



Can Impedance-pH Testing on Medications Reliably Identify Patients with GERD as Defined by Pathologic Esophageal Acid Exposure off Medications?

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Abstract

Introduction Impedance-pH testing (MII-pH) while patients are on acid suppression medications is frequently used to evaluate persistent reflux symptoms. The aim of this study was to determine whether MII-pH *on* medications can reliably identify patients with gastroesophageal reflux disease (GERD) as defined by pathologic esophageal acid exposure *off* medications, and to determine if there is a threshold of total reflux episodes *on* medications where pH testing *off* medications may be unnecessary.

Methods A retrospective review identified all patients between 1/2010 and 4/2017 who underwent MII-pH testing *on* PPI medications and subsequently had pH testing *off* medications. GERD was defined on pH testing *off* medications by an abnormal DeMeester Score (DMS) and on MII-pH *on* medications by ≥ 48 total reflux episodes. Patients with an abnormal DMS by MII-pH *on* medications were excluded.

Results There were 71 patients, (22 males; 49 females), with a median age of 52 years. Based on ≥ 48 total reflux episodes by MII-pH testing *on* medications, 42 patients (59%) had GERD. When tested *off* medications, an abnormal DMS was present in 44 patients (62%). Among those with GERD based on impedance testing *on* medications, 31% did not have GERD based on pH testing *off* medications. Further, in the 29 patients with ≤ 48 total reflux episodes on MII-pH (normal test), 15 patients (52%) had pathologic acid exposure off medications. When there were > 73 reflux events with MII-pH *on* medications, all 15 patients in our series had pathologic acid exposure on pH testing *off* medications.

Conclusion MII-pH testing *on* medications in patients with refractory GERD symptoms does not reliably correlate with a diagnosis of GERD as defined by pathologic esophageal acid exposure off medications. The commonly used abnormal MII-pH test value of ≥ 48 total reflux episodes is not validated and should not be used. However, in our series, patients with > 73 total reflux episodes had a high likelihood of having pathologic acid exposure off medications. Overall, the preferred strategy to evaluate patients with persistent GERD symptoms on acid suppression therapy should be pH testing *off* medications.

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Introduction

Gastroesophageal reflux disease (GERD) is a world-wide clinical problem with an increasing prevalence in the USA.¹ The diagnosis of GERD is most commonly made based on heartburn and regurgitation symptoms, and typically, these patients are given a trial of acid suppression therapy with proton pump inhibitor (PPI) medications. Persistent or poorly controlled symptoms are reported to occur in a third or more of patients, and management options for these patients include altering the medical regimen or objective reflux testing.² Dose escalation of the PPI is often done clinically, but current practice guidelines recommend objective testing.^{3, 4}

The gold standard for the objective diagnosis of GERD is ambulatory pH monitoring *off* acid suppression medications looking at the percent time pH < 4 in the esophagus or the esophageal acid exposure score (DeMeester score: DMS). One perceived limitation of traditional pH monitoring with a trans-nasal catheter or the Bravo wireless pH probe (Medtronic, Shoreview, MN, USA) is the inability to measure reflux events with a pH > 4.0, so-called weakly acidic reflux.⁵ Multichannel intraluminal impedance can measure all types of reflux events, and when combined with pH (MII-pH) can determine whether a reflux event was acidic (pH ≤ 4), weakly acidic (pH > 4 but ≤ 7), or non-acid (pH > 7).⁶ The addition of MII-pH has spurred interest in the evaluation of patients with refractory symptoms while *on* acid suppression medications. The rationale for this is three-fold: (1) it can assess whether the current regimen of acid suppression is adequate to normalize esophageal acid exposure; (2) it can detect weak and non-acid reflux, which has been postulated to cause persistent symptoms despite adequate acid suppression;^{7, 8} and (3) it eliminates the need to hold PPIs prior to testing which can exacerbate symptoms related to rebound hyperacidity.

There are two ways MII-pH can be abnormal *on* antireflux medications. First, inadequate acid suppression may be identified. These patients have increased esophageal acid exposure despite being *on* PPI therapy. Treatment options in these patients include increasing the PPI dose, changing medications, or referring the patient for antireflux surgery. The second way that the MII-pH test can be abnormal is based on the total number of reflux episodes or the symptom correlation with reflux events.⁹ These patients have normal acid exposure but an increased number of reflux events or positive symptom correlation and are often referred for antireflux surgery since there is little to gain with medication adjustment. There are several problems with using the total number of reflux episodes or symptom scores to define an abnormal MII-pH study. First, while normal values for the total number of reflux events

detected by impedance *on* and *off* medications have been reported, data from around the world suggests that these values vary by diet and ethnicity.^{10–15} Second, the relationship between an increased total number of reflux episodes *on* MII-pH while *on* medications and the presence of GERD as defined by pathologic esophageal acid exposure *off* medications is poorly defined. Lastly, the use of symptom scores to define reflux disease is unreliable given concerns regarding the methodology and statistical significance of these scores.¹⁶

Consequently, there were two aims for this study. First, we sought to determine whether currently used values for the number of reflux events with MII-pH testing *on* medications could reliably identify patients with GERD as defined by the presence of increased esophageal acid exposure with pH testing *off* medications. Second, we sought to determine if there was a threshold value of total reflux episodes by MII-pH *on* medications where pH testing *off* medications was not necessary since nearly all patients would have an abnormal test. Our a priori hypothesis was that the diagnosis of GERD determined by an *on*-medication MII-pH would not be equivalent to the gold standard *off*-medication pH test, but that at some number of reflux events *on* medications, there would be a high likelihood of finding pathologic esophageal acid exposure *on* pH testing *off* medications.

Methods

Patients

We retrospectively reviewed the charts of all patients who had both an MII-pH *on* acid suppression medication and a subsequent pH study (trans-nasal or Bravo) *off* medication from January 2010 to April 2017. We excluded one patient with increased esophageal acid exposure *on* MII-pH testing despite being *on* PPI therapy. All other patients had normal esophageal acid exposure *on* MII-pH testing while *on* medications. None of the patients included in this study had prior foregut surgery. This study was approved by the Portland Providence Hospital IRB.

pH Testing

MII-pH monitoring was performed while patients were *on* at least once-daily PPI therapy, and all patients had been *on* medications for a minimum of 1 month before evaluation. MII-pH monitoring was done using a combined MII-pH monitoring device (Sandhill Scientific Inc., Highlands Ranch CO), which includes a data recorder (Sleuth System, Sandhill Scientific Inc) and a 2.1-mm diameter catheter with 1 pH

and 6 impedance sensors at predefined positions. All catheters were placed trans-nasally and secured 5 cm above the upper border of the manometrically identified lower esophageal sphincter (LES). After 24 h, the patients returned for catheter removal and data review. Patients with ≥ 48 total reflux events were considered to have an abnormal test.¹⁷ Although symptom scores were often obtained, we did not analyze these as part of this study given our concerns regarding methodologic and statistical flaws with these scores.

In preparation for pH testing *off* medications, patients were instructed to discontinue PPI medications for a minimum of 7 days. Trans-nasal catheter-based pH monitoring was performed in similar fashion to MII-pH described above. Ambulatory Bravo pH monitoring was performed for 48 h. The Bravo capsule was endoscopically placed 6 cm above the gastroesophageal junction. After completion of the study, data was downloaded from the recording device by using Datalink software (Medtronic). Pathologic esophageal acid exposure was defined as a DMS > 14.7 for catheter pH studies and on Bravo analysis if either day was abnormal (DMS > 14.0) the test was considered positive for GERD.¹⁸

Statistical Analysis

Values were not normally distributed. As a result, they are presented as medians and the 95th percentile value. Clinical and demographic data was dichotomized based on established normal values unless otherwise specified. The *T* test was used to assess differences between groups. To determine whether there was an association between impedance findings on therapy and pH testing off therapy, a Pearson χ^2 test was performed. Statistical analysis was performed by SPSS Statistics software (IBM Corp., Armonk, NY, USA). A *p* value < 0.05 was considered significant.

Results

There were 71 patients with a median age of 52 years, of whom 49 were females (69%). All patients had both MII-pH testing *on* medications and a pH test *off* medications. The median time interval between tests was 4 months. The primary symptoms that led to MII-pH testing on medications in these patients were refractory heartburn (70%) and regurgitation (78%). The median DMS by MII-pH while on medications in all 71 patients was 2.1, with no patient having increased esophageal acid exposure by study design. The median number of total, weak acid, and non-acid reflux events for all patients was 51, 8, and 38, respectively. Using the threshold value of abnormal being ≥ 48 total reflux events, 42 patients (59%) were considered to have an abnormal MII test.

Ambulatory pH testing *off* medications was performed using catheter-based pH testing in 25 patients and using the

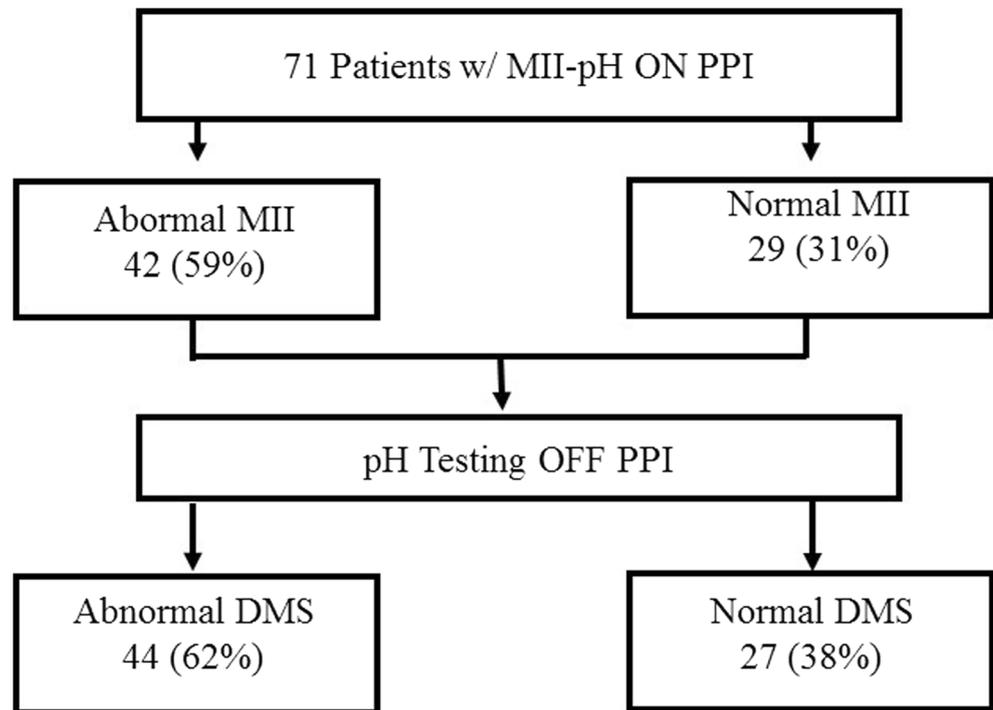
Bravo system in 46 patients. The median % time pH < 4 for all patients *off* medications was 10.1% and the median DMS was 32.2. Pathologic esophageal acid exposure on pH testing *off* medications was present in 44 patients (62%) (Fig. 1). Among the 42 patients with ≥ 48 total reflux events on medications and therefore an abnormal MII test, only 29 patients (69%) were confirmed to have pathologic esophageal acid exposure on pH testing *off* medications. This frequency was not significantly different than the 52% frequency of an abnormal pH test *off* medications in patients who had a normal MII-pH *on* medications ($p = 0.09$) (Fig. 2). The relationship between MII-pH testing *on* medications and pH testing *off* medications for all patients is summarized in Table 1. The sensitivity and specificity for MII-pH on medications using a threshold of ≥ 48 total reflux events as abnormal to predict reflux disease based on increased esophageal acid exposure on pH testing *off* medications was 66% and 52% respectively. This gave a positive predictive value for an abnormal MII-pH on medications for identifying patients with increased esophageal acid exposure *off* medications of 69% and a negative predictive value of 48%.

The median number of total reflux events by MII-pH testing *on* medications for all patients was 51, and the total number of reflux events was significantly higher in patients found to have abnormal acid exposure when tested *off* medications (median 58 events) compared to those with normal esophageal acid exposure when tested *off* medications (median 34 events) [$p < 0.05$]. The 95th percentile for having increased esophageal acid exposure on pH testing *off* medications was 67 total reflux events on MII-pH testing while on medications. When there were > 73 total reflux events on MII-pH testing on medications, all patients ($n = 15$) subsequently were confirmed to have increased esophageal acid exposure on pH testing *off* medications with a median DMS of 35.7. Using this threshold of > 73 total reflux events to predict increased esophageal acid exposure on pH testing *off* medications, the specificity was 100% but the sensitivity was only 34%. Figure 3 shows the relationship between total reflux events by MII-pH testing *on* medications and the DMS by pH testing *off* medications for each patient.

Discussion

The Montreal consensus defined GERD as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.¹⁹ The assumption within that definition is that reflux of stomach contents into the esophagus is occurring. Symptoms do not necessarily define a disease, and even typical GERD symptoms are not always secondary to reflux of gastric juice into the esophagus. Further, some degree of reflux is normal and only becomes pathologic when excessive. To improve upon the Montreal

Fig. 1 Flow chart of MII-pH on and pH testing off medications



definition of GERD, the PPI test is often added. Patients with reflux symptoms and a good response to PPI are presumed to have GERD. However, approximately a third of patients with GERD symptoms have inadequate or poor symptom relief with acid-suppression medications.²⁰ Whether these patients have GERD that is refractory to medical therapy or some other etiology for their symptoms is unclear. The next step for many of these patients is MII-pH testing *on* medications. Patients with increased esophageal acid exposure *on* medications are thought to need an increased dose or alternative medication, or are considered to be refractory to PPI medications and referred for consideration of antireflux surgery. In patients with normal esophageal acid exposure *on* medications, efforts have been made to link symptoms with reflux events, and the total

number of reflux episodes has been used to define an abnormal impedance test.

The use of total reflux events by impedance to assess for the presence of GERD makes sense since patients with GERD are known to have more reflux events than baseline controls. However, in the well-validated DeMeester scoring system, the number of reflux events has the highest standard deviation and is less sensitive and specific for confirming GERD than other parameters such as % time pH < 4.²¹ In addition, the published normal values for the total number of reflux events by MII-pH monitoring on and off medications range from 45 to 99 depending on the patient population, with lower total reflux events in Italian volunteers on a Mediterranean diet and higher values in populations from the USA and Europe

Fig. 2 Results of pH testing off medications in patients with either normal or abnormal MII-pH testing using ≥ 48 total reflux events as the definition of an abnormal impedance study

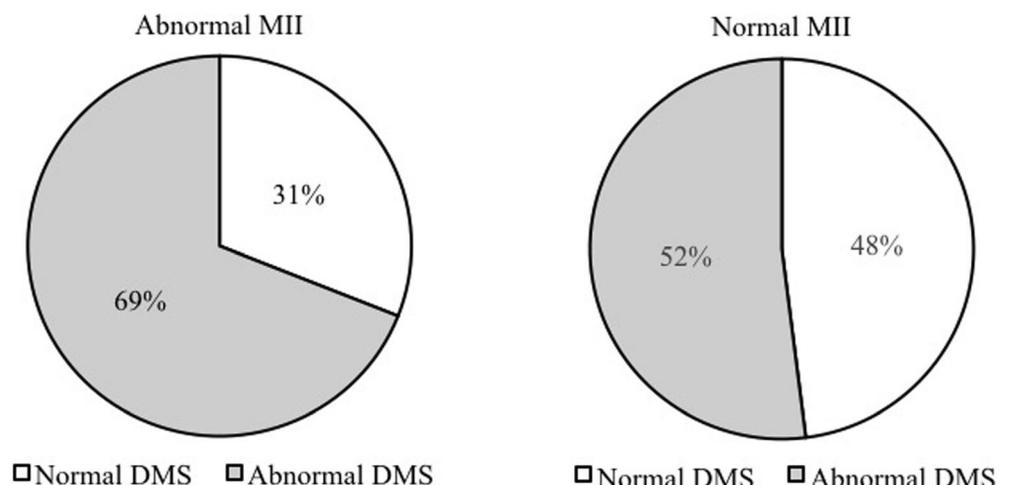


Table 1 Relationship between Impedance on medications and pH off medications for all patients

	Abnormal impedance on medications (≥ 48 total reflux events)	Normal impedance on medications (< 48 total reflux events)
Abnormal pH off medications ^a	N = 29 (41%)	N = 15 (21%)
Normal pH off medications	N = 13 (18%)	N = 14 (20%)

^aDMS > 14.7 for catheter or > 14.0 for Bravo pH testing on either study day

(Table 2).^{10–15} Incredibly, the widely used normal value of < 48 total reflux events on MII-pH monitoring on medications was established from an abstract with data that was never published.¹⁷

There are four important findings and conclusions from the data in our study. First, the total number of reflux events by MII-pH *on* medications cannot be used to reliably confirm the presence of GERD as it does not sufficiently correlate to increased esophageal acid exposure based on pH testing *off* medications. Patients with as few as 13 total reflux episodes had objective evidence of GERD on pH testing off medications while patients with as many as 73 total episodes did not have GERD. In our patient population, we found that everyone with more than 73 total reflux episodes on MII-pH on PPI medication had an abnormal pH test off medications, suggesting that perhaps in these patients, pH testing off medications is unnecessary to confirm GERD. Caution must be used before utilizing this number of > 73 total reflux events since there were only 15 patients that met this criterion in our study. Further, Moawad et al. used a threshold of ≥ 73 total reflux episodes to define an abnormal MII-pH test *on* medications and reported that only 50% of these patients had increased esophageal acid exposure when tested *off* their PPI medication.²² Almost certainly, threshold values for an abnormal total number of reflux events by MII-pH on and off medications are population specific, since Doulami et al. showed

that in obese Greek, normal volunteers up to 99 total reflux events were normal.¹⁵ It is likely that there is a threshold value for total reflux events on MII-pH testing *on* medications beyond which all patients will have objective evidence of GERD, but that number may be so high that although specific, it lacks sensitivity. In our study population, the specificity for GERD in patients with > 73 total reflux events on MII-pH on medications was 100%, but the sensitivity was very low at 34%.

The second important finding from our study is that the frequently used value of ≥ 48 total reflux events on MII-pH testing *on* medications to define an abnormal impedance result should no longer be accepted. When using this value, 31% of patients considered abnormal by MII had normal esophageal acid exposure by pH testing *off* medications, giving a sensitivity, specificity, and positive predictive value of 66%, 52%, and 69%, respectively. Similar to our findings, Pritchett et al. reported that Bravo pH testing off medications confirmed increased esophageal acid exposure in only 60% of patients with abnormal impedance based on > 48 total reflux episodes on medications.²³ These percentages are far too low to be useful for selecting patients for an endoscopic or surgical antireflux procedure since many patients would be given an intervention that would be unlikely to improve their symptoms.

Our third important finding is that MII-pH testing *on* medications cannot be used to rule out GERD. In our study, 29

Fig. 3 Scatterplot showing total reflux events by MII-pH on PPI therapy and the corresponding DeMeester score by pH testing off PPI therapy for each patient. The cutoff line at 14.7 defines normal (below) and abnormal (above) DeMeester score

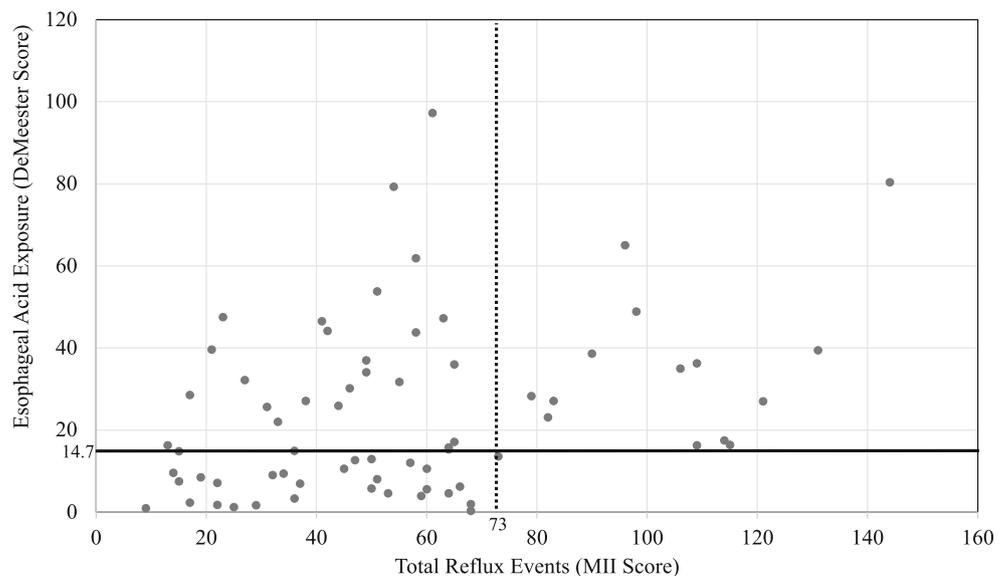


Table 2 Normal values for total reflux events by MII-pH on and off medications

Study (author/year)	Number: demographic of subjects	On/Off PPI	Total reflux events normal
Shay et al. 2004	60: American	Off	73
Zerbib et al. 2005	72: Belgo-French	Off	75
Zentilin et al. 2006	25: Italian	Off	48
Xiao et al.	70: Chinese	Off	75
Zerbib et al. 2012	46: French	Off	53
		On	57
Doulami et al. 2016	22: Obese Greek	Off	99.7

patients had a normal MII-pH test *on* medications, yet pathologic esophageal acid exposure was present on pH testing *off* medications in 52% of these patients. We found no difference in the frequency of pathologic acid exposure on pH testing *off* medications between patients with < 48 or \geq 48 total reflux episodes by MII-pH testing *on* medications. In our study, a patient with only 13 total reflux episodes on MII-pH testing on medications had increased esophageal acid exposure on pH testing *off* medications. In a study by Pritchett et al., there were 25 patients that had \leq 48 total reflux episodes on MII-pH and were considered normal, yet 60% of these patients had abnormal esophageal acid exposure by Bravo pH testing *off* medications. They concluded that MII-pH *on* medications was unable to determine which patients with refractory symptoms on twice daily PPI had and did not have reflux disease as defined by abnormal esophageal acid exposure *off* medications.²³

Lastly, our study calls into question the usefulness of MII-pH testing *on* acid suppression medication in patients with refractory symptoms who have not been previously confirmed to have GERD based on pH testing *off* medications. We found that 38% of patients that had MII-pH testing *on* medications for persistent or poorly controlled reflux symptoms did not have increased esophageal acid exposure on pH testing *off* medications. Many of these patients had been on daily or twice-daily PPI medications for years. Our results are very similar to the study by Herregods et al. that showed that over 30% of patients with refractory reflux symptoms *on* medications did not have GERD when objectively studied by pH testing *off* medications.²⁴ Given recent concerns about the potential for long-term side effects and complications of PPI medications, it appears unjustifiable to not use pH testing *off* medications to first confirm the presence of GERD in patients with persistent symptoms *on* medications, especially since one person in every three tested will not have increased esophageal acid exposure.^{25–28}

A benefit of pH testing *off* medications as the preferred strategy in patients with persistent symptoms on medications is that an alternative etiology can be sought in those patients found not to have GERD on objective testing. Some of these patients may benefit from treatment for functional heartburn, perhaps with visceral pain modulators. In patients with

confirmed GERD on pH testing *off* medications, an assessment of the efficacy of PPI therapy with pH testing *on* medications can be performed if the patient prefers to stay on PPI therapy. However, in our series, there was only one patient with persistently increased esophageal acid exposure while on PPI therapy. This would suggest that it may be a small group of patients on highly effective modern acid suppression medications that are abnormal based on the pH portion of MII-pH testing *on* medications, particularly on PPI twice a day. Further, numerous studies have shown that compared to impedance-pH evaluation *off* therapy, patients *on* therapy have a similar number of total reflux events, but acidic reflux events are reduced and weakly acidic events increase.²⁹ Consequently, the added information by impedance-pH testing on medications appears to be very limited.

This study has both strengths and weaknesses. The strengths are that all patients had both a MII-pH *on* medications and a pH test *off* medications within a short period of time. In addition, all testing was done within the confines of a multi-specialty physician group with a close working relationship. Weaknesses include the retrospective nature of the study, the limited number of patients, and the inability to reinterpret and confirm the original MII-pH studies. All MII-pH studies *on* medications were performed outside our lab and as a result, we could not reanalyze the tracings. Ideally, we would have been able to review the raw data from each study. However, all studies were done in high-volume gastroenterology motility laboratories and this represents a clinically relevant scenario for practicing gastroenterologists and surgeons.

Conclusion

In conclusion, the total number of reflux events on MII-pH in patients *on* medications is unable to reliably determine which patients have GERD as defined by increased esophageal acid exposure on pH testing *off* medications. Consequently, MII-pH testing *on* medications should not be used to select patients for an antireflux procedure. Instead, the first appropriate study for patients with persistent symptoms on medications should be a pH study *off* medications. Those with increased

esophageal acid exposure are candidates for alterations in their medical regimen or consideration of an antireflux procedure, while those with normal esophageal acid exposure should have their PPI discontinued and be evaluated for an alternative etiology for their symptoms. In our patient population greater than 73, total reflux events by MII-pH on medications always correlated with an abnormal pH test *off* medications, indicating that repeat testing was unnecessary. However, this finding may be population specific and further investigation is required before this number of reflux events on MII-pH testing on medications can be applied to other patient populations and centers.

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Compliance with Ethical Standards

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