

# ORIGINAL ARTICLES

## Combined Multichannel Intraluminal Impedance and pH Esophageal Testing Compared to pH Alone for Diagnosing Both Acid and Weakly Acidic Gastroesophageal Reflux

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**Background & Aims:** Twenty-four-hour multichannel intraluminal impedance and pH (MII-pH) esophageal monitoring detects reflux episodes at all pH levels, including acid reflux and weakly acidic reflux (WAR). The aim of this study was to assess the accuracy of pH monitoring alone in detecting acid reflux and WAR compared with MII-pH.

**Methods:** For the detection of acid reflux: 60 consecutive MII-pH studies of patients off acid suppression were included. All studies initially were read by exclusively analyzing pH tracing for acid reflux episodes. Subsequently, all studies were blindly read again analyzing MII-pH-detected acid reflux episodes (pH decrease of <4 and MII-detected reflux). For the detection of weakly acidic reflux 40 MII-pH studies were included. Each study initially was read by identifying WAR on the pH tracing. Subsequently, studies were re-analyzed using MII tracings, classifying MII-detected reflux episodes into acid, WAR, or nonacid reflux.

**Results:** For the detection of acid reflux the pH alone compared with MII-pH yielded a specificity of 68%, 67%, and 58%, respectively, for either abnormal percentage time of pH less than 4, positive symptom index, or both. The percentage time that the pH was less than 4 was significantly higher using pH alone compared with MII-pH. Eighty-one percent of acid gastroesophageal reflux episodes exclusively detected by pH were associated with MII-detected swallow. For the detection of WAR compared with MII, pH alone had a sensitivity of only 28%. Eighty-three percent of WAR episodes detected by pH were not associated with MII-detected reflux. **Conclusions:** The use of pH alone for the detection of acid reflux is very sensitive but lacks specificity compared with MII-pH. pH alone may overdiagnose abnormal acid reflux in up to 22% of tested patients. Also, the use of pH for the detection of WAR has poor sensitivity.

In the United States, up to 40% of the adult population experiences some degree of symptoms from gastroesophageal reflux (GER), mainly heartburn and regurgitation.<sup>1</sup> A Gallup survey<sup>2</sup> estimated that 7% of individuals in the general population experience GER symptoms daily, and 14% have these symptoms at least once a week.

Twenty-four-hour combined multichannel intraluminal impedance and pH (MII-pH) esophageal monitoring allows the detection of both acid and nonacid GER by identifying retro-

grade fluid movement in the esophagus. Thus, the addition of MII to traditional pH monitoring allows the detection of reflux independently from the pH of the refluxate. This method has been shown to achieve the highest sensitivity for the detection of GER episodes.<sup>3-5</sup> In fact, a panel of esophageal experts recently reviewed the most current technologies for GER monitoring and concluded that intraluminal impedance monitoring is the only recording method that can achieve high sensitivity for the detection of all types of reflux episodes, whereas the addition of pH is required for the characterization of reflux acidity.<sup>6</sup> This panel also proposed a revised classification of GER episodes based on MII-pH. The definition of acid GER remains unchanged and refers to MII-detected reflux episodes with a concomitant decrease in pH to less than 4 (Figure 1A). MII-detected GER episodes with a nadir pH between 4 and 7, with a decrease of more than 1 unit, and lasting longer than 4 seconds (Figure 1B),<sup>6</sup> are classified as weakly acidic reflux (WAR). MII-detected GER episodes without a pH change or without a decrease to less than 7 are considered nonacid reflux episodes (Figure 1C).

Standard 24-hour pH monitoring detects changes in pH, and defines reflux when the pH decreases to less than 4. Agrawal et al<sup>7</sup> found that acidic foods commonly are ingested and are likely to produce an artifact that mimics reflux during pH monitoring (Figure 2). In this study, 10 frequently ingested substances were shown to produce a decrease in intraesophageal pH to less than 4. These foods were as follows: cola beverage, coffee, ketchup, tea, orange juice, apple juice, lemonade, red wine, white wine, and strawberry juice. It also has been suggested that it is possible to detect WAR using pH monitoring alone, thus reducing the need for MII. In this report we show the results of studies that have assessed the accuracy of pH monitoring alone in detecting acid and weakly acidic reflux compared with MII-pH.

### Materials and Methods

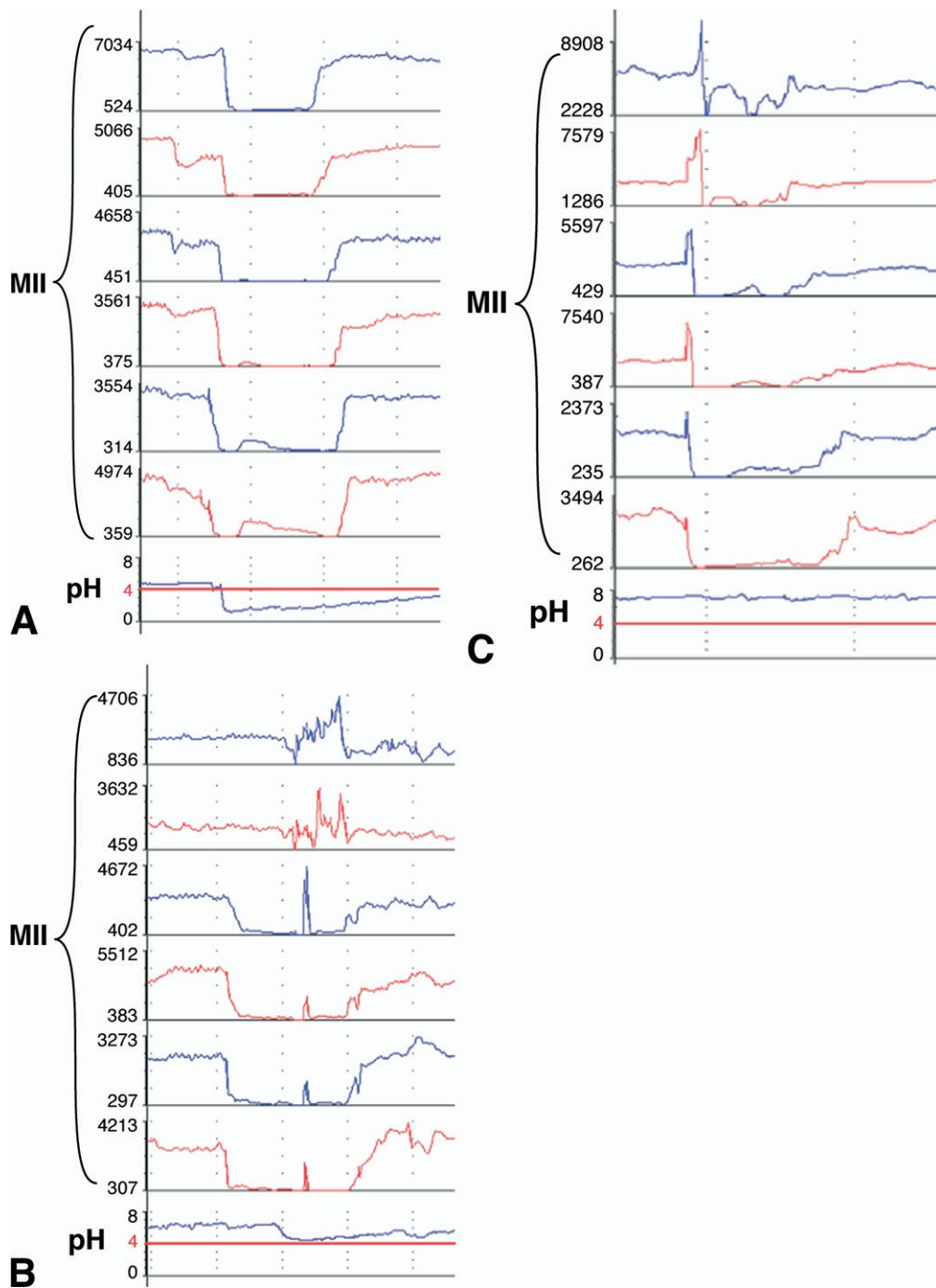
This was a retrospective cohort study. This article presents data from 2 separate studies, 1 study regarding acid reflux

**Abbreviations used in this paper:** GER, gastroesophageal reflux; MII, multichannel intraluminal impedance; PPI, proton pump inhibitor; SE, standard error; SI, symptom index; WAR, weakly acidic reflux.

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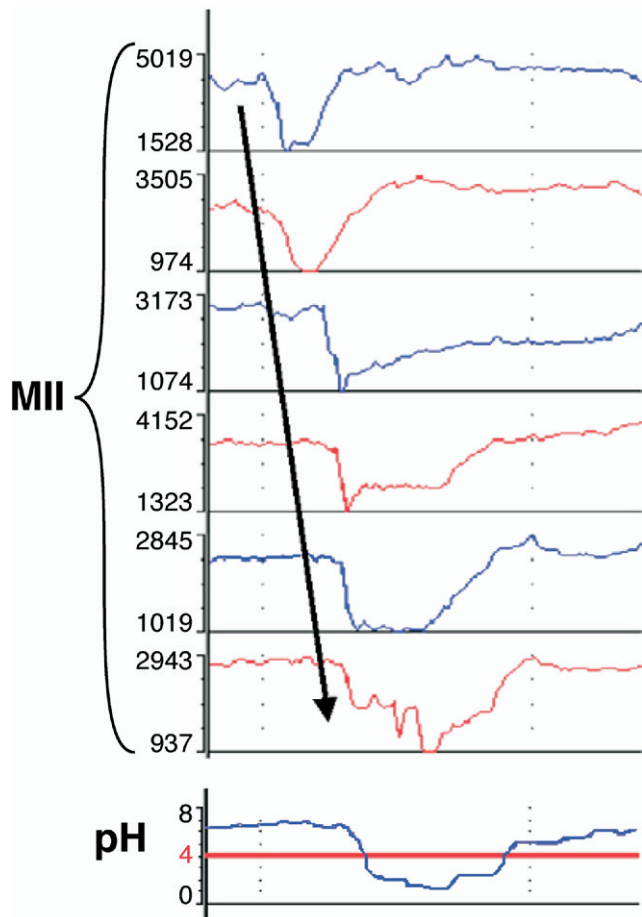
**Figure 1.** (A) An MII-pH–detected acid reflux episode. (B) An MII-pH–detected WAR episode. (C) An MII-pH–detected nonacid reflux episode.

and the other study addressing WAR. Both were 2 separate studies performed by the same people but at 2 different times. They were included here in the same article because they addressed 2 facets of the same issue regarding the comparison of pH alone with MII-pH.

All patients had an MII-esophageal manometry study performed before the MII-pH study, both for localization of the lower esophageal sphincter and for evaluation of esophageal function. In this article we present data that emanated from 2 evaluations performed separately. However, both studies related to the accuracy of pH alone compared with MII-pH, thus we

present the data in the same report as 2 arms of a study. These 2 components are the detection of acid reflux and the detection of WAR.

The same MII-pH recording materials were used for both arms of the study. The MII-pH catheter consists of a 2.1-mm polyurethane catheter incorporating 6 impedance segments and 1 pH-measuring electrode (Sandhill Scientific, Denver, CO). It contains 6 impedance segments placed 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter, plus a pH electrode at 5 cm above the lower esophageal sphincter (Figure 3). This configuration allows the detection of the



**Figure 2.** A swallow as detected by MII-pH, with a decrease in pH to less than 4.

progression of refluxate in the esophagus, and also the ability to define whether this bolus movement is cephalad or caudate, thus distinguishing between a swallow (Figure 2) or a reflux episode (Figure 1A). The sampling frequency for the MII-pH catheter is 50 Hz.

The pH electrode of the MII-pH catheter initially was calibrated in buffer solutions of pH 4 and pH 7. The MII-pH probe was introduced through the nose. All patients on acid-suppression therapy were on a proton pump inhibitor (PPI). Patients were asked to follow a regular activity and meal regimen during the 24-hour study period, mimicking as much as possible a regular day for them. All patients also were asked to refrain from consuming any drinks, other than water, outside of meal or snack periods, which they were asked to note on the diary and mark on the data recorder by pressing the meal button. Patients were given a personal diary to note meal times, medication intake, time in the recumbent position, and the timing of any symptoms (regurgitation, heartburn, chest pain, and so forth). Data from the MII-pH probe was transmitted and recorded on a portable data recorder (Z-logger; Sandhill Scientific). At the end of the 24-hour period, the MII-pH probe was removed. The recorded data were downloaded to a computer and interpreted with the help of Bioview MII software (Sandhill Scientific). The meal periods were excluded from the analysis.

**Detection of Acid Reflux**

We retrospectively reviewed 60 consecutive ambulatory MII-pH studies of patient’s off acid-suppressing therapy. All studies were performed in the esophageal laboratory at the Medical University of South Carolina in Charleston, South Carolina, between June 2003 and August 2005.

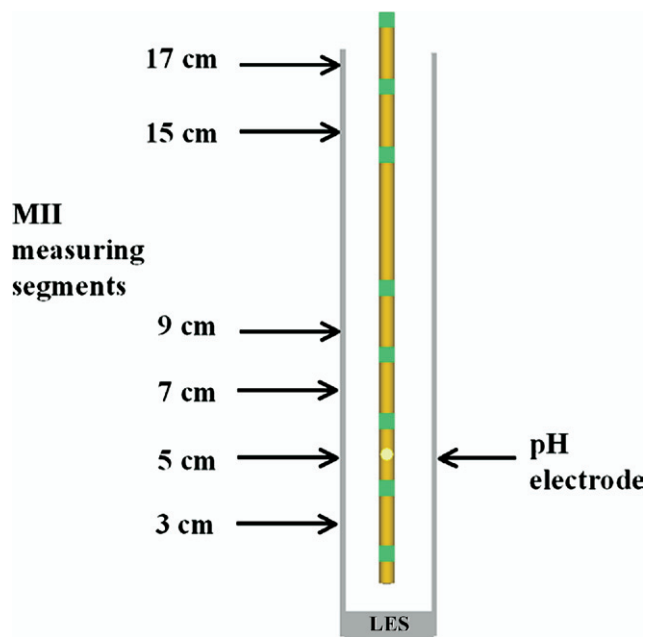
These studies were ordered on patients with typical or atypical reflux symptoms by physicians practicing in our institution or referring to it. No inclusion or exclusion criteria were assigned other than the need to be off any acid-suppressing therapy for at least 1 week before the testing.

All the studies initially were read by blinding the reader to the MII portion of the tracing, and exclusively analyzing the pH tracing for acid reflux episodes as shown by a decrease in pH to less than 4. The meal periods were excluded from the analysis. The symptom index (SI) with pH-detected acid reflux also was evaluated. For heartburn, regurgitation, chest pain, cough, and throat clearing, a symptom was considered as associated with reflux if it occurred within 5 minutes of the start of a pH-detected reflux episode. A SI of 50% or greater was considered to show positive symptom-reflux association.

Subsequently, all studies were read again with the reader blinded to the results of the first reading and analyzing acid reflux episodes, defined as an MII-detected reflux episode and a decrease in pH to less than 4. The meal periods were excluded from the analysis. The SI with MII-pH-detected acid reflux also was evaluated. Abnormal total reflux was defined as greater than 4.2% of the time the pH was less than 4, abnormal upright reflux was greater than 6.3% of the time the pH was less than 4, and abnormal recumbent reflux was greater than 1.2% of the time the pH was less than 4.<sup>8</sup>

**Detection of Weakly Acidic Reflux**

We retrospectively reviewed 20 consecutive ambulatory MII-pH studies recorded off acid-suppressing therapy, and 20 consecutive ambulatory MII-pH studies recorded on acid-sup-



**Figure 3.** Esophageal placement of an MII-pH catheter.

**Table 1.** Sensitivity and Specificity of pH Alone Compared With Combined MII-pH for Detection of Acid Gastroesophageal Reflux Disease

|             | Diagnostic criterion |      |                      |
|-------------|----------------------|------|----------------------|
|             | % time pH < 4        | SI   | % time pH < 4 and SI |
| Sensitivity | 100%                 | 100% | 100%                 |
| Specificity | 68%                  | 67%  | 58%                  |

SI, symptom index.

pressing therapy (PPIs once or twice a day). All the studies were performed in our laboratory between July 2002 and October 2004. All the studies were ordered on patients with typical or atypical reflux symptoms by physicians practicing in our institution or referring patients to it. No inclusion or exclusion criteria were assigned.

WAR episodes (as defined earlier) were divided into 2 categories: those with a decrease in pH of more than 1 but no more than 2, and those with a pH decrease of more than 2. All studies initially were read blinded to the MII portion of the tracing, exclusively analyzing the pH tracing for WAR episodes. Subsequently, these pH-detected WAR episodes were assessed by re-reading the MII-pH tracings to evaluate their association with MII-detected reflux. Finally, to identify the full spectrum of reflux types, all studies were read again, with the reader blinded to the results of the first reading, this time identifying reflux on the MII tracings, and classifying each MII-detected reflux into acid, weakly acidic, or nonacid reflux based on the pH nadir.

Statistical analysis was performed using Prism software version 3.00 (GraphPad, San Diego, CA). The Wilcoxon signed rank test and 1-way analysis of variance (Friedman test) were used, with a level of significance set at a *P* value of less than .05.

## Results

### Detection of Acid Reflux

A total of 60 ambulatory MII-pH tracings were analyzed for this part of the study. There were 36 female and 24 male patients, with a mean age of 52.7 years (range, 16–77 y). By using only the percentage time of pH of less than 4 as the diagnostic criteria, we found that pH alone compared with MII-pH had a sensitivity of 100% and a specificity of 68% for the detection of acid GER. By using positive SI with acid GER as the only diagnostic criteria, we found that pH alone compared with MII-pH had a sensitivity of 100% and a specificity of 67% for the detection of symptomatic acid GER. By using both the percentage time of pH of less than 4 and/or positive symptom association with acid GER as the diagnostic criteria, we found that pH alone compared with MII-pH had a sensitivity of 100% and a specificity of 58% for the detection of acid GER. These results are summarized in Table 1.

In the upright position, the percentage time of a pH of less than 4 was greater in all patients using pH alone (median, 2.2; mean, 6.6; standard error [SE], 1.2) compared with using MII-pH and requiring an associated MII-detected reflux before considering a decrease in pH to less than 4 as a reflux episode (median, 1.5; mean, 3.5; SE, 0.6). This difference was statistically significant (*P* < .0001; Wilcoxon signed rank test).

In the recumbent position, the percentage time of a pH of less than 4 was greater in all patients using pH alone (median, 0.3; mean, 4.4; SE, 1.0) compared with using MII-pH (median, 0.05; mean, 1.4; SE, 0.4). This difference was statistically significant (*P* < .0001; Wilcoxon signed rank test).

Over the total duration of the study, the percentage time of pH of less than 4 was greater in all patients using pH alone (median, 2.7; mean, 5.8; SE, 0.9) compared with using MII-pH (median, 1.2; mean, 2.7; SE, 0.4). This difference was statistically significant (*P* < .0001; Wilcoxon signed rank test). Figure 4 illustrates these results.

In these 60 patients, MII-pH detected 1133 acid reflux episodes whereas pH alone detected 2307 apparent acid-reflux episodes (*P* < .0001). Thus, 51% of the latter were not confirmed as caused by reflux by MII.

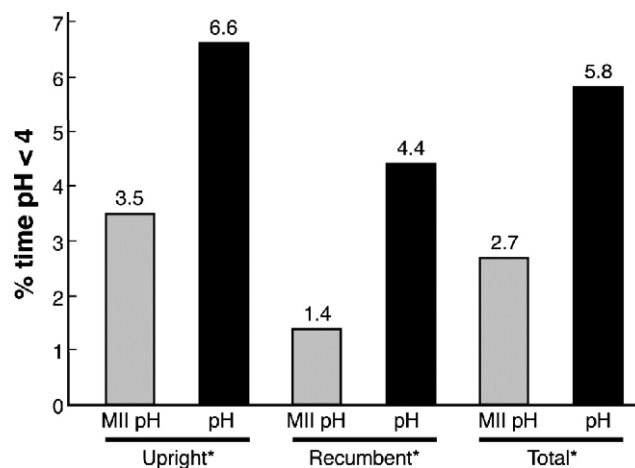
Eighty-one percent of the acid GER episodes exclusively detected by pH were associated with a swallow as shown by MII (Figure 2). In the remaining 19% of acid GER episodes exclusively detected by pH, there was no associated impedance-detected bolus movement in the esophagus.

Of the 60 patients, 13 were diagnosed as having an abnormal 24-hour pH test (based on both the percentage time of pH of <4 and/or positive SI with acid GER as the diagnostic criteria), that were negative for acid GER when the MII was included in the evaluation. Thus, the use of pH alone erroneously diagnosed acid GER disease in 22% of patients.

### Detection of Weakly Acidic Reflux

A total of 20 ambulatory MII-pH tracings off acid-suppressing therapy and 20 MII-pH tracings on acid-suppressing therapy (PPIs once or twice a day) were analyzed. There were 24 female and 16 male patients, with a mean age of 43.6 years (range, 1–77 y).

For all patients, we used pH alone for the detection of WAR episodes and then we added the MII analysis. In the 20 patients off acid-suppression therapy we found that for WAR with a decrease in pH of more than 1 but of 2 or less, the mean number of pH-detected WAR episodes was 4.6 when MII detected reflux and 24.5 when MII did not detect reflux. In these same patients, we also found that for WAR with a decrease in pH of greater than 2, the mean number of pH-detected WAR



**Figure 4.** Mean percent time pH < 4 MII-pH and pH only detected acid reflux (\**P* < .0001).

episodes was 2.4 when MII detected reflux and 3.2 when MII did not detect reflux.

By using the same analysis method, in the 20 patients on acid-suppression therapy, we found that for WAR with a decrease in pH of between 1 and 2, the mean number of pH-detected WAR episodes was 2.1 when MII detected reflux and 20.8 when MII did not detect reflux. In these same patients, we also found that for WAR with a decrease in pH of greater than 2, the mean number of pH-detected WAR episodes was 1.6 when MII detected reflux and 3.3 when MII did not detect reflux.

Table 2 summarizes these results and provides the mean number of both acid and nonacid reflux episodes detected by MII-pH for both groups.

Thus, for nonacid and WAR, as compared with MII-detected reflux, pH alone had a sensitivity of 28%. Also, when using pH alone, the vast majority (1039 of 1254; 83%) of pH-detected WAR episodes were not associated with reflux identified by impedance. This was true whether or not the patient was taking PPIs. When combining data from both groups, there were 1039 pH-detected WAR episodes with no MII-detected reflux, and 215 WAR episodes detected by both pH and MII (Figure 5).

Both the on- and off-therapy groups yielded similar results regarding WAR, with pH detecting numerous episodes not associated with reflux on MII, mostly evident with a pH decrease of 1–2 units. Eighty-nine percent of the episodes exclusively detected by pH were associated with a swallow as shown by MII. As expected, the on-therapy group had more nonacid reflux episodes, whereas the off-therapy group had mostly acid reflux episodes (Table 2).

### Discussion

Combined MII-pH monitoring has received worldwide interest primarily because of its ability to detect nonacid reflux. However, the results of our study show that it is more accurate than pH alone for the detection of both acid reflux and WAR. Only 49% of acid reflux episodes and 18% of WAR episodes detected by pH alone also were associated with a retrograde bolus movement on MII, thus indicating reflux. Our data also show a significant disparity in the percentage time of pH of less than 4 detected by pH alone compared with combined MII-pH. In fact, when pH was used alone for defining acid reflux, it yielded about a 2-fold higher estimation than MII-pH over the total period of the study (mean % time pH < 4 of 2.7 vs 5.8, respectively).

Finally, both parts of the study show that pH alone overestimates both acid reflux and WAR, most often because of undetected swallows, which are the cause of exclusively pH-

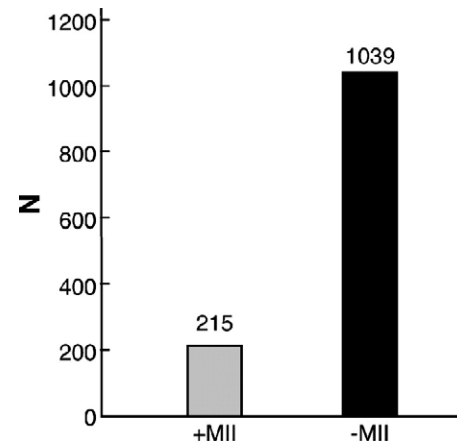


Figure 5. Weakly acidic reflux episodes detected by pH.

detected reflux in 81% and 89% of patients, respectively. All patients are told that if they ingest anything but water, they should report this. However, this often is not performed, and many patients will sip on an acidic beverage, such as Coke (The Coca-Cola Company, Atlanta, GA), all day long even though they are told not to. Normal values are based on healthy volunteers, who are likely to be more compliant than the general patient population, and often studies involving healthy volunteers are performed in a controlled environment.

In the remaining 19% of acid GER episodes exclusively detected by pH there was no associated impedance-detected bolus movement in the esophagus. It is possible that impedance lacks sensitivity and is unable to detect these remaining 19% acid episodes as either reflux or swallows. The latter seems unlikely because Srinivasan et al<sup>9</sup> showed MII to be sensitive to swallowed volumes as small as 1 mL. These could be reflux episodes in which the refluxate reached the pH electrode but did not close the gap between the 2 impedance rings at that level. However, this doubt only concerns about one fifth of the episodes and MII clearly shows that the other four-fifths are swallows, and these definitely should be excluded.

MI I has been introduced as a technique to investigate bolus movement in the esophagus.<sup>3,10</sup> In 1991, MII was first validated for the detection of bolus presence using fluoroscopy as the gold standard.<sup>3</sup> A recent study by Simren et al<sup>11</sup> further validated the accuracy of the impedance technique to measure esophageal volume clearance by tracking the movement of a swallowed barium bolus with simultaneous fluoroscopy and impedance. A strong correlation was found between the 2 methods, showing that impedance was able to determine the timing of esophageal lumen filling and emptying accurately.

The ability of combined MII-pH to detect and characterize GER by the presence of liquid in the esophagus represents an important advance for clinical testing of all types of reflux. Shay et al<sup>12</sup> found that MII is accurate in detecting reflux episodes identified by manometry and/or pH probe, their composition, and their clearing. The emerging data on MII led a panel of esophageal experts to conclude that intraluminal impedance monitoring is the only recording method that can achieve high sensitivity for the detection of all types of reflux episodes.<sup>6</sup>

In a pediatric study, Wenzl et al<sup>13</sup> found that only about 60% of pH-detected apparent acid reflux episodes were confirmed to be reflux by MII. These findings are quite similar to ours, raising

Table 2. Mean Number of Episodes Detected for Each Type of Reflux

|        | 1 < pH decrease ≤ 2 |       | pH decrease > 2 |       | Nonacid reflux<br>+ MII | Acid reflux<br>+ MII |
|--------|---------------------|-------|-----------------|-------|-------------------------|----------------------|
|        | + MII               | - MII | + MII           | - MII |                         |                      |
| On Rx  | 4.6                 | 24.5  | 2.4             | 3.2   | 20.2                    | 7.8                  |
| Off Rx | 2.1                 | 20.8  | 1.6             | 3.3   | 7.2                     | 21.3                 |

Rx, acid suppression therapy.

the question of whether this difference in number of detected acid reflux episodes affects diagnosis. We found that pH alone may lead to overdiagnosis of abnormal acid reflux in 22% of patients.

Symptoms caused by acid reflux are very common,<sup>1,2</sup> and acid reflux is associated with complications, such as esophagitis and an increased risk of esophageal adenocarcinoma.<sup>8,14</sup> Our study found that even though pH monitoring has been the gold standard for diagnosing acid reflux, the new MII-pH technology should provide better accuracy and more specificity. In fact, using positive SI with acid GER as the only diagnostic criteria we found that pH alone compared with MII-pH had a specificity of 67% for the detection of symptomatic acid GER. This is very important because patients present to their physicians with complaints regarding their symptoms, which are used as the basis for both diagnosis and assessment of response to therapy. Thus, improving the capacity of a test to assess symptom association has important clinical implications.

Less-acidic (weakly acidic) reflux also may induce symptoms of GER, such as heartburn, regurgitation, and noncardiac chest pain.<sup>15-17</sup> A multicenter study including 60 normal adult volunteers showed that WAR accounted for one third of all reflux events.<sup>5</sup> WAR is more likely to occur early after a meal both in controls and in patients with GER disease. A recent study showed that rapid food intake increases the number of reflux episodes in the first postprandial hour, predominantly by increasing WAR.<sup>18</sup> It also has been shown that WAR may impair the quality of life in adult patients on PPI therapy who have persistent symptoms, including regurgitation,<sup>19</sup> chronic cough,<sup>20</sup> or voice changes.<sup>21</sup> In fact, Sifrim et al<sup>20</sup> found that 50% of reflux episodes in patients with positive symptom association between cough and reflux were WAR episodes, thus reinforcing the importance of WAR as a cause of symptoms in certain patients.

The use of pH alone for the identification of WAR is tempting. However, our study clearly suggests that this would be unadvisable because pH alone overestimates WAR episodes, primarily owing to swallowing. The use of pH alone may result in inappropriate emphasis on aggressive antireflux therapy, especially if the patient's symptoms are persistent even after effective acid-suppression therapy.

In conclusion, the use of pH alone for the detection of acid reflux is very sensitive but lacks specificity compared with combined MII-pH. It may overdiagnose abnormal acid reflux in up to 22% of patients. Also, the use of pH for the detection of weakly acidic and nonacid reflux has poor sensitivity. Impedance technology is the preferred test for the evaluation of weakly acidic and nonacid reflux, and it appears to improve the specificity of detection of acid reflux. We believe that combined MII-pH monitoring should be considered the gold standard for acid reflux detection because of its potential to provide more accurate diagnostic information.

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