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Reflux Events Detected by pH-MII Do Not Determine Fundoplication Outcome

Rachel Rosen[*], **Phillip Levine**[*], **Jessica Lewis**[*], **Paul Mitchell**[†], and **Samuel Nurko**[*]

[*]Center for Motility and Functional Gastrointestinal Disorders, Children's Hospital Boston, Boston, Massachusetts

[†]Clinical Research Program, Biostatistics Core, Children's Hospital Boston, Boston, Massachusetts

Abstract

Background—Because of complications and its invasive nature, fundoplication is often a treatment of last resort for children with gastroesophageal reflux. Gastroesophageal reflux testing does not always predict who will benefit from antireflux surgery. Furthermore, there are no studies to determine whether a higher preoperative reflux burden, including acid and nonacid reflux, is associated with an improved postfundoplication outcome. The aim of the study was to determine predictors of fundoplication outcome including acid and nonacid reflux burden.

Patients and Methods—We retrospectively reviewed preoperative pH-multichannel intraluminal impedance tracings and medical records of 34 patients who underwent fundoplication. Patients were categorized as improved or not improved, and the demographic and reflux characteristics were compared between groups. Multivariate analysis was performed to determine predictors of outcome.

Results—No single reflux marker, including the number of acid, nonacid, total events, or the percentage of time that reflux was in the esophagus, predicted fundoplication outcome ($P > 0.1$). Neither a positive symptom index nor a positive symptom sensitivity index predicted postoperative improvement ($P > 0.4$). Receiver operating characteristic curve analysis failed to reveal an ideal value to maximize sensitivity for either the symptom index or the symptom sensitivity index.

Conclusions—pH- multichannel intraluminal impedance testing may not be a useful tool in predicting fundoplication outcome.

Keywords

fundoplication; gastroesophageal reflux; impedance; pH probe; symptom index; symptom sensitivity index

The mainstays of medical treatment for gastroesophageal reflux disease include H2 blockers and proton pump inhibitors (PPIs). Despite these significant improvements in medical therapy, some children do not experience symptomatic relief. Until recently, if there was no response to acid suppression therapy or if pH-probe testing was negative, a patient's

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Address correspondence and reprint requests to Rachel Rosen, MD, MPH, Division of Gastroenterology and Nutrition, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115 (Rachel.rosen@childrens.harvard.edu).

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symptoms were considered “reflux-unrelated” (1). There are, however, patients in which clinical reflux was suspected despite negative pH testing, and in whom a fundoplication was performed with good results, suggesting that the evaluation for acid reflux using a pH probe may be unable to consistently predict which patients with reflux will benefit from a fundoplication (2–4). One reason for this is that the pH probe is blind to nonacid reflux. With the use of multichannel intraluminal impedance testing (MII), clinicians have recognized that nonacid reflux may cause symptoms that may not be responsive to acid suppression therapy and may be effectively treated with fundoplication (5,6).

Presently, there are no outcome studies to determine whether the total amount of reflux, including nonacid reflux, is associated with fundoplication outcome. Small case series have shown that fundoplication can effectively treat both acid and nonacid reflux, but there are no large outcome studies to determine whether total reflux burden, including nonacid reflux burden, is associated with a favorable postoperative outcome (7–9).

The goals of the present study were to determine whether the amount of nonacid reflux is associated with outcome after fundoplication and to determine whether a temporal relation between symptoms and reflux (detected by pH-MII) is associated with outcome after fundoplication.

MATERIALS AND METHODS

Hospital inpatient and outpatient billing records were reviewed for patients with billing codes 44.66 or 44.67 (Nissen fundoplication, gastric cardioplasty, restoration of cardio-esophageal angle). Medical records were retrospectively reviewed to determine whether the patient did, in fact, undergo a fundoplication and whether the patient had a preceding pH-MII study. Those patients who had undergone surgery and had a baseline pH-MII study were included. Patient data were included in the analysis if there was a minimum of 1 follow-up visit at Children’s Hospital Boston within 1 year after fundoplication. Patients were considered “improved” if there was clinical improvement in symptoms reported by the patient’s pulmonologist, gastroenterologist, and/or surgeon or if the patient was able to discontinue acid suppression therapy with no adverse effect on symptoms. In patients with multiple follow-up visits, patients were considered “improved” (IM) or “not improved” (NIM) if there was a mention of a change in clinical status in at least 2 notes. Symptom improvement was determined without knowledge of the pH-MII results. Hospitalizations were considered reflux related if the discharge summary had a primary or secondary diagnosis of vomiting, reflux, aspiration, aspiration pneumonia, respiratory distress, or pneumonia. The change in the number of reflux-related hospitalizations in the year before and after fundoplication were compared between the IM and NIM groups.

Definitions

Each of the pH-MII tracings was manually analyzed by 1 investigator (R.R.) who was blinded to the clinical history of the patient, and each reflux episode was individually scored. A nonacid reflux episode detected by impedance was defined as a retrograde drop in impedance to >50% of the baseline impedance value in the distal 2 channels with no associated drop in pH to <4. An acid reflux episode detected by impedance was defined as a retrograde drop in impedance to >50% of the baseline impedance value in the distal 2 channels with an associated drop in pH to <4. Acid clearance time was calculated as the time from a drop in pH to <4 to the time of its recovery to pH >4. Bolus clearance time was defined as the time from a drop in impedance to >50% of its baseline value to its recovery to 50% of the baseline value in the distal-most impedance channel.

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Acid reflux episodes are those that are detected by both pH and impedance sensors. Nonacid episodes are those episodes detected by impedance sensors only. pH-only episodes are those episodes detected by the pH sensor only and need to be a minimum of 5 seconds in length. Full-column reflux was defined as an episode that reached the highest pair of impedance sensors. The percentage of time that reflux (acid, nonacid, and total) was in the esophagus was determined by summing the bolus clearance times (as detected by MII) and dividing by the study duration. A pH probe was considered abnormal if the pH was <4 for >6% of the 24-hour study for children older than 1 year and for >12% of the children younger than 1 year (1).

Symptom indices were calculated based on the following definitions. A symptom was temporally associated with a reflux event if it occurred within 2 minutes before or 2 minutes after a reflux event. The symptom index (SI) was defined as:

$$\frac{\text{The number of symptoms associated with reflux}}{\text{The total number of symptoms over 24 hours}}$$

The symptom sensitivity index (SSI) was defined as:

$$\frac{\text{The number of reflux events associated with symptoms}}{\text{The total number of reflux events over 24 hours}}$$

SI values >50% and SSI values >10% were considered abnormal (10,11). Patients who did not experience symptoms during testing (n = 2) did not have a calculable SI because the denominator was 0.

Patients were classified as having normal/abnormal pH-MII testing using total number of reflux events and using normal adult standards (12). No pediatric normal values exist for pH-MII in this age group, although pediatric control data suggest that pediatric normal values may be similar to those in adults (13).

Statistical Analysis

Summary statistics for continuous variables were expressed as either mean ± standard deviation or median with associated interquartile range according to the shape of the distribution suggested by the histogram. Frequency distributions were used for categorical variables. Tests of group differences in the outcome were made using Student *t* test or the Wilcoxon rank-sum test depending on whether or not the covariate was approximately normally distributed. Pearson χ^2 or Fisher exact test was used in the case of categorical covariates. Investigation of covariates associated with fundoplication outcome was performed using multivariable logistic regression. Receiver operating characteristic (ROC) curves for the SI and SSI were then created and the area under the curve was determined. Multivariable logistic regression was performed to determine predictors of fundoplication outcome.

The present study was approved by the Institutional Review Board at Children's Hospital Boston. Data analysis was generated using SAS/STAT software, version 9.1 of the SAS System for Windows.

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RESULTS

A retrospective review of patients meeting inclusion criteria found 37 patients that underwent fundoplication with a preceding pH-MII study. Three of the 37 patients did not have recorded outcome data and were therefore excluded. Therefore 34 patients are included in the present study. The mean number of follow-up visits after fundoplication per patient was 4.8 ± 3.7. The mean elapsed time from the time of the impedance to fundoplication was 4.9 ± 3.9 months. The mean age at the time of surgery was 8.2 ± 6.2 years (range 2 months – 22 years), and their baseline characteristics are shown in Table 1. Two out of the 34 patients were younger than 1 year of age. Nine patients discontinued acid suppression therapy 48 hours before pH-MII testing and 25 patients were taking acid suppression therapy at the time of pH-MII testing. All of the patients received medical therapy before fundoplication. Twenty-three patients were taking a PPI, 7 were taking an H2 blocker, and 4 were taking both a PPI and an H2 blocker. Eleven patients were also taking a prokinetic agent (metoclopramide or erythromycin).

Response to Fundoplication

Twenty-two (65%) patients had symptomatic improvement (IM) after fundoplication and 12 patients (35%) had no improvement (NIM); 15 patients experienced improvement in respiratory symptoms and 20 patients experienced improvement in gastrointestinal (GI) symptoms. Following fundoplication, there was a decrease in reflux-related hospitalizations in the year after fundoplication compared with the year before fundoplication in the IM group compared with the NIM group, though not statistically significant (−0.19 ± 1.17 vs 0.40 ± 1.71, respectively; $P = 0.27$). In patients who remained symptomatic, 11/12 patients had an upper GI series; 9/12 showed that the fundoplication was intact, 1/12 showed some reflux but a visually intact fundoplication, and 1/12 showed a partially slipped fundoplication. In the patient with the partially slipped fundoplication, an impedance was performed that showed no evidence of pathologic reflux.

There was no significant change in the mean difference between reflux-related hospitalizations in the year immediately before fundoplication and the mean number of hospitalizations in the year after fundoplication for those that improved (0.3 ± 1.1) compared with those that did not improve (−0.4 ± 1.7, $P = 0.2$).

pH-Impedance Testing

Twenty-five patients were taking acid suppression medications at the time of pH-MII testing, 10 (83%) patients in the NIM group, and 15 (68%) in the IM group ($P = 0.30$).

The mean duration of pH-MII testing was 22.3 ± 1.8 hours. The pH and impedance profiles in patients that did and did not improve after fundoplication are shown in Table 2; the only significant difference was a higher percentage of full column reflux in the IM group, although in both groups it still fell within the normal expected range. There was no significant difference between the IM and NIM groups with respect to the proportion of patients that had normal or abnormal pH-probe results, normal or abnormal pH-MII results, or positive or negative symptom indices (Table 3). The mean symptom indices by type of symptom in patients that did and did not improve after surgery are shown in Table 4.

Additional univariate analyses showed no significant relation with outcome and neurological status, age, or any reflux parameter detected by pH probe analysis or pH-MII ($P > 0.05$). Multivariate analyses did not reveal any covariates including neurological status and reflux burden that were significantly associated with outcome, postfundoplication improvement ($P > 0.05$).

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Respiratory and GI symptom-specific ROC curves were generated and area under the curve and *P* values for ROC are shown in Table 5. There was no clear cut-off for the SI or SSI value that would best predict surgical outcome.

DISCUSSION

This is the first study to address the impact that the detection of nonacid reflux (as detected by pH-MII) will have in predicting the outcome after fundoplication in children. In the present series, 65% of patients improved after fundoplication, but surprisingly neither the detection of nonacid reflux events nor their association with symptoms accurately predicted surgical outcome. This is the first study to show that improved detection of nonacid reflux events using pH-MII may not result in better patient selection for fundoplication in children. Additionally, even with more accurate SI values that reflect the inclusion of nonacid reflux, the indices were still poor predictors of fundoplication outcome. Further, even after adjusting for other covariates using logistic regression, symptom association remains a weak tool to predict outcome. Unfortunately, the generation of ROC curves for the SI and SSI also did not result in a better “cut-off value” to predict which patients will experience postoperative improvement.

The only potential advantage that pH-MII recording may offer is the ability of the catheter to detect the height of the refluxate. In the present study, patients who had a favorable postoperative outcome had more full column reflux preoperatively than those patients with a less favorable outcome. This suggests that full column reflux may be more strongly associated with symptoms and therefore symptom improvement after fundoplication. Although this may be the case, the percentage of full column events in the NIM group was only 17%, which is significantly less than the previously reported percentages for normal patients (12). Similarly, 38% of reflux episodes were full column in those patients in the IM group which is not significantly different from the normal percentage of full column episodes (12). Therefore, any conclusions based on height should be tempered until further studies are performed, because the percentage of full column reflux in our study population was lower than previously reported.

A lack of predictive value in fundoplication outcome has previously been reported when using a single pH probe as a tool to detect reflux both in children and adults. Pediatric data suggests that pH probes do not effectively predict postoperative outcome. Valusek et al (4) studied children who had undergone fundoplication for acute life threatening events, 96.3% of whom improved postoperatively. When comparing those patients that did and did not improve after fundoplication, there was no significant difference in the pH probe results between the 2 groups, although the number of patients in the “no improvement” group was small (n = 3). Similarly, Mattioli et al (2) studied 49 children who underwent fundoplication for atypical gastroesophageal reflux disease symptoms. Forty-four out of 49 patients reported some symptomatic postoperative improvement but no diagnostic test, including the detection of acid reflux, predicted outcome after fundoplication. Tovar et al (3) reported on 14 children who underwent fundoplication with normal pH monitoring, of which 13/14 of the families reported satisfaction with the surgery despite no evidence of pathologic reflux by pH probe, thus reinforcing that pH probe is an imperfect tool.

Studies in the adult population have shown similar results, providing further evidence that the pH probe does not effectively predict fundoplication outcome. Morgenthal et al (14) studied 174 adult patients who underwent fundoplication, of which 75% had a successful outcome. There were no differences between pH results of patients that did and did not improve after surgery. Similarly, So et al (15) surveyed 34 adults pre- and postfundoplication to determine degree of symptom improvement and found that 44% of

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patients with atypical symptoms had no improvement in symptoms despite abnormal pH monitoring. Pidoto et al (16) studied 25 adults undergoing Nissen fundoplication and also found that pH probe results did not predict long term outcome after fundoplication. Only 1 adult study found that pH probe predicted outcome; O'Boyle et al (17) studied 262 patients who underwent fundoplication, of which 119 also had preoperative pH testing. The authors found that patients with an abnormal pH probe were more satisfied with their surgical outcome 5 years postoperatively than patients who had normal preoperative pH probes.

One hypothesis for this failure of pH probes to accurately predict outcome is that pH testing fails to detect nonacid reflux that may be a contributor to symptoms, particularly respiratory symptoms (8,18). Given that the use of impedance allows the detection of nonacid reflux, and that sensitivity studies show that the use of impedance increases the number of positive symptom indices because more total reflux events are detected (19,20), the question remains whether or not this increased detection translates into improved prediction of outcome after fundoplication.

Up to this point there is only 1 published study that has looked at the role of impedance in predicting fundoplication outcome. Mainie et al (7) studied 19 patients who underwent fundoplication after preceding pH-MII testing. Two (11%) patients experienced no symptomatic improvement; of these 2 patients, 1 had a negative SI for heartburn and 1 had a positive SI with a complaint of chronic hoarseness. There was no discussion about the number of reflux events between those that did and did not improve, and the number of fundoplication failures is so small that meaningful comparisons between groups are not feasible. However, the authors suggest that pH-MII may be useful in predicting outcome after fundoplication.

Our study does not support the hypothesis that the detection of nonacid reflux will allow for improved patient selection for fundoplication. One difference that may explain the differences between our data and the results by Mainie et al (7) is the possibility that children referred for fundoplication tend to have more severe disease. In general, fundoplication, which is invasive and can have complications, is reserved as a treatment of last resort; pediatric patients referred for fundoplication often present with intractable symptoms that have not responded to PPI therapy or other therapies. Adult data suggest that patients who respond to acid suppression therapy have better fundoplication outcomes than those that do not have a medical response, so this difference in surgical referral patterns may account for this difference (14,15,21–23). Finally, our data may differ from Mainie et al (7) because of the sample size; our case series is the largest in both the adult and pediatric literature and so may be more representative of pH-MII utility.

There are several limitations to the present study. First, this is a retrospective review and therefore may not accurately reflect symptomatic improvement. Although we recognize this limitation, the percentage of patients with a favorable outcome is similar to that reported in the literature, so we feel that these results are valid (24–26). Furthermore, because of the relative rarity of fundoplication, even in a larger quaternary care institution, we felt that a review of the data during the last 6 years would provide important groundwork for future long-term prospective studies. Second, given that we do not have normal pediatric standards, the determination of which patients have normal or abnormal number of reflux episodes was done based on adult standards. This could have overestimated the number of children with abnormal number of reflux episodes if the assumption is that children tend to have more reflux than adults. Studies with pH probes, and our own preliminary published information on impedance results in a limited number of controls, show that the total number of reflux in a 24–hour period is similar to adult normal values (13). Third, patients often underwent fundoplication for a variety of factors, of which pH-MII was only 1 factor, so one would not

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expect pH-MII results alone would predict outcome. Unfortunately, when we performed multivariate analyses to determine if other non–pH-MII factors such as neurological status or age at the time of fundoplication predict outcome, we found similar results; these demographic factors also did not predict outcome in this series. Fourth, many of the patients that did not improve after fundoplication did not undergo repeat pH-MII testing to determine the efficacy of the wrap. Therefore, the failure to respond symptomatically may be because of wrap failure. Although patients in our study had repeat upper GI series to assess this and we limited our analysis to the year following surgery to minimize the likelihood of wrap failure, we suggest that in future studies, responders and nonresponders should have follow-up pH-MII testing. Finally, fundoplication at our institution is pursued only after failure of multiple medical interventions so that these patients may be more intractable than other populations.

Despite these limitations, the present data calls into question the ability of pH-MII to predict which children will respond favorably to a fundoplication. The data also suggests that symptom indices and number of reflux episodes should be only 2 of the factors that are considered before a fundoplication. Clinicians should consider a variety of clinical factors before referral to fundoplication. Large prospective outcome studies are needed to try to determine the best predictors of fundoplication success.

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TABLE 1

Baseline characteristics in patients who did and did not improve postoperatively

	Improved N = 22	Not improved N = 12	*P*
Median age in y (range)	5.6 (0.2–22.2)	10.6 (1.8–19.2)	0.4
No. with gastrointestinal symptoms (%)	20/22 (82%)	9/12 (75%)	0.5
No. with pulmonary symptoms (%)	15/22 (73%)	8/12 (67%)	0.5
No. neurologically abnormal (%)	13/22 (59%)	4/12 (33%)	0.14
No. abnormal swallow study (%)	5/12 (42%)	4/5 (80%)	0.18
No. with esophagitis (%)	3/15 (20%)	3/6 (50%)	0.2

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TABLE 2

Reflux profiles in patients that did and did not improve postoperatively (interquartile range)

	Improved (N = 22)	Not improved (N = 12)	*P*
No. acid events	13 (5, 25)	18 (5, 72)	0.36
No. nonacid events	19 (10, 29)	15 (2, 23)	0.21
No. pH-only events	18 (8, 30)	16 (8, 24)	0.71
% full column reflux	38 ± 23	17 ± 14	0.005
% time acid (MII)	1.4 ± 2.2	0.8 ± 1.5	0.4
% time nonacid (MII)	1.3 ± 2.6	0.6 ± 1.0	0.3
% time all MII events (MII)	2.7 ± 3.5	1.4 ± 2.4	0.3
pH <4 for % (pH)	7.9 ± 7.7	13.7 ± 13.8	0.12

MII = multichannel intraluminal impedance.

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TABLE 3

Number of patients with normal and abnormal reflux testing in IM and NIM groups

	Improved	Not improved	*P*
Normal pH probe*	14/22	6/12	0.4
Abnormal pH probe*	8/22	6/12	
Normal # reflux events pH-MII†	14/22	10/12	0.2
Abnormal # reflux events pH-MII†	8/22	2/12	
Negative SI	8/22	5/12	0.8
Positive SI	14/22	7/12	
Negative SSI	15/22	10/12	0.3
Positive SSI	7/22	2/12	
Normal pH-MII‡	5/22	3/12	0.8
Abnormal pH-MII‡	17/22	9/12	

MII = multichannel intraluminal impedance; SI = symptom index; SSI = symptom sensitivity index.

*pH <4 for >6% of the time in children >1-year old or >12% in children <1-year old.

†Total number of reflux events >73/24-hour study.

‡>73 reflux events or an abnormal SI or SSI.

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TABLE 4

Mean (±SD) symptom indices, divided into respiratory and gastrointestinal symptoms, in improved and not improved patients (Wilcoxon rank-sum test)

	Improved	Not improved	*P*
SI (GI)	70 ± 46 (n = 14)	65 ± 42 (n = 8)	0.49
SI (RESP)	11 ± 14 (n = 14)	14 ± 34 (n = 8)	0.54
SSI (GI)	48 ± 30 (n = 15)	50 ± 44 (n = 8)	0.80
SSI (RESP)	7 ± 6 (n = 15)	5 ± 6 (n = 8)	0.39

GI = gastrointestinal; RESP = respiratory; SD = standard deviation; SI = symptom index; SSI = symptom sensitivity index.

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TABLE 5

Area under the curve or c statistic

	AUC
Overall improvement: SI	0.57
Overall improvement: SSI	0.40
Gastrointestinal symptom improvement: SI	0.71
Gastrointestinal symptom improvement: SSI	0.41
Respiratory symptom improvement: SI	0.58
Respiratory symptom improvement: SSI	0.54

AUC = area under the curve; SI = symptom index; SSI = symptom sensitivity index.