, without RE. No correlation was found between histology and macroscopic findings (OR=3.273, CI: 0.802-13.350).

Combined pH-MII

Conventional pH-MII parameters

In the 14 infants, median reflux index (RI) was 5.25 % (0.00-19.8) and 2 (14%) had a RI ≥10%. These latter two also had a positive SAP. The median number of acid and non-acid reflux episodes was 36 (1-129) and 76 (8-169) respectively. The overall pH-MII result was positive in 4 infants.
In the older children, RI was 3.85% (0.10-13.6), 11 patients had a normal RI (<3%), 9 patients intermediate (3%≤RI≥7%), and 6 patients an abnormal RI (≥7%). Two had a SAP above 95% of which one had a RI≥3. The median number of acid and non-acid reflux episodes was 17 (2-102) and 83 (8-214) respectively. The overall pH-MII result was positive in 16 children.

**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 segment was 2812±920Ω. Baselines were 3154 Ω (2050- 4411) in group 1 (n=11), 2612 Ω (1341-4567) in group 2 (n=9), and 2778 Ω (767- 3570) in group 3 (n=12), for the most distal segment (figure 1).

Associations between MII baselines and conventional pH-MII parameters

A significant association was found between MII baselines in the most distal esophageal segment and RI (p=0.009, B=-125.65, figure 2). No associations were found between MII baselines and SAP, nor between MII baselines and the number of acid and/or non-acid reflux episodes.

In patients with a positive overall pH-MII result a significant difference was found between MII baselines in the distal esophagus compared to baselines of the most proximal MII segment (figure 3). In patients with negative conventional pH-MII results, no such difference was found.

**Associations between pH-MII and endoscopic findings**

Associations between conventional pH-MII parameters and endoscopic findings

Nine out of the 13 patients (69.2%) with RE had an overall positive pH-MII result.

Associations between pH-MII results and endoscopy findings are shown in table 1.
Thirteen out of the 20 (65%) patients with histology suggestive of esophagitis had an overall positive pH-MII result. No associations were found between conventional pH-MII parameters and histology findings (table 1). When acid-SAP was entered into the model instead of SAP, no association was found between acid-SAP and histology nor between acid-SAP and the presence of RE (data not shown).

Associations between MII baselines and endoscopic findings.

No significant associations were found when baselines were entered in the logistic model together with the conventional pH-MII parameters (p=0.366, OR=0.999 for RE and 0.997, OR=1.000 for histology suggestive for esophagitis). When comparing baselines between group 1 to 3, no significant differences were found (figure 1), neither for the difference between the proximal and distal esophagus (data not shown). In addition, in children with RE or histology suggestive of esophagitis, MII baselines did not differ significantly (p=0.099 and p=0.255 respectively) between the proximal and distal esophagus (figure 3).

**DISCUSSION**

This is the first study to assess the relation between novel pH-MII parameters and endoscopy findings in children with GERD. Despite MII baselines having been suggested to be indicative of mucosal integrity (13), we did not find a relationship between MII baselines and endoscopy findings. However, MII baselines were significantly higher in patients with a lower RI. In addition, we found that distal MII baselines differ significantly from proximal MII baselines in children with a positive RI and/or a positive overall pH-MII result.

In adult RE patients the visible disruption of the mucosa and inflammatory exudate results in electrical potential difference of the esophagus (20), causing lower baselines (13). In adult
NERD patients, esophageal integrity is disturbed by dilated intercellular spaces (DIS), which has been shown to result in lower baselines as well (13,21,22). In this study we could not confirm these findings in children. We did find that a high acid exposure in the esophagus results in lower baselines which has been shown in adults as well (21,23). However, we found a significant difference in MII baselines between the distal and proximal esophagus of children with a high RI and/or a positive overall pH-MII outcome. This difference is interesting as acid exposure in the distal esophagus is associated with low baselines in the distal and proximal esophagus in adults (21,24). Our results are likely to be the result of local reactions to acid exposure, which occurs more often in the distal esophagus.

PPI therapy, has been shown to increase MII baseline, both in children and adults (14,22). It would therefore be very interesting to test MII baselines and perform endoscopy in RE patients before and after PPI therapy 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 (13,14,23). We recently published an algorithmic analysis method to calculate baseline values (19). In this study we show perfect correlation with manual sub-analysis. This algorithm has the significant advantage of being far less time consuming and not subject to observer variability and bias as all previously used methods were.

SAP scores that describe a temporal relation between GER episodes and symptoms results showed a significant association with reflux esophagitis. However, the clinical significance of this finding is disputable, given the odds ratio of 1.018 (CI 1.001-1.035) This result, although novel in children, is not entirely surprising as many studies have tried and failed to reliably correlate endoscopy findings with clinical symptoms (3,25,26,27)).
We did not demonstrate any association between conventional pH-MII parameters and RE. The importance of this finding is not clear as previous pH-metry studies have reported inconsistent associations (6,7,28) and the one study using pH-MII in children, found no association between conventional pH-MII parameters and histology either (8).

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 baselines, is the absence of normal values for MII parameters. Cut-off points were therefore chosen based on common practice in infants and established best practice guidelines (ESPGHAN/NASPGHAN) in older children (18). In addition, the use of automated analysis to analyze MII data is thought to be inferior to manual readings by some. 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 (29).

In conclusion, MII baselines do not correlate with endoscopic findings and although there is an association between SAP and RE, the clinical value of this is limited. Nevertheless, some acid related parameters show a relation with baseline values. Large prospective studies should be performed to establish the exact clinical role of MII baselines in pediatric GERD patients with and without RE. The perfect correlation between an automated MII-baseline calculation and manual analysis largely enhances the possibilities of performing such studies.

REFERENCES


**Figure 1.** Multichannel intraluminal impedance (MII) baselines of the most distal segment per group (with range, median and p-values). Group 1 = Patients with normal macroscopy and negative conventional pH-MII; group 2 = Patients with normal macroscopy and with positive conventional pH-MII; group 3 = Patients with reflux esophagitis.
Figure 2. A higher reflux index (RI) is associated with a lower multichannel intraluminal impedance (MII) baseline of the most distal esophageal segment.
Figure 3. Multichannel intraluminal impedance (MII) baselines of the most distal segment compared with the most proximal segment (median and range). (d=distal; p=proximal; R I positive = R I ≥ 10 (infants) or ≥ 3 (older children); pH-MII positive = R I ≥ 10 or ≥ 3 and/or SAP ≥ 95%). *p = 0.049.