Clinical and pH study characteristics in reflux patients with and without ineffective oesophageal motility (IEM)

ABSTRACT

Background: The aetiology and clinical impact of ineffective oesophageal motility (IEM) remain poorly understood, but the condition is thought to worsen supine gastro-oesophageal reflux acid reflux (GERD).

Aims: In this retrospective cohort analysis of symptomatic patients with abnormal oesophageal acid exposure, we sought to determine any clinical or functional characteristics that would distinguish those with normal peristalsis from those with IEM, defined using the Chicago classification. We hypothesised that the impaired oesophageal clearance in IEM would be contributing to more severe degrees of pathological acid exposure, as well as clinical and endoscopic GERD severity.

Methods: Consecutive symptomatic patients with GERD underwent clinical, endoscopic and functional evaluation that included high-resolution impedance manometry (HRIM) and ambulatory pH monitoring performed 'off' acid suppressive therapy.

Results: Of the 114 patients with abnormal oesophageal acid exposure, 71 had normal oesophageal motility by HRIM and 43 were diagnosed with IEM (38% prevalence). Age, gender and symptom duration were similar between the two groups. Both groups had similar magnitude and frequency of symptoms, making a distinction clinically impossible. Endoscopically, the two groups had similar rates of erosive disease, hiatal hernia and Barrett’s oesophagus. Ambulatory pH, proton pump inhibitor (PPI) dosage and PPI response rates were also similar. Nevertheless, patients with IEM had significantly more impairment of oesophageal clearance (mean 56.9±6.4) than those with normal motility (mean 32.4±5.0) (p<0.003).

Conclusions: Symptomatic patients with IEM exhibit significant impairment of oesophageal clearance but are otherwise clinically indistinguishable from those with normal oesophageal motility. Whether IEM reflects a cause or effect phenomenon and to what degree it plays a clinical role in GERD management is unclear.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is widely prevalent, afflicting up to 20% of the population and has significant implications on healthcare costs, with more than 7 million annual visits in the USA. Although oftentimes the disease can be diagnosed based on typical symptoms and response to empiric proton pump inhibitor (PPI) therapy, in some patients additional diagnostic testing such as endoscopy, high-resolution manometry (HRM) and ambulatory pH monitoring may be indicated. Refractory GERD is seen in up to 45% of patients placed on empiric PPI therapy, and often results from non-compliance, misdiagnosis or poor oesophageal pH control. Ambulatory impedance/pH or Bravo wireless pH monitoring are particularly useful in patients with
typical reflux symptoms refractory to PPI therapy referred to gastroenterologists.

Using the Chicago classification (V.3), ineffective oesophageal motility (IEM) is defined by a distal contractile integral (DCI) \( <450 \text{ mm Hg s cm} \) on HRM in \( \geq 50\% \) of test swallows. \(^3\) IEM is a common manometric abnormality, with an estimated prevalence of 20–30\% and may contribute to GERD symptoms and non-obstructive dysphagia with the hypothesis that it contributes to defective bolus transit. \(^5\) The simultaneous assessment of oesophageal pressure topography and bolus clearance using a catheter combining HRM with high-resolution multichannel intraluminal impedance (HRM) has shed new light in the assessment of IEM. \(^6\)

IEM has been hypothesised to worsen supine GERD and possibly contribute to refractory symptoms and endoscopic disease severity. In a study using water-perfused system, patients with IEM demonstrated a distinctive recumbent reflux pattern, similar to that seen in patients with progressive systemic sclerosis (PSS). \(^7\) Currently however, IEM, as well as fragmented peristalsis, are considered as ‘minor’ disorders of peristalsis and their clinical significance remains debatable. \(^4\) \(^8\) Although PPI and prokinetic therapy is useful in many patients, there are no proven effective therapies available to restore the oesophageal peristalsis. \(^9\) Moreover, the clinical implications of this manometric finding are uncertain as this pattern can be seen in healthy asymptomatic controls.

In this retrospective cohort study of symptomatic patients with abnormal oesophageal acid exposure by pH monitoring, we sought to determine any clinical or functional characteristics that would distinguish those with underlying normal oesophageal motility or IEM. We hypothesised that impaired oesophageal clearance would be contributing to more severe degrees of pathological acid exposure as well as clinical and endoscopic GERD severity.

**PATIENTS AND METHODS**

**Patients:** This retrospective cohort study of prospectively collected data was approved by the Institutional Research Board of El Camino Hospital and was conducted at the Neuro-gastroenterology and Motility Center of Silicon Valley Gastroenterology, in Mountain View, California, USA. The study was considered exempt from the need for individual informed consent from participating patients. **Inclusion criteria:** We included consecutive patients with pathological oesophageal acid exposure by pH monitoring who were all evaluated because of various GERD symptoms, such as dysphagia, heartburn, acid regurgitation, chest pain and/or belching. A detailed review of patient’s medical, endoscopic, manometric, pH and histological records was then performed to ensure proper inclusion in the study (see study flow in figure 1). On presentation, all patients in the cohort were symptomatic with oesophageal symptoms that were recorded on questioning and formal questionnaire-based assessment. **Exclusion criteria:** Patients \( <18 \) years old, those with known obstructive oesophageal disease by endoscopy (ie, cancer, strictures), scleroderma, oesophagogastric junction (EGJ) outflow obstruction (mean integrated relaxation pressure \( \geq 15 \text{ mm Hg} \)), achalasia, absent peristalsis (100\% of swallows with failed peristalsis), diffuse oesophageal spasm, and jackhammer oesophagus, as defined by the Chicago classification (V.3) and those who had previously undergone oesophageal surgery (ie, antireflux surgery or myotomy) or endoscopic intervention (ie, transoral fundoplication) were excluded. Patients with atypical (ear, nose and throat or respiratory) symptoms only and those with oropharyngeal dysphagia without associated oesophageal symptoms were also excluded. Of note, the study, albeit community-based, was on a referral population to a gastroenterology unit with emphasis on oesophageal disease.

**Questionnaires:** In order to qualify for inclusion into the study, patients had to be symptomatic on a simple and previously validated questionnaire that was filled out on initial presentation in the absence of treatment with acid blockers, prokinetics or other drugs affecting gastrointestinal motility. In this questionnaire, the symptoms were graded with scores for dysphagia, heartburn, regurgitation, lower chest pain and belching \( (0=\text{no symptom}, 1=\text{mild symptom}, 2=\text{moderate symptom and} 3=\text{severe symptom, occurring at various frequencies (once a week}=0, 2 to 6 times a week}=1, 7 to 15 times a week}=2 \) and more than 15 times a week}=3)). \(^10\) Since available therapies for IEM are sparse, all study patients were given a PPI trial, given the potential of these drugs to reduce gastric volume and thereby volume reflux. \(^11\) Patients were then reassessed 2 months later for PPI responsiveness. ‘Full’ response was recorded if on
follow-up, patients had complete control of their symptoms, their questionnaire values were ‘zero’, they were happy with the treatment and were willing to continue with it. ‘Partial’ response was recorded if on follow-up, patients noted improvement but they were still seeking further therapy (pharmacological, endoscopic or surgical) and their questionnaire scores were above ‘zero’. ‘No’ response was recorded if on follow-up, patients noted no improvement, their questionnaire scores were above ‘zero’ and they were seeking other therapy (additional pharmacological, endoscopic or surgical). Many of these patients underwent additional pharmacological (ie, H2 blockade, prokinetics), endoscopic or surgical therapies (ie, antireflux surgery) for symptom control (data not shown), based on their symptom patterns, physiological evaluation and treatment preferences.

Endoscopy and biopsies: Upper endoscopy with random proximal and distal oesophageal biopsies as well as targeted biopsies of oesophageal lesions was performed as part of the structural assessment of the cohort. Patients were classified in various disease categories as follows: Normal: endoscopy-negative; Erosive oesophagitis: endoscopy-positive for any Los Angeles classification grades; Barrett’s oesophagus (BE): Endoscopically visible and histologically proven intestinal metaplasia. The diagnosis of eosinophilic oesophagitis was based on the histological presence of ≥15 eosinophils per high-power field. Sliding hiatal hernia was defined endoscopically and also confirmed by HRM and graded in cm length. Oesophagitis and BE were also independently assessed histologically, using standard criteria.12–14

Ambulatory pH monitoring: Oesophageal ambulatory pH monitoring was performed ‘off’ PPI therapy using a dual sensor impedance/pH catheter connected to a portable digital data recorder that stored data for up to 24 hours or a wireless 48-hour Bravo pH system (Medtronic, Sunnyvale, California, USA). The positioning of the pH catheter was established based on the pH difference between the distal (gastroduodenal) and proximal (oesophageal) sensors and previous lower oesophageal sphincter identification by HRM or directly, on demarcation of the EGJ during endoscopy. The catheter’s distal sensor recorded pH 10 cm below the gastro-oesophageal junction and its proximal sensor recorded 5 cm above the lower oesophageal sphincter; the Bravo pH capsule was placed 6 cm proximal to the EGJ. Patients were instructed to carry out normal daily activities without dietary restrictions during the study. No instructions were given in regards to consumption of food or drink between dinner and bedtime. The pH data were analysed using standard software. The pH test was considered abnormal when total oesophageal pH<4 was >4.2% of the time or the DeMeester score was >14.7.15 In the patients who underwent wireless pH monitoring, the data from the day with the worse pH profile was used. Patients were divided into two groups, those with normal and those with IEM as defined above. Total pH times <4.0 as well as upright and supine times were recorded as percentages.

High-resolution impedance manometry: A solid state HRIM catheter with 4.2 mm outer diameter with 36 circumferential sensors located at 1 cm intervals incorporating impedance measurements to assess the success or failure of bolus movements through the oesophagus was used for the study (Manoscan Eso-Z module, Medtronic, Sunnyvale, California, USA). Manometric studies were performed with patients in supine position after at least a 6 hour fast. The impedance sensors were positioned to record from the end of the proximal oesophageal segment through the distal oesophagus and into the proximal stomach.6 The manometric protocol included 30 s without swallows to assess basal EGJ pressure and morphology followed by 10 5 mL swallows of 0.3% saline. The high-resolution EPT of each swallow was analysed for integrity of the 20 mm Hg isobaric contours. The length of the break within 20 mm Hg isobaric contour (IBC) was measured using the smart mouse tool in ManoView Software (Medtronic, Sunnyvale, California, USA). Oesophageal peristalsis was defined as intact if no break longer than 5 cm was observed within the IBC. The final diagnosis was made according to the Chicago Classification V.3, where ineffective swallows were characterised by a DCI ≤450 mm Hg s cm and IEM was defined as ≥50% ineffective swallows. Fragmented peristalsis was also recorded, defined as ≥50% swallows with large (>5 cm) defects in the 20 mm Hg IBC and a DCI ≥450 mm Hg s cm.1 Individual swallows were excluded from analysis in case of double or multiple swallows that could lead to deglutitive inhibition of peristalsis. The impedance sensors were positioned to record from the termination of the proximal oesophageal segment through the distal oesophagus and into the proximal stomach with approximately two intragastric impedance measurements. Complete bolus clearance was defined as bolus entry followed by sequential bolus clearance at all impedance-recording sites. Conversely, incomplete bolus clearance was defined as bolus entry without bolus clearance at one or more oesophageal impedance-recording sites. Hence, each swallow was characterised as either complete or incomplete bolus clearance and the total percentage was calculated accordingly.6

Treatment: After their baseline evaluation, all participating patients were treated with acid suppressive therapy using PPI, taken either once or twice daily and with additional H2 receptor antagonists, if they persisted experiencing symptoms. All commercially available agents were used as directed by patients’ choice, insurance coverage and tolerability. PPI therapy was taken 30 min before breakfast and, in the case of twice daily dosing, before dinner as well. Additional H2 antagonists were used at night time and as needed for symptoms in some patients. Symptom improvement or resolution was then validated during subsequent visits using the GERD questionnaire, based on severity and frequency of symptoms (see questionnaire assessment above). Additional therapies, such use of prokinetics, radiofrequency energy
therapy of the EGJ or laparoscopic fundoplication, were also used in order to improve symptoms in selected patients who had incomplete symptom control and questionnaire scores above 0 despite maximum acid suppressive therapy. The period of follow-up was variable, ranging from 2 to 14 months.

Statistics: Statistical analysis was performed using commercial statistical software (Minitab Express). The 2-tailed t-test was used to compare continuous variables. For all statistical analyses, the level of significance was set at p < 0.05. Results are depicted as tables, bar graphs and box plots, as needed.

RESULTS
Over a period of 2 years, 243 consecutive patients presenting with dysphagia, heartburn, regurgitation, chest/epigastric pain or belching underwent clinical, endoscopic and functional evaluation that included HRIM and pH/impedance or Bravo pH monitoring ‘off’ or ‘on’ PPI therapy (figure 1). Of the 142 patients with abnormal oesophageal acid exposure, 28 were excluded from analysis since they had achalasia (n=4), PSS (n=2), systemic illness (n=3), prior surgery (n=3), study on PPI flow obstruction (n=5) (see Methods section); of the remaining 114 patients, 71 had normal oesophageal motility and 43 were diagnosed with IEM (see Methods section). Hence, the prevalence of IEM (by Chicago V.3 criteria) in our study was 38%.

Table 1 shows the patients’ characteristics. Age, gender and symptoms duration were similar between the 2 groups. Similarly, erosive reflux disease and sliding hiatal hernia were equally seen in both groups. Specifically, there were 11 patients with grade B, 1 with grade C and 1 with grade oesophagitis in the normal motility group and 7 with grade B and 1 with grade C oesophagitis in the IEM group. Although there were numerically more patients with BE in the IEM group, this was not statistically different. The mean length of BE was 4 cm in the normal motility group and 5.2 cm in the IEM group. None of the patients with BE had dysphasia. The manometrically defined length of hiatal hernias was also similar between the groups. Figure 2 shows the symptom scores; both groups had similar magnitude and frequency of chest/epigastric pain, heartburn, regurgitation, dysphasia and belching, making the distinction of the two groups clinically impossible. Overall, both groups were moderately symptomatic, representing a patient cohort referred to gastroenterology for further diagnosis and management.

Figure 3 highlights the similarities of the DeMeester scores in the two groups represented in box plots; Table 2 depicts the key HRM findings and pH parameters of the two groups. Only the DCI and percentage of fragmented peristalsis were significantly different (p<0.0001), as expected. Refuting our hypothesis, the overall acid exposure times, the number and duration of long (>5 min) reflux events and the number of supine acid events (all potentially reflecting impaired oesophageal body clearance) were similar between the groups (NS). When separately analysed, patients with GERD with and without fragmented contractions (large, ≥5 cm, defects in the 20 mm Hg IBC and a DCI ≥50 mm Hg s cm) did not show different clinical, pH or endoscopic characteristics (n=10; data not shown). Figure 4 depicts the representative tracings of patients in the two groups, one with normal oesophageal motility (DCI=2952 mm Hg s cm) (figure 4A) and another with IEM (DCI=411 mm Hg s cm) (figure 4B). Figure 5 depicts the box plots of the percentages of impaired oesophageal clearance in the two groups. Patients with IEM had a significant impairment of clearance (mean 56.9±6.4) versus those with normal motility (mean 32.4±5.0) (p=0.008). Figure 4C is from a patient with normal motility (DCI=1870 mm Hg s cm) but with frequent (70%) impaired clearance by HRIM (shown in magenta colour). There was no correlation between scores and DCI values (Pearson correlation 0.10; p=0.25; data not shown).

The mean daily PPI dose in patients with IEM was 1.1±0.1 while in those with normal motility it was 1.05±0.07 (p=0.65). In the IEM group, the proportions of patients with complete, partial and no response to PPI therapy were 9.3%, 35.4% and 37.2%, respectively, similar to those with normal motility (15.4%, 52.1% and 32.3%, respectively). Both groups required similar additional (pharmacological, endoscopic and/or surgical) therapies in order to achieve symptomatic resolution. Of the IEM group’s partial or non-responders, four received prokinetics, six endoscopic therapy and two modified fundoplication (27% of total). Of the normal group’s partial or non-responders, five received prokinetics, nine endoscopic...
therapy and five modified fundoplication (26% of total). Therapeutic outcomes in such patients were not collected (data not shown).

DISCUSSION
The aim of our study was to determine any clinical or functional characteristics that would distinguish those patients with pathological acid exposure and either IEM or normal oesophageal motility. We had hypothesised that impaired oesophageal clearance would be contributing to more severe degrees of pathological acid exposure as well as clinical and endoscopic GERD severity. We have instead demonstrated that such patients cannot be recognised on the basis of clinical history, endoscopic findings or oesophageal acid exposure, particularly long (>5 min) or supine reflux events. We nevertheless found that patients with IEM were more likely to exhibit impaired oesophageal clearance by HRIM.

These results have several key implications: IEM is associated with similar degrees of GERD symptoms, pH findings as well as PPI use and response rates as those patients with normal motility and puts at question the overall clinical significance of manometrically demonstrable IEM. Based on our data, patients with IEM may not need more aggressive treatment of their GERD or more intense clinical surveillance to ensure that complications do not develop or worsen as a result of the

Figure 2  Symptom scores in the two groups of patients, those with normal motility and those with ineffective oesophageal motility (IEM). There were no differences between the two groups.

Figure 3  Box plot graphs highlighting the DeMeester scores defined by ambulatory oesophageal pH monitoring. The 114 patients studied were separated into normal (DCI >450 mm Hg*s*cm; n=71) and IEM (DCI ≤450 mm Hg*s*cm; n=43) groups. The plots display the distribution of data as: minimum (bottom whisker), first quartile (lower part of box), median (line in box), third quartile (upper part of box) and maximum (top whisker). Asterisks represent data outliers. DCI, distal contractile integral; IEM, ineffective oesophageal motility.
IEM/GERD combination. The clinical implications of impaired oesophageal clearance by HRIM remain uncertain.

Despite multiple investigations to date, the significance of IEM remains unclear but up to 50% of such patients may suffer from associated GERD. The minimum threshold of the wave amplitude to clear liquids from the oesophagus (on 80% or more occasions) is 30 mm Hg. However, abnormal bolus transit is present in only ∼45% of patients with IEM undergoing multilumen impedance measurement. This discrepancy may relate to the length of the oesophagus affected by poor contractility. Several recent studies have found that the longer the affected segment, the greater is the likelihood of impaired bolus transit. Some studies on both animals and humans suggest that inflammatory cytokines associated with oesophagitis, such as interleukin (IL)-1β, IL-6 and platelet-activating factor, play a role in the reduction of muscle contractility by reducing the release of acetylcholine from excitatory myenteric neurons to the oesophageal smooth muscle. The cornerstones of GERD/IEM treatment are still management of acid reflux symptoms with diet/lifestyle modifications and PPI therapy, since no proven effective therapy exists for oesophageal muscle hypomotility. It has also been described that antireflux surgery may restore defective oesophageal peristalsis.

To date, there has been limited data on patients with GERD and IEM as compared to their counterparts with normal oesophageal motility. The establishment of a direct causal link between GERD and IEM has been questionable at best, with some studies suggesting a causal association and others not. In one study, and in contrast to ours, patients with IEM demonstrated significant increases in recumbent median percentage of time of pH<4 (4.5%) and median distal oesophageal acid exposure (4.2 min/episode) compared to those with normal motility (0.2%, 1 min/episode). Recumbent acid exposure in IEM did not differ significantly from that in patients with scleroderma for either variable (5.4%, 4.2 min/episode). Further, although we did not determine a clinically distinguishable link in our study, one between IEM and respiratory symptoms of GERD has been previously suggested. Studies have also suggested different resolution patterns of oesophageal hypocontractility depending on the chronicity of symptoms. Acute oesophagitis-associated hypocontractility is more likely reversible than its chronic counterpart. These findings suggest that severe and chronic GERD may negatively impact the neuromotor oesophageal functioning rather than vice versa.

There are some notable limitations to our study. First, it was a retrospective cohort analysis of a select patient population who were willing to undergo full endoscopic as well as functional testing with pH monitoring and HRIM. Our use of several exclusion criteria (see Methods section) selected the cohort further to idiopathic cases of IEM. Second, this was a one-time assessment of clinical and functional characteristics of the two

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<th>Manometric and ambulatory 24 hour pH scores in the two groups</th>
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<td></td>
<td>Normal (n=71)</td>
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<tr>
<td><strong>HRIM</strong></td>
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<tr>
<td>LESP (mean±SEM in mm Hg)</td>
<td>22.8±1.5</td>
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<tr>
<td>DCI (mean±SEM in mm Hg<em>s</em>cm)</td>
<td>1649.5±162</td>
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<tr>
<td>Fragmented peristalsis (%±SEM)</td>
<td>16.2±2.6</td>
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<td><strong>Ambulatory pH</strong></td>
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<tr>
<td>pH time pH&lt;4.0 (mean %±SEM)</td>
<td>16.0±1.9</td>
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<tr>
<td>Number of long reflux episodes (mean±SEM)</td>
<td>7.7±0.8</td>
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<tr>
<td>Duration of long reflux episodes (mean±SEM)</td>
<td>35.0±5.3</td>
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<tr>
<td>Per cent supine pH&lt;4.0 (mean±SEM)</td>
<td>16.1±2.7</td>
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*p<0.001. DCI, distal contractile integral; HRIM, high-resolution impedance manometry; IEM, ineffective oesophageal motility; LESP, lower esophageal sphincter pressure.

Figure 4 Representative tracings of patients in the two groups. (A): Pattern seen in a patient with normal oesophageal motility (DCI=2952 mm Hg*s*cm). (B): Pattern seen in a patient with IEM (DCI=411 mm Hg*s*cm). (C): Pattern seen in a patient with normal motility (DCI=1870 mm Hg*s*cm) but with frequent (70%) impaired clearance by HRIM (shown in magenta colour). DCI, distal contractile integral; HRIM, high-resolution impedance manometry; IEM, ineffective oesophageal motility.
groups in our cohort that does not allow an appreciation of the long-term implications of our findings, particularly the discrepancy between oesophageal acid exposure and impaired clearance. Many of the patients were on PPI and hence only ∼20% of patients had erosive esophagitis; this could affect the results, as some patients may have healed esophagitis when they presented to endoscopy, even if they had persistent symptoms. Since we did not perform repeat HRIM studies in our cohort, the reproducibility of the IEM diagnosis remains unclear. Nevertheless, we feel that our findings are relevant to everyday clinical practice where HRIM is performed once and decisions are based on its findings. Third, patients in the study did not have fixed therapeutic dosing regimens with PPI, standardised diet and lifestyle measures or long-term follow-up, and hence we cannot comment on their evolution over time, either in the form of improvement, deterioration or stability. Given that the duration of their GERD symptoms was not different between the two groups, we have no reason to believe that, overtime patients with normal motility will develop IEM, particularly under acid suppressive therapy. Fourth, we did not assess GERD-related respiratory symptoms. IEM has been shown to be the most prevalent motility abnormality in such patients due to the associated delayed oesophageal acid clearance.25 We also cannot comment on the effect of antireflux surgery in these patients. Finally, we evaluated only patients with abnormal oesophageal acid exposure and it is possible that a distinction between patients with IEM and those with normal motility would have been more apparent in review of symptomatic or asymptomatic patients with normal acid exposure. Nevertheless, we were able to demonstrate some physiologically relevant and important results in a cohort of symptomatic, community-based, patients with GERD with good generalisability.

In conclusion, symptomatic patients with GERD with IEM exhibit significant impairment in oesophageal clearance but are otherwise indistinguishable from those with normal oesophageal motility both clinically and by pH criteria. Whether IEM reflects a cause or effect phenomenon and to what degree it plays a clinical role in GERD management is unclear and it will require further study.

**REFERENCES**