Pediatric gastroesophageal reflux and upper gastrointestinal tract motility: the use of multichannel intraluminal impedance and high resolution manometry

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Characterization of intraluminal impedance patterns associated with gas reflux in healthy volunteers

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Marc Benninga
Geoffrey Davidson
Taher Omari

ABSTRACT

Background: Multichannel intraluminal impedance (MII) recording allows assessment of flow through the esophagus and differentiation between liquid and gas contents. Existing MII criteria for recognition of gas gastroesophageal reflux (GER) have not been validated during known gas GER in humans.

Aim: (i) Characterize MII patterns of known gas GER and optimize criteria. (ii) Clarify interrelationships between magnitude of maximal impedance change, luminal diameter and electrode-mucosa contact.

Methods: Ten healthy volunteers (six male, 21–37 years) were studied using an esophageal MII-manometry catheter. After catheter placement, subjects were asked to drink 600 mL of carbonated soft drink. Recordings were made for 20 min and the protocol repeated. Reported belches confirmed manometrically (triggered by transient lower esophageal sphincter relaxations) were included for analysis. Those episodes were compared against commonly used criteria. Another five subjects (three male, 26–52 years) underwent simultaneous MII and videofluoroscopy using the same protocol. Videofluoroscopic images were analyzed for luminal diameter and the presence of electrode–mucosa contact.

Results: All analyzed gas GER episodes (n = 88) were associated with a pattern of impedance rise which was either retrograde (62.5%), synchronous (19.3%) or antegrade (18.2%). Depending on the exact criteria used, sensitivity ranged from 33% to 75%. A multivariate regression model including luminal diameter and the presence of electrode-mucosa contact as independent factors accounted for 53% of all variation in impedance changes.

Conclusion: A significant number of gas GER episodes does not meet criteria for their recognition. New criteria are proposed to include specific antegrade patterns of impedance rise. Luminal diameter and the extent of contact between the esophageal mucosa and MII-electrodes influence the magnitude and patterning of impedance change.
INTRODUCTION

Transient lower esophageal sphincter relaxation (TLESR) is the main underlying mechanism of gastroesophageal reflux (GER) in healthy volunteers and patients with GER disease in all age groups.\textsuperscript{1-4} This has been shown for both liquid and gas GER.\textsuperscript{5}

Multichannel intraluminal impedance measurement (MII) was recently introduced for the detection of flow of liquids and gasses throughout the esophagus. Electrical impedance is a measure of resistance against alternating electrical current, which can be measured by closely spaced electrodes mounted on an esophageal catheter. Each pair of neighboring electrodes reveals the impedance of that segment. Conductive fluids within the esophagus, such as saline or refluxate, will lower baseline impedance values, while gases (air swallows and belches) are non-conductive and will increase impedance values. Theoretically, impedance values are also related to the cross sectional area between two electrodes (i.e. the diameter of the esophageal lumen and/or bolus size) and the distance between each pair of electrodes.\textsuperscript{6}

These properties make MII a technique that can be used to assess esophageal bolus flow without the use of radiological exposure and for the detection of all GER episodes, independent of acidity or consistency. Due to the multiple measuring segments it can also differentiate between GER and swallowed material. The MII technique for the detection of swallowed liquid boluses and swallowed air has been validated against videofluoroscopy in humans.\textsuperscript{7-10} For gas GER detection, however, validation studies were performed in vitro and sedated cats only.\textsuperscript{11} Commonly used MII-criteria for the detection of gas GER (table 1) are based on these experiments, but not validated in humans.\textsuperscript{11,12} It has been shown in adults and children that the inclusion of gas GER increases the diagnostic yield of pH-impedance monitoring for identifying reflux related symptom episodes and therefore the development of validated criteria for gas GER detection are important for diagnosis of GER disease (GERD).\textsuperscript{13,14} Therefore, there is a need for evidence based criteria, which can more reliably detect gas GER episodes. It is important to realize that not all gas GER episodes (retrograde flow of gas from the stomach into the esophagus) fall under the definition of a belch (a subjective perception, which is assumed to be the result of gas GER episodes and is often accompanied by airflow from the mouth).

The aim of our study was to characterize MII patterns of known gas GER episodes, compare these with commonly used criteria for gas GER detection and optimize existing criteria. Furthermore, we aimed to clarify interrelationships between magnitude of maximal impedance change, luminal diameter and electrode-mucosa contact.
MATERIALS AND METHODS

Subjects

Healthy volunteers were recruited in two centres. (Women’s and Children’s Hospital, Adelaide, Australia and University Hospital at the Catholic University, Leuven, Belgium). All were free of gastro-intestinal complaints. Subjects with previous gastrointestinal or diaphragmatic surgery, known structural gastroesophageal abnormalities and those taking medication recognized to influence gastrointestinal motility were excluded. Relevant protocols were approved by the Research Ethical Committee of the Women’s and Children’s Hospital and the University Hospital Ethics Committee of the Catholic University of Leuven. All subjects gave written informed consent before commencement of the study. The two experimental protocols detailed below were used in this study.

Figure 1. Design of catheters used in protocol 1 (panel A) and protocol 2 (panel B). MII: multichannel intraluminal impedance; IMP: impedance segment; LES: lower esophageal sphincter. Distances shown are relative to LES sleeve midpoint (protocol 1) or relative to proximal border of the LES when positioned under videofluoroscopic guidance (protocol 2).
Protocol 1: Impedance patterns recorded in association with manometrically determined gas GER

Recording techniques
A purpose built combined esophageal MII / manometric sleeve catheter was used. The manometric assembly incorporated a 5 cm long sleeve sensor for lower esophageal sphincter (LES) pressure recording and 7 manometric side holes for gastric (one), esophageal body (five), and pharyngeal (one) pressure measurement (figure 1A). All side holes and the sleeve were perfused with sterile degassed water at 0.15 mL/min. Cylindrical electrodes for the recording of intraluminal impedance were mounted on the catheter at 3, 6, 9, 12, 15, 18 and 21 cm proximal to the LES-sleeve midpoint, resulting in six impedance segments throughout the esophagus. Data acquisition was performed with the use of the BioView GER monitoring and manometry system (Sandhill Scientific, Denver, CO, USA). MII was recorded at an acquisition frequency of 50 Hz; manometry with 20 Hz.

Study protocol
All subjects fasted for at least four hours prior to the study. The appropriate catheter was passed trans-nasally into the esophagus with the tip in the cardia of the stomach and the manometric sleeve straddling the LES. After 15 minutes of adaptation in the upright position, subjects were asked to drink 600 mL of a carbonated soft drink as fast as possible. After 20 minutes, subjects were asked to consume another 600 mL of carbonated soft drink. Twenty minutes after the last soft drink the study was terminated. At the end of the study, three of the volunteers were asked to swallow a mouthful of air (air-swallows) for up to five times. MII/manometry recordings were made continuously during the entire protocol. Subjects were asked to report any belches, which were marked on the tracing.

Analysis
The periods during which the subject drank the test drink were excluded from analysis. TLESRs were manometrically defined using criteria previously described by Holloway et al: i) absence of swallowing for 4 s before to 2 s after the onset of LES relaxation; ii) relaxation rate of > 1 mmHg/s; iii) time from the onset of relaxation to complete relaxation of < 10s; and iv) nadir pressure of < 2 mmHg. Excluding LES relaxations associated with multiple swallows, LES pressure falls that fulfill the last three criteria but have a duration of > 10 s were also judged to be TLESRs, irrespective of the timing of the onset of the LES pressure fall to swallowing. A common cavity was defined as a rise in esophageal body pressure to level gastric pressure that occurred within 1 s and that was maintained for at least 0.5 s in at least the three most distal esophageal body pressure tracings. Swallows were defined as a short sudden rise of pharyngeal pressure.
The manometric tracing was analyzed for TLESRs and common cavities, blinded from impedance tracings and belchmarkers. Gas GER episodes were subsequently selected for analysis only when a reported belch was accompanied by a previously identified TLESR and common cavity, without any subsequent rise in gastric pressure of more than 2 mmHg (straining).

On the impedance tracing, gas GER episodes were classified as synchronous, when a pattern of impedance rise occurred in all channels at the same time or with an average velocity of 150 cm/s or more in any direction (highest speed which can reliably be detected with this catheter and a sample frequency of 50 Hz). Other gas GER episodes were classified retrograde or antegrade based upon the direction of propagation of impedance rise onset. For gas GER episodes that produced an antegrade pattern of impedance rise, the rate of propagation of the impedance rise was calculated by dividing the time from onset of impedance rise in the most proximal segment to the most distal segment, by the distance between the segments. Air swallows also produced a pattern of antegrade impedance rise and were similarly analyzed. For all included gas GER episodes, impedance characteristics were verified against existing criteria (Table 1) and antegrade patterns as a result of belching were compared with those resulting from air swallows.

All included gas GER episodes were compared with gas GER episodes that resulted from other mechanisms.

**Protocol 2: Impedance patterns recorded in association with videofluoroscopically determined gas GER**

**Recording techniques**

A seven channel MII-catheter (Aachen University of Technology, FEMU, Aachen, Germany), with cylindrical electrodes positioned at 2, 4, 6, 8, 10, 12, 14, 16, 18, 19 and 21 cm proximal to the tip, was used (Figure 1B). Videofluoroscopy recordings were made in frontal direction with a frequency of 25 Hz and a maximal recording time of 60 seconds, leading to a maximal radiological exposure of 0.067 mSv.

Synchronization between impedance, videofluoroscopy and data acquisition was carried out using purpose designed computer impedance and video acquisition hardware/software.

**Study Protocol**

Catheter placement occurred under videofluoroscopic guidance, such that it was positioned as shown in Figure 1B. Subjects received the same test drinks as per protocol 1. MII was recorded continuously. Subjects were asked to report the urge to belch, upon which videofluoroscopy recordings were started for the duration of a subsequent belch.
If no belch occurred, videofluoroscopy recordings stopped after 10 seconds. When the maximum recording time of 60 seconds was reached, the study was terminated.

**Analysis**

Recordings were included for analysis when a belch was reported by the subject and videofluoroscopic images of the entire episode were available. Impedance measurements were analyzed as per protocol 1. Videofluoroscopic images were analyzed by two investigators, blinded from impedance tracings and each other’s results. Images were analyzed for luminal diameter at the level of each visible electrode at the time of maximal esophageal distension. The data from two neighbouring electrodes were then averaged to be able to examine a correlation with impedance values. In addition, the presence of visible contact between MII electrodes and the esophageal mucosal wall was scored. In case of disagreement, both investigators reviewed the episode together and consensus was found.

**Statistical analysis**

Descriptive parameters are used to describe included gas GER episodes. As normality of impedance values could not be assumed, we used the Kruskal Wallis test to examine overall differences between segmental impedance values. Post hoc analyses were carried out with Wilcoxon’s signed rank test. Correlation between the luminal diameter (at maximal impedance level) and maximal impedance change compared with baseline was calculated by Spearman’s correlation. Krusal Wallis test was used to look for a relationship between the number of impedance electrodes that were in contact with the mucosa and maximal impedance change compared with baseline. Post hoc analyses were carried out with Wilcoxon’s signed rank test. Multiple linear regression analysis was performed using a model including maximum impedance change as dependent variable and luminal diameter and the number of impedance electrodes making contact with the mucosa as independent variables. The explained variance ($R^2$) was determined and tested using the F-test. T-values and their significance were calculated to test the hypothesis that the contribution (regression coefficient ($\beta$)) of the entered independent variables significantly differed from zero.

Differences were considered significant when $p < 0.05$. All statistical analyses were carried out using SPSS 16.0.2 (SPSS Inc. Chicago, USA).

**RESULTS**

**Demographics**

Ten (six male, 21-37 years) and five (three male, 26-52 years) healthy volunteers were enrolled in the two protocols respectively. All subjects completed the studies.
### Existing and proposed criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Number (%) of gas GER episodes fulfilling criteria (n=88 episodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sifrim</strong>&lt;sup&gt;11,12&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• retrograde or simultaneous pattern of impedance rise in ≥ 2 consecutive segments</td>
<td>72 (81.8%)</td>
</tr>
<tr>
<td>• increase in impedance of ≥ 3 kΩ/s in ≥ 2 consecutive segments</td>
<td>82 (93.2%)</td>
</tr>
<tr>
<td>• absence of swallowing</td>
<td>88 (100%)*</td>
</tr>
<tr>
<td><strong>All 'Sifrim – criteria'</strong></td>
<td>66 (75.0%)</td>
</tr>
<tr>
<td><strong>Sandhill Scientific Inc. Bioview – software (J Mabary, personal communication)</strong></td>
<td></td>
</tr>
<tr>
<td>• retrograde or simultaneous pattern of impedance rise in ≥ 2 consecutive segments</td>
<td>72 (81.8%)</td>
</tr>
<tr>
<td>• ≥ 50% increase in impedance in &lt; 2 seconds in ≥ 2 consecutive segments</td>
<td>80 (90.9%)</td>
</tr>
<tr>
<td>• ≥ 3 kΩ increase in impedance ≥ 1 segment</td>
<td>66 (75.0%)</td>
</tr>
<tr>
<td>• Impedance rise to ≥ 5 kΩ in ≥ 1 segment</td>
<td>67 (76.1%)</td>
</tr>
<tr>
<td>• Duration of episode ≥ 0.25 seconds</td>
<td>88 (100%)</td>
</tr>
<tr>
<td><strong>All 'Sandhill – criteria’</strong></td>
<td>50 (56.8%)</td>
</tr>
<tr>
<td><strong>MMS international Ohmega – software (JW van der Wal, personal communication)</strong></td>
<td></td>
</tr>
<tr>
<td>• retrograde pattern of impedance rise</td>
<td>54 (61.4%)</td>
</tr>
<tr>
<td>• impedance rise to ≥ 5000 Ω or any distinct quick increase in impedance followed by a similar decrease within 1.5 sec, either in at least 3 segments for pure gas GER episodes or in 2 segments for mixed GER episodes.</td>
<td>66 (75.0%)</td>
</tr>
<tr>
<td>• most distal segment must fulfill the above criteria</td>
<td>65 (73.9%)</td>
</tr>
<tr>
<td><strong>All 'MMS – criteria’</strong></td>
<td>29 (33.0%)</td>
</tr>
<tr>
<td><strong>Proposed criteria</strong></td>
<td></td>
</tr>
<tr>
<td>• retrograde or simultaneous pattern of impedance rise in ≥ 2 consecutive segments OR an antegrade pattern of impedance rise in ≥ 2 consecutive segments with a recorded speed of ≥ 0.75 m/s&lt;sup&gt;−1&lt;/sup&gt;</td>
<td>88 (100%)</td>
</tr>
<tr>
<td>• increase in impedance of ≥ 3 kΩ/s in ≥ 2 consecutive segments</td>
<td>82 (93.2%)</td>
</tr>
<tr>
<td>• absence of impedance pattern suggestive of a liquid swallow</td>
<td>88 (100%)</td>
</tr>
<tr>
<td><strong>All proposed criteria</strong></td>
<td>82 (93.2%)</td>
</tr>
</tbody>
</table>

Table 1. Existing and proposed criteria and the number and percentage of gas GER episodes fulfilling these. *The absence of swallowing was part of our definition of a gas GER episode. As a direct consequence, none of the episodes analyzed were accompanied by swallowing.
Protocol 1: Impedance patterns recorded in association with manometrically determined gas GER.

Of a total of 221 belches reported by the volunteers, 88 (39.8%) were included in the analysis as they coincided with a pre-identified TLESR and common cavity episode and were therefore not the result of straining or supragastric belching.

Of the 88 TLESR triggered belches, 52 were pure gas GER, while 36 showed a mixed impedance pattern (25 liquid first, followed by gas and 11 vice versa). Fifty-five (62.5%) showed a retrograde pattern of impedance rise, 17 (19.3%) were classified as synchronous and 16 (18.2%) as antegrade (figure 2). Of those 16 gas GER episodes with an antegrade pattern of impedance rise, nine were pure gas and seven were mixed. The difference between mixed and pure gas episodes was not noted by any of the volunteers. All episodes were perceived as belches.

Sixty (75.0%), fifty (56.8%) and twenty-nine (33.0%) episodes of gas GER fulfilled existing criteria for gas GER detection used by Sifrim, Sandhill Scientific Inc (J. Mabary, Personal...
communication) and MMS international (J. W. van der Wal, Personal communication) respectively (see table 1 for more detailed analysis).

**Segmental analysis**
Impedance values at baseline had an average of 2303 ± 1082 Ω. Baselines were significantly higher in proximal compared to distal channels (p<0.001, figure 3). The commonly used cut off value of 5000 Ω was not reached in 57.2% of all impedance segments. In twenty-one (23.9%) gas GER episodes, 5000 Ω were reached in less than two segments. Twenty-two (25.0%) gas GER episodes had a maximum impedance rise less than 3000 Ω. Proximal channels reached higher levels (p<0.001, figure 3). More specifically, the most proximal impedance segment had higher impedance levels (baseline and maximum) compared with more distal segments and baselines were significantly lower in the distal two segments (figure 3). The median absolute impedance rise was
Median of impedance rise in the segment with maximum rise was 4253 (1056 – 10350) Ω. Median (range) propagation rate of antegrade impedance rises associated with gas GER episodes was 1.42 (0.75-1.50) ms⁻¹, this compared with 0.039 (0.024-0.088) ms⁻¹ for air swallows. Based on these data, MII criteria for detection of gas GER with a sensitivity of 93.2% were established by using the previous criteria by Sifrim et al. and include antegrade patterns of impedance rise in ≥ 2 consecutive segments with a recorded speed of ≥ 0.75 ms⁻¹ (table 1).

Included gas GER episodes did not differ from straining induced gas GER episodes with respect to episode duration, maximum impedance level, absolute or relative impedance rise, nor the ascending speed within the esophagus (data not shown). Gas GER episodes as a result of sustained low LES pressures were not seen frequently enough to perform meaningful statistical analyses.

Protocol 2: Impedance patterns recorded in association with videofluoroscopically determined gas GER.

In the five volunteers included, 15 gas GER episodes were recorded. For all events combined, an association was found between the luminal diameter of the esophagus at the time of maximal impedance values and impedance rise that had occurred compared with baseline (Spearman’s rho: 0.68, p<0.001, figures 4 and 5). In addition, impedance rise in a segment was significantly lower when one or both electrodes were in contact with the mucosa (7000 (1400 – 9100) Ω, 2400 (-500 – 7800) Ω and 1700 (0 – 8100) Ω for none, one and two electrodes respectively, p<0.005). On post hoc testing, a significant

![Figure 4. Correlation between luminal diameter (mm) at maximal impedance level and maximal impedance change compared to baseline. Spearman’s correlation, rho = 0.68, p < 0.001.](image)
difference was found between no electrodes and one electrode being in contact with the mucosa (p=0.001) as well as between no electrodes and two electrodes (p<0.005). No difference was found between one or two electrodes being in contact with the mucosa. Using multiple linear regression, the impedance rise could be significantly explained by the proposed model (F=29.7, df=2, p<0.001; adjusted R²=0.53). Only luminal diameter was significantly related to the rise of impedance compared to baseline (β-value: 0.72, p<0.001).

Four gas GER episodes produced a clearly antegrade pattern of impedance rise. During these events, examination of the videofluoroscopy recordings showed that the distension of the proximal esophagus was more pronounced and occurred earlier than distension of the distal esophagus.

Figure 5. A combined videofluoroscopic / multichannel intraluminal impedance (MII) example of the relationships between luminal diameter, mucosal contact and impedance levels. Videofluoroscopic images are shown on top with accompanying MII tracings on the bottom. Numbers in white indicate the impedance segments on the MII catheter, numbers in black represent the impedance measured over that segment. For easier recognition, the mucosal wall, left diaphragm and the MII catheter with relevant electrodes are drawn over the fluoroscopic image. The vertical line through the impedance tracing is corresponding with the moment of the videofluoroscopic image. Consequently, the left panel is a representation of the moment just before the belch occurred, while the right panel represents the moment where impedance levels are at their maximal level. Note that this healthy volunteer has a (previously unrecognized) hiatal hernia.
DISCUSSION

This study shows that current criteria for gas GER detection by MII are poorly sensitive. It furthermore demonstrates that the magnitude of impedance change is mostly dependent on luminal diameter (i.e. the presence of esophageal distension) and, to a lesser extent, contact between impedance electrodes and the mucosal wall. Criteria for detection of gas GER, were developed using in vitro experiments and in vivo studies in sedated cats. Other existing criteria are those incorporated in analysis software packages by Sandhill Scientific Inc (Bioview) and MMS international (Ohmega). Although commonly used, these are not directly based on any published data. We used combined MII/manometry to detect gas GER episodes that were based on manometric criteria (the presence of TLESRs and common cavities) and hence were not the result of straining or supragastric belching. Analysis of these episodes revealed sensitivity of criteria for detection to be as low as 33%. Our data indicate that caution is needed with the interpretation of MII tracings with respect to the presence of gas GER and that strict adherence to existing criteria will lead to under detection of gas GER. This is especially relevant to clinical diagnostic studies of symptoms in relation to GER episodes. Several reports have shown that pure gas GER can be perceived as heartburn and that the addition of gas GER episodes to impedance analysis increases the diagnostic yield of the test in terms of showing a positive symptom-GER association overall. The observation that volunteers perceive both mixed and pure gas GER episodes similarly as a belch further demonstrates that objective measurements are needed to differentiate between types of GER and optimization of gas GER detection criteria is diagnostically important. Further studies are needed to explore the possibility of tailoring therapy specifically to patients with symptoms predominantly related to gas GER.

To improve gas GER detection, we propose modifying the Sifrim criteria to recognize that antegrade patterns of impedance rise do occur with gas GER episodes. This increases sensitivity from 75% to 93.2% overall. As with other criteria currently in use, the available data are insufficient to assess the specificity of these modified criteria, hence the false positive rate is unknown. However, as the rate of ≥ 0.75 ms$^{-1}$ proposed is the lower limit of recorded gas GER episodes and greatly exceeds the upper limit observed with air swallows (0.088 ms$^{-1}$), we would not expect that this simple modification would decrease specificity. Therefore we think that, being based on human investigations of known episodes of gas GER, the criteria detailed in the results section are the best available. Possibilities to further increase sensitivity can be derived from this study and include shifting focus from all impedance segments to the more proximal ones, as this study indicates a more pronounced rise in impedance in these segments. However, we cannot be sure whether this will result in more false positive gas GER episodes. We therefore suggest this to be used only when uncertainty arises during manual correction/confirmation of automatic analyses.
In this study, we also show that the magnitude of impedance rise seen during gas reflux is strongly related to luminal diameter and therefore the degree of luminal distension. This is in concordance with theoretical predictions. Although fluoroscopic images are a two-dimensional representation of a three-dimensional structure, our regression model indicates that more than 50% (adjusted $R^2=0.53$) of all variation in the magnitude of impedance rise is related to the combination of measured diameter and the number of impedance electrodes that are visibly in contact with the mucosal wall. This suggests that our measurement method is a good representation of actual esophageal diameter.

An interesting observation arising from this study was that antegrade patterns of impedance rise do accompany some gas GER episodes in some subjects. Our videofluoroscopy recordings showed that in these cases, distension of the proximal esophagus preceded distension of the distal esophagus which may relate to differences in the compliance of the esophagus along its length or to failure of the upper esophageal sphincter to relax normally\textsuperscript{20,21} preventing gas from venting to the pharynx and mouth and causing the proximal esophagus to distend. This may have some important implications with respect to patients with GERD who have a less distensible esophagus compared to healthy controls and therefore may demonstrate lower degrees of impedance change during gas GER\textsuperscript{22,23}.

The results from this study clearly complicate the development of automatic reflux detection software and hence indicate that manual correction/confirmation of automatic analyses should be performed routinely.

MII patterns of TLESR induced gas GER episodes did not differ from those induced by straining. Therefore, MII cannot be used to determine mechanisms underlying gas GER episodes.

In conclusion, we have shown that current criteria for gas GER detection using MII have poor sensitivity. We have proposed criteria which are more sensitive than any of the existing criteria and can be used for future clinical and research studies. Perhaps more importantly, we provide a better understanding of factors, such as segmental differences, luminal diameter, electrode mucosa contact and esophageal distensibility, which influence the magnitude and patterning of impedance change seen in association with gas GER and should be taken into account when analyzing clinical studies.
REFERENCES


