Multichannel intraluminal impedance accurately detects fasting, recumbent reflux events and their clearing

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Shay, Steven S., Steven Bomeli, and Joel Richter. Multichannel intraluminal impedance accurately detects fasting, recumbent reflux events and their clearing. Am J Physiol Gastrointest Liver Physiol 283: G376–G383, 2002.—Multichannel intraluminal impedance (MII) is a new diagnostic test for gastroesophageal reflux disease (GERD). The objective of this report is to determine the accuracy of MII in detecting individual reflux events (REs) identified by pH probe and manometry, as well as their clearing in patients with severe GERD compared with normal volunteers. Ten severe GERD patients and 10 normal volunteers underwent simultaneous manometry (7 sites: gastric, lower esophageal sphincter, esophagus, pharynx), pH, and MII (6 sites in esophagus) for 15 min in the left and right recumbent posture while fasting. We found that patients had 30-fold more REs than normal volunteers (41 ± 11 vs. 1.3 ± 0.4), and 95% of all REs were detected by MII. An average 15-fold fall in impedance with liquid and fivefold rise with gas made REs and their composition easy to detect with MII. In the right recumbent posture, nearly all REs detected by MII were liquid (98%, 98/100). In contrast, all 283 REs detected by MII in the left recumbent posture were gas. Nearly all REs detected by MII were cleared (98%, 368/374). Mean acid clearing time left recumbent posture were gas. Nearly all REs detected by pH (98%, 98/100). In contrast, all 283 REs detected by MII and manometry (15 s) or MII (13 s), primarily due to acid rereflux, i.e., additional acid REs during acid clearing. We conclude that MII is accurate in detecting REs identified by manometry and/or pH probe, their composition, and their clearing.

pH monitoring; common cavities; gastroesophageal reflux disease

Multichannel intraluminal impedance (MII) is a new method for gastroesophageal reflux disease (GERD) patients that assesses transit based on changes in resistance to current flow between adjacent electrodes when a bolus passes between them (2). MII detects gastroesophageal reflux events (REs) when aboral flow occurs across two or more distal electrodes in the esophagus, and MII can also assess whether the composition of the refluxed gastric contents is gas, liquid, or mixed.

Three recent reports (6, 7, 9) examined the promising role of MII combined with pH in detecting acid and nonacid REs. Two reports compared GERD patients with normals, one utilizing postprandial simultaneous manometry, pH, and MII in the upright posture, and the other ambulatory 24-h MII-pH. Both reports found that total REs were similar in normals and GERD patients, although acid REs made up a greater proportion of REs in GERD patients. In addition, mixed REs were more common than liquid-only REs (6, 7). In another report of combined MII-pH after a refluxogenic meal in GERD patients, omeprazole decreased acid REs; however, total REs were unchanged, because nonacid REs increased (9). In these reports, mean RE frequency was 10.5/hr (6) and 10/hr (9) in the short-term studies but only 46 per 24 h in the 24-h study (7).

Present reflux tests have fundamental differences in the measurement parameter analyzed. The pH probe measures acid concentration in a volume of unknown amount. Thus when gastric contents with a pH of 2 refluxes into the esophagus, a gallon of refluxant with pH 2 looks the same to the pH probe as an ounce of refluxant with pH 2. Conversely, the common cavity (detected by manometry) can't assess concentration of any chemical component, especially acid. Instead, the common cavity detects when enough volume of gastric contents enters the esophagus to raise intraesophageal pressure to that of intragastric pressure. However, that threshold volume and the final refluxed volume is unknown. Measurement characteristics of REs detected by impedance are unknown.

The purpose of this report is fourfold: 1) to validate the accuracy of MII in detecting individual REs in the most challenging situation, which is maximizing RE frequency by studying only patients with severe GERD and maximizing RE detection by combining manometry and pH monitoring; 2) to compare clearing of REs by pH, MII, and manometry; 3) to compare refluxant composition in different postures; and 4) to assess the measurement characteristics of impedance.

MATERIALS AND METHODS

Study Population

Ten symptomatic patients (age 53 ± 4; 5 males, 5 females) with severe GERD were selected on the basis of two criteria: 1) moderate or severe GERD by endoscopy (thin erosions; n = 4); confluent ulcerations (n = 2); long-segment Barrett's esophagus (4); confluent ulcerations (1); moderate or severe GERD by endoscopy (thin erosions (1); long-segment Barrett's esophagus (1). The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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esophagus (n = 4); and 2) ≥10 common cavities detected during standard esophageal manometry. Other findings of severe GERD were present on barium esophagram (7/7 with both reflux and hiatal hernia) and 24-h pH (8/8 with abnormal acid exposure; %time pH 4/time monitored: total = 25 ± 8%; upright = 21 ± 7%; recumbent = 30 ± 11%). Ten normal volunteers (age 35 ± 4; 6 males, 4 females) were studied for comparison.

**Study Design**

All subjects underwent simultaneous manometry, pH, and MII in the fasting left and right recumbent postures. Some severe GERD patients were also monitored after a nonrefluxogenic meal. Subjects were studied in accordance with protocol 3565, which was approved by the Institutional Review Board of the Cleveland Clinic Foundation on March 15, 2000. Written informed consent was obtained.

**Simultaneous esophageal manometry, MII, and pH monitoring.** A multichannel esophageal manometry catheter with a 7-cm distal sleeve (DentSleeve) was passed through the nose and into the esophagus so that it straddled the lower esophageal sphincter (LES). A 2.13-mm MII-pH catheter (model Z-TC; Sandhill) was passed adjacent to the manometry catheter such that the perfused side ports and MII sites had the configuration shown in Fig. 1. Swallows were recorded by an air-perfused hypopharyngeal port. All data were recorded simultaneously by the Sandhill Insight data-acquisition system for subsequent analysis.

Continuous fasting recordings were obtained for 15 min on the left and then the right recumbent postures. Severe GERD patients with fewer than five liquid REs in the right recumbent posture by MII were then given 8 oz of yogurt (Dannon; lemon flavor) and 8 oz of water, and monitored for an additional 15 min on their right side.

**Definition of REs and clearing.** The pH probe defined a RE traditionally (pH-RE); i.e., a fall in pH from >4 to <4, and acid clearing time (ACT) of seconds until pH 4 was again achieved. Manometry defined a RE as when a common cavity occurred. A common cavity was defined as an increase in intraesophageal pressure from gastroesophageal pressure equilibration that was not associated with increased intraesophageal pressure from a swallow, dysmotility, or movement. Its duration was seconds until the peristaltic contraction decreased intraesophageal pressure to baseline. Acid reflux was defined as a common cavity while pH was already <4, i.e., reflux of acidified gastric contents into the esophagus before successful acid clearing after a traditional pH-RE (Figs. 2, 3, and 4).

When a pH-RE or common cavity occurred, the MII channels were examined for concomitant reflux. Liquid RE was defined by impedance (MII-RE) when a fall in impedance ≥50% from baseline occurred in at least the two distal channels in an aboral direction and for 2 s in the distal channel (9). Its clearing time was seconds until return to the impedance level denoting MII-RE onset in the distal channel. A gas RE was defined by impedance when a simultaneous or near-simultaneous rise in impedance ≥50% from baseline occurred in at least two consecutive channels. Distal channels did not need to be involved in gas reflux.

**Statistical analysis.** Descriptive data are presented as means ± SE. Comparative data were by Mann-Whitney rank-sum test and Wilcoxon’s signed-rank test.

**RESULTS**

**MII Detection of Acid and Nonacid REs in Patients and Normal Volunteers**

Patients had 30-fold more REs detected by the pH probe and/or manometry than normal volunteers (41 ±

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**Table 1. MII detection of acid and nonacid REs in severe GERD patients and normal volunteers**

<table>
<thead>
<tr>
<th>RE Type</th>
<th>Detected by MII</th>
<th>RE Composition by MII</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Yes (%)</td>
</tr>
<tr>
<td><strong>Severe GERD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid reflux events</td>
<td>119</td>
<td>101(85)</td>
</tr>
<tr>
<td>Traditional</td>
<td>57</td>
<td>44(77)</td>
</tr>
<tr>
<td>Acid reflux*</td>
<td>62</td>
<td>57(92)</td>
</tr>
<tr>
<td>Nonacid reflux event</td>
<td>289</td>
<td>285(99)</td>
</tr>
<tr>
<td>Normal volunteers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid reflux events</td>
<td>3</td>
<td>3(100)</td>
</tr>
<tr>
<td>Traditional</td>
<td>3</td>
<td>3(100)</td>
</tr>
<tr>
<td>Acid reflux</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nonacid reflux event</td>
<td>10</td>
<td>10(100)</td>
</tr>
</tbody>
</table>

Values are number (No.) of reflux events (REs). GERD, gastroesophageal reflux disease; MII, multichannel intraluminal impedance. *28% (17/60) of acid reflux REs had a pH fall >1 unit and 72% <1 unit.
11 vs. 1.3 ± 0.4; P < 0.001), and MII detected 95% of all REs. Because REs were uncommon in normal volunteers, only data from patients are subsequently presented (see Table 1).

Most traditional acid REs (77%) and nearly all acid reflux events (92%) were detected by MII. Most acid reflux events were undetectable by the pH probe even when using expanded pH criteria of a further pH fall >1 unit while pH was <4, because 72% had a pH fall <1 unit. As expected, most of the traditional acid REs (77%, 33/43) and nearly all acid reflux events (98%, 56/57) were liquid rather than gas determined by MII. Only one RE was of mixed composition, i.e., a gas RE followed <3 s later by a liquid RE.

Nonacid REs were 2.4-fold (289:119) more common than acid REs, and 99% were detected by MII. The vast majority (96%, 275/285) of nonacid REs detected by MII contained only gas.

Characteristics of Liquid and Gas REs Detected by MII

The magnitude of impedance fall with liquid and rise with gas was typically dramatic, making REs detected by MII easy to detect. The average fall in impedance due to liquid reflux with traditional acid REs (740 ± 150 to 45 Ω) and acid reflux events (781 ± 67 to 0 ohms) was nearly identical, and >15-fold from baseline (Fig. 4). The large variation in baseline impedance was a result of a low baseline before some MII-REs. Additionally, frequent acid reflux in some patients prevented an impedance rise >400 between REs (Fig. 2).

The average rise in impedance due to gas reflux was fivefold (1,657 ± 100 to 8,475 ± 160 Ω; Fig. 4). During the course of all studies, an impedance value >7,000 was unusual except in the presence of gas in the esophagus. Nonacid liquid reflux was too infrequent for meaningful characterization.

The proximal extent of aboral liquid or gas flow could be determined by MII. Only 33% (33/99) of fasting liquid REs reached either of the two proximal sites despite being in the recumbent posture. However, 63% (179/286) of fasting gas REs reached a proximal site.

Comparison of Left vs. Right Recumbent Posture on Fasting RE Frequency and Composition

REs detected by pH probe and/or manometry were 2.5-fold (286:122; P < .01) more common in the left recumbent posture than the right. Of individual patients, 9 of 10 patients had ≥10 (range 11–70) REs on the left side. In contrast, only two patients had ≥10 REs on the right side (Table 2; Figs. 2–5).

In the right recumbent posture, 83% (101/122) of REs detected by pH and/or manometry were detected by MII, and 98% (99/101) of these REs were characterized by MII as liquid (Figs. 2 and 4).

In the left recumbent posture, 99% (283/286) detected by pH and/or manometry were detected by MII. All left recumbent REs detected by MII were characterized as gas only (Figs. 3 and 4). Only 3% (8/283) of these gas-only REs were associated with a fall in pH to <4.

Clearing of REs

Nearly all REs detected by MII were cleared (98%, 368/374). Acid REs and common cavities were cleared by definition. Acid clearance time was longer (47 ± 16 s; n = 45; P < 0.01) than clearance time by MII or manometry (15 ± 2 and 13 ± 1 s, respectively) in REs detected concurrently as a traditional acid RE and a RE by MII and/or manometry. However, clearing of the traditional acid REs occurred in two very different patterns. In the first pattern, traditional acid REs were not interrupted by acid reflux and cleared in a similar amount of time to either MII or manometry. In contrast, 38% (17/45) of traditional acid REs had clearing interrupted by acid reflux, resulting in their mean ACT being sevenfold longer (101 ± 40 s; P < 0.001). An average of four acid reflux events (range 1–28) occurred during clearing of these traditional acid REs, resulting in the prolonged ACT (Table 3 and Fig. 2).

Clearing time by MII was very similar to manometry in either an acid or nonacid environment in REs detected by both methods. Qualitatively, the magnitude of impedance change made clearing easier to detect by MII, which typically showed a small overshoot (Fig. 4). As Figs. 2 and 3 show, liquid or gas reflux by MII was completely cleared before the primary or secondary esophageal peristaltic contraction that followed each common cavity.

Postprandial (Nonrefluxogenic Meal) Reflux, Right Recumbent Posture

All six patients with fewer than five REs in the right recumbent posture had liquid REs after the nonrefluxogenic meal. The mean was 8.3 ± 2, and range 1–14. All MII characteristics were similar to fasting liquid REs, except that more reached a proximal esophageal site (58%, 34/59) (Fig. 5).

DISCUSSION

A primary goal of this study was to determine whether MII was capable of distinguishing frequent individual REs occurring close together. The challenge was great, because our gold standard (RE detected by either or both manometry and pH) detected a mean frequency of 41 REs per 30 min, 5-fold more than the frequency of previous reports (6, 7). This goal was achieved because 95% were detected by MII.

Another goal was to compare clearing by the three methods, once a RE was detected. Clearing of REs by pH was slower than either manometry or MII, which were nearly identical in duration. This was for two reasons. First, acid clearing is a two-step process: 1) rapid volume clearing of nearly all of the bolus and 2) slow neutralization by saliva of the acidified residual (1). Neither manometry nor impedance were sufficiently sensitive to detect the small acid residue in the second step of acid clearing. Second, and more impor-
Table 2. MII detection of REs as liquid or gas on the right vs. left recumbent side

<table>
<thead>
<tr>
<th>Acid reflux events*</th>
<th>Right Recumbent Posture</th>
<th>Left Recumbent Posture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. MII-RE</td>
<td>Liquid/Gas Ratio</td>
</tr>
<tr>
<td>Traditional</td>
<td>48</td>
<td>35(73%)</td>
</tr>
<tr>
<td>Acid rereflux**</td>
<td>61</td>
<td>56(92%)</td>
</tr>
<tr>
<td>Nonacid RE</td>
<td>13</td>
<td>10(77%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*There was 1 mixed RE (gas, then liquid), in the right recumbent posture; **28% (17/62) of acid rereflux REs had a pH fall >1 unit and 72% <1 unit.

Fig. 2. Four episodes of acid rereflux over a low basal LES pressure (LESp) are shown (see vertical lines 1–4) during simultaneous manometry, pH, and MII. Ten seconds into the tracing, a pH fall of 1 unit occurs, whereas pH is <4 from a previous traditional acid reflux event (RE). There is simultaneous detection by both MII and manometry: 1) the distal 3 MII channels show retrograde liquid reflux as impedance falls >50% from baseline (to 0 in 2 leads); and 2) a common cavity occurs simultaneously with the onset of the MII-RE. Acid rereflux similar to above occurs on 3 other occasions, although 2 have a pH fall <1 unit (lines 3 and 4), and one (line 2) occurs in the vulnerable period 2–3 s after a swallow. The first 3 MII-REs and common cavities clear concurrently to their original baselines denoting clearance after a secondary (n = 2) or primary (n = 1) esophageal contraction, although the 4th is not cleared because the tracing ends. However, acid clearing to pH 4 is never achieved.
tant, our report found that additional acid REs detected by MII or manometry during acid clearing (or acid rereflux) commonly aborted acid clearing attempts after traditional acid REs, often repeatedly, before acid clearance was finally achieved. This supports and extends our previous reports on the role of acid rereflux in patients with severe GERD. First, simultaneous manometry, pH, and scintigraphy found that 67% of acid REs in patients with severe esophagitis postprandial were acid rereflux rather than traditional acid REs (4), and our present study extends these findings to the fasting interval. Second, we found that acid rereflux after a traditional acid RE is the most common cause of prolonged daytime traditional acid REs in severe GERD patients, rather than decreased peristaltic amplitude or decreased swallowing rates (5).

The dramatic effect of posture on RE composition confirms and extends our previous report (3). In that study, fasting patients with severe GERD had recurring common cavities with a pH >4 in the left recum-
bent posture, which we assumed to be gas in the absence of a method to confirm gas-only reflux. MII confirms that fasting REs in the left recumbent posture are nearly always composed only of gas. Our previous report also found primarily acid reflux by pH probe in the right recumbent posture (3), and MII confirms nearly all REs in the right recumbent posture are liquid only. We (3) previously studied the effect of posture on RE composition by barium ingestion in different postures (Fig. 6), and showed that refluxant composition is a result of the EG junction’s location relative to the stomach’s air-fluid interface. In the left recumbent posture, liquid gastric contents (or barium) lie in the dependent body of the stomach, and only gas is available at the EG junction for reflux into the esophagus. This recurring gas-only reflux is profoundly abnormal, because gas reflux is suppressed in recumbent normal individuals (10). However, it is not pathophysiologically important, because it contains no damaging component. In contrast, the right lateral posture places the EG junction in a dependent position where liquid gastric contents (or barium) collect above or near a submerged EG junction. Thus acidified liquid gastric contents are present at the EG junction and are available for reflux.

MII’s measurement characteristics are more similar to the common cavity than the pH probe. MII identified nearly all nonacid and acid reflux REs detected by the common cavity and not by the pH probe. Furthermore, clearing times by MII and manometry (common cavity) were nearly identical in acid, nonacid, gas, or liquid environments, and shorter than in acid clearing.
In our opinion, qualitative and technical advantages favor MII rather than the common cavity as a complementary test to the pH probe in GERD patients. First, the magnitude of impedance change with MII allowed REs to be more easily detected than the intraesophageal pressure increase in a common cavity and also made RE clearing more easily assessed than intraesophageal pressure fall at the end of a common cavity. Second, MII is not affected by events that increase intraesophageal pressure, such as movement or talking. Third, whether the refluxant is acid or nonacid, or mixed liquid-gas or gas only in composition, can be discerned by MII and not by manometry. Finally, MII can be combined with pH in the same 2.13-mm catheter, which allows prolonged ambulatory studies.

There were two unexpected findings in this study. First, <1% of REs were mixed (both liquid and gas) in composition compared with 68% in GERD patients during 24-h ambulatory MII pH. This may be related to our study being only recumbent and fasting. Second, there were 2.5-fold fewer MII-REs on the right than on the left side. This may have been a result of patient selection, because we selected patients who had frequent REs during standard manometry performed on the left side. However, we also found twofold more fasting REs on the left than on the right side in a previous report in a larger population of patients with severe GERD (3). Further studies should be done on a larger number of patients to determine whether these findings are consistent in a larger patient population.

A limitation to this report is that we included patients with only very severe GERD with severe endoscopic esophagitis who were already known to have the left side. This may have been a result of patient selection, because we selected patients who had frequent REs during standard manometry performed on the left side. However, we also found twofold more fasting REs on the left than on the right side in a previous report in a larger population of patients with severe GERD (3). Further studies should be done on a larger number of patients to determine whether these findings are consistent in a larger patient population.

Table 3. Comparing pH, MII, and manometry in clearing REs detected by that method

<table>
<thead>
<tr>
<th>RE Type</th>
<th>pH REs</th>
<th>MII</th>
<th>Manometry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>ACT</td>
<td>No.</td>
</tr>
<tr>
<td>pH + MII/Manometry*</td>
<td>45</td>
<td>47±16</td>
<td>44(42)</td>
</tr>
<tr>
<td>No acid reflux</td>
<td>28</td>
<td>15±4</td>
<td></td>
</tr>
<tr>
<td>Acid reflux</td>
<td>17</td>
<td>101±40</td>
<td></td>
</tr>
<tr>
<td>MII + Manometry</td>
<td>374</td>
<td>12±5</td>
<td>374</td>
</tr>
<tr>
<td>While pH &lt;4**</td>
<td>89(85)</td>
<td>13±1</td>
<td>89</td>
</tr>
<tr>
<td>While pH &gt;4</td>
<td>285(283)</td>
<td>11±5</td>
<td>285</td>
</tr>
</tbody>
</table>

Values are means ± SE; No., no. of events (no. cleared in parentheses). ACT, acid clearing time (in s); CT, clearing time (in s). *Detected by both pH as well as MII and/or manometry; **includes both liquid pH REs (n = 33) and liquid acid reflux REs (n = 56).
repeated common cavities over a low basal LESp during standard manometry. This was intentional to maximize the opportunity to compare REs by the three study methods. Thus the results in this study may not apply to GERD populations with less severe disease.

Also, there are limitations to RE detection by MII. First, we found that frequent liquid REs may cause impedance to remain low (Fig. 2). Second, Barrett’s mucosa has been found to have a low baseline impedance in the distal electrode pairs (8). A low baseline for either reason will make RE detection difficult. Third, analysis of MII-pH tracings is labor intensive. Further experience will determine whether MII is limited by these and other methodological shortcomings, and automated analysis will be necessary for the technique to have broad application.

In summary, MII accurately detects individual REs, even when they occur close together. The duration of MII-REs and common cavities is nearly identical and shorter than acid clearing primarily due to acid reflu x. MII confirms previous reports in fasting patients that gas-only REs predominate in the left recumbent posture and liquid-only REs on the right. Measurement characteristics of MII are more similar to the common cavity than the pH probe, although the qualitative and technical advantages of MII make it a better volume method than manometry in RE detection and clearing. The ability to combine pH and MII in the same 2.13-mm catheter is ideal for prolonged ambulatory studies. For example, the roles of acid reflu x, RE composition, and proximal extent of reflu xant can be assessed in GERD patients with typical and atypical presentations.

REFERENCES