Gastroesophageal reflux in children: the use of pH-impedance measurements and new insights in treatment
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Citation for published version (APA):
Measurement of mucosal conductivity using multichannel intraluminal impedance: A potential marker of mucosal integrity that is restored in infants receiving acid suppression therapy

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ABSTRACT

Esophageal multichannel intraluminal impedance (MII) allows measurement of the conductivity of adjacent contents. During esophageal rest raw impedance levels may represent mucosal integrity. We assessed the influence of proton pump inhibitors (PPI’s) on presumed mucosal integrity by re-analyzing raw MII levels of 21 pH-MII tracings from infants with gastroesophageal (GER) disease before and after esomeprazole treatment. Median (IQR) esophageal MII increased during treatment, 938 (652-1304) vs 1885 (1360-2183) Ohm, p<0.0001. Patients with lower MII levels demonstrated a larger increase on therapy: Spearman $r^2=0.28$, p=0.014. No correlation with standard GER parameters was observed. In conclusion, PPI therapy increases MII levels in infants with symptomatic GER disease.
INTRODUCTION

Esophageal multichannel intraluminal impedance (MII) is a technique which uses impedance to indirectly measure the conductivity of the esophageal lumen between multiple electrodes on a catheter and has been used for the detection of gastroesophageal reflux (GER) episodes in adults and in children. Esophageal boluses with high ionic content, such as saliva or gastric fluids cause a drop in impedance in all subjects, whereas a less conductive bolus, such as air, causes an increase in impedance signal. During rest, the esophagus is collapsed and the level of impedance measured represents the inverse conductivity of the esophageal mucosa. The level of raw impedance shows high variability between subjects and low overall impedance levels appear to be a characteristic feature of patients with GER disease (GERD). Farre et al., have recently reported that exposure of the esophageal lumen to acid solutions, both in vitro and in vivo, causes a temporary drop in impedance level measured at times when no reflux or swallow was noted. This was attributed to an increased conductivity of the esophageal mucosa related to an increase in transcellular ionic transport due to dilated intracellular spaces (DIS). These data suggest that low impedance levels do indeed reflect the integrity of the esophageal mucosa and have the potential for being a marker of the existence of mucosal damage. This new diagnostic paradigm may have potential in infants, who are difficult to endoscope safely and therefore are frequently prescribed proton-pump inhibitors without proof of mucosal changes. Furthermore, diagnosing GERD in infants is challenging as typical GER symptoms such as crying, irritability and vomiting are not exclusive to and correlate poorly with GERD. The integrity of the esophageal mucosa reflected by the measurement of raw impedance levels may guide use of acid suppression therapies. While proven effective for healing acid-related inflammatory changes in adult GERD and for reducing acid exposure in infants, PPIs do not improve symptoms in infants treated empirically. In addition, we have previously shown that PPI (esomeprazole) therapy does not alter the frequency of impedance-detected bolus reflux episodes (liquid, mixed and gas) in infants with typical reflux symptoms. A better way is clearly needed to diagnose GERD in infants and to target PPI therapy to the few infants who may benefit from this therapy. To date, it is unknown whether PPI therapy changes raw impedance in infants, children and adults with pathologic GER disease. The hypothesis of this study was that PPI therapy would increase raw impedance values in infants with symptoms of GERD and evidence of increased esophageal acid exposure.

METHODS

The study cohort comprised preterm and term infants. Results on PPI effectiveness on frequency of impedance-detected bolus reflux episodes, acid-exposure, study procedures and symptom recording were published previously in detail. Informed consent for the
The initial study was obtained in all children and the study protocol was approved by the Human Research Ethics and Drug Therapeutics Committees of the Women’s and Children’s Hospital, North Adelaide (South Australia). These tracings were reanalyzed retrospectively for the purpose of this study. An abridged description follows:

All infants were referred for 24h pH-impedance monitoring due to symptoms suggestive of GERD such as vomiting, coughing, feed refusal, irritability, crying, back arching, failure to thrive, apnea and failure to respond to a trial of non-pharmacological therapy. Infants with a baseline acid exposure showing a pH<4 for over 5% of the study period received oral esomeprazole, 0.5 mg per kilogram for seven days once daily in the morning, 30 minutes before feeding. A pH-MII study was repeated on-therapy.

Symptom episodes of vomiting, apnea, choking, irritability/fussing/crying, back arching, facial grimacing, and gagging were scored during both 24h studies by staff responsible for the routine care of the infant or the infant’s parents.

### Data analysis

Twenty hours of raw MII values for the most distal MII segment was exported from each recording in text format at one sample per 10sec (Sandhill Scientific, USA) yielding 7181 (range 6131-7197) data points. To remove the potential confounding effects of gas reflux the raw data-set was further filtered to remove all data points >5000 Ohm (the standard cut-off for definition of the presence of gas in the esophagus). The median impedance value for all remaining data points was then calculated. The objectively derived impedance level was compared for each infant before and during therapy. All other reflux and symptom data were taken from our existing records unmodified and no re-analysis of any of these data was performed.

### Statistical analysis

The impedance data were not normally distributed and are shown as medians (interquartile range). Comparisons were made using Wilcoxon’s signed rank test and Spearman’s correlation statistics. Statistical significance is defined as p<0.05.

### RESULTS

Twenty-one preterm and term infants (mean age: 7.4 ± 4.2 weeks, all <1 month term corrected age) were included for analysis. Median weight at baseline was 2930 (range 1910-4145) grams.

### Standard Reflux Parameters Before and During PPI Therapy

Traditional pH-MII reflux variables of acid exposure in the distal esophagus (reflux index, % of time pH<4), number of GER events, GER events lasting >5 sec and quality of GER as well as the number of symptoms recorded during the 24-hr pH-MII study pre and post treatment are presented in Table 1.
The median (IQR) esophageal impedance level increased significantly during PPI treatment, 938 (652-1304) Ohm pre treatment vs. 1885 (1360-2183) Ohm on treatment, p<0.0001.

Data per individual patient before and during treatment are shown in Figure 1A. At baseline, most infants had impedance levels in the range of 0-1500 Ohms, but there appeared to be a bi-modal distribution of impedance levels, with a second cluster of four infants with impedance levels of >2000 Ohms (Figure 1A). This contrasts with the

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of study</th>
<th>p-value</th>
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<tr>
<td>Acid exposure (%time)</td>
<td>13.6 (9.2-18.0)</td>
<td>3.7 (2.2-6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GER events Total number</td>
<td>103 (77-134)</td>
<td>88 (74-121)</td>
<td>0.4</td>
</tr>
<tr>
<td>Acid</td>
<td>31 (24-44)</td>
<td>8 (5-13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non acid</td>
<td>74 (42-105)</td>
<td>83 (64-107)</td>
<td>0.08</td>
</tr>
<tr>
<td>GER events &gt; 5 seconds</td>
<td>9(6-13)</td>
<td>2(1-4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptoms</td>
<td>22 (16-35)</td>
<td>9 (7-22)</td>
<td>0.09</td>
</tr>
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Table 1. Baseline characteristics of pH-MII measurements per group (N=21).
The reflux index, and number of acid bolus GER decreased significantly after PPI treatment. The total number of GER events does not change, therefore the number of weakly acid GER episodes increases. The number of symptoms recorded during the 24hr study is not reduced in these 21 patients.

**Figure 1**

A. Impedance level changes before and after PPI therapy per patient.
B. Frequency distribution impedance levels before and after PPI therapy. Impedance levels before PPI treatment are lower compared to after PPI therapy.
C. Correlation between initial impedance level and change in impedance level on therapy. Patients with a low initial impedance level pre treatment have a larger increase in impedance level after treatment that those with an initial higher impedance level. Spearman r²=0.28, p=0.014

**Impedance Level before and during PPI therapy**
The median (IQR) esophageal impedance level increased significantly during PPI treatment, 938 (652-1304) Ohm pre treatment vs. 1885 (1360-2183) Ohm on treatment, p<0.0001. Data per individual patient before and during treatment are shown in Figure 1A. At baseline, most infants had impedance levels in the range of 0-1500 Ohms, but there appeared to be a bi-modal distribution of impedance levels, with a second cluster of four infants with impedance levels of >2000 Ohms (Figure 1A). This contrasts with the
impedance levels on-therapy of 1000-3000 Ohms with no apparent bi-modal distribution (Figure 1B). The four infants with high impedance levels at baseline did not increase impedance level further on therapy (2469(2168-2729) vs. 2630(2252-2915) Ohms, p=0.5), whilst the remaining infants with impedance levels <1500Ohm did (850(590-1101) vs. 1831(1326-2008) Ohm, p=0.0001). Furthermore, we observed a significant correlation between the baseline impedance level and the change in impedance during PPI treatment; patients with lower impedance levels demonstrated a larger increase on therapy: Spearman $r^2=0.28$, p=0.014 (Figure 1C).

While both impedance and acid exposure were significantly changed by PPI therapy overall, on a patient by patient basis the level of impedance did not correlate with the reflux index (Spearman $r^2=0.09$, p=0.21). Neither did the change in impedance correlate with the change in reflux index (Spearman $r^2=0.11$, p=0.17). Correlations of impedance level with other reflux variables were also insignificant.

**DISCUSSION**

In this study we have shown that esophageal impedance levels increase in infants in response to PPI treatment. This increase is larger in patients with lower initial impedance levels. There was no correlation between the impedance level and conventional parameters of esophageal acid exposure and reflux, suggesting that this effect relates to factors beyond the simple reduction of esophageal exposure to containing H+ ions.

We were unable to assess the presence of esophageal mucosal damage in the patients studied because endoscopic investigations in this age group are only considered in very therapy resistant patients and there are no non-invasive markers for this. However, based on adult studies which clearly link impedance levels to mucosal integrity, our findings do show that some infants have low impedance levels that are suggestive of altered mucosal integrity. With erosive esophagitis being uncommon in infants undergoing endoscopy, the low impedance levels may reflect more subtle changes in mucosal integrity, as is the case with non-erosive reflux disease patients who have high levels of esophageal acid exposure but no esophagitis.

One postulated mechanism leading to higher mucosal conductance is the presence of DIS. DIS reduce transepithelial resistance by increasing transcellular ionic transport. In patients with erosive and non-erosive GER disease, DIS are present and the extent of DIS is reduced by PPI therapy in these patients. The presence of DIS may explain the low impedance levels recorded in our population when studied off PPI therapy. It also explains the correlation between the low impedance level before treatment and the change in impedance during PPI treatment. The fact that the impedance levels change so dramatically after only a relatively short period of time (seven days) is also suggestive that the mechanisms involved are subtle. Whist healing of esophagitis may take weeks
and months, this presumed presence of DIS is readily and quickly reversed in response to reducing the duration of time that the esophageal mucosa is exposed to acid. In conclusion, we have demonstrated that PPI therapy increases impedance levels measured by MII in preterm and term infants with symptomatic GER disease. The true meaning of low impedance (high esophageal mucosal conductance) for research and clinical purposes needs to be determined. However our observations may be explained by acid suppression restoring the DIS and therefore mucosal integrity of the esophagus. Furthermore, this incidental finding does suggest that the level of impedance over a 24h period may be a parameter worthy of further investigation in terms of potential clinical relevance, particularly in infants in whom endoscopy is usually inappropriate.
REFERENCE LIST


