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Making sense of oesophageal contents

Mark Fox, Werner Schwizer

Everybody experiences gastro-oesophageal reflux on occasion. In health, reflux of air (“belching”) occurs most commonly during transient lower oesophageal sphincter relaxations (TLOSRs) triggered by gastric distension. Acid secretions and semidigested food may also pass into the oesophagus during such events. Gastro-oesophageal reflux disease (GORD) is present when this reflux of gastric contents causes symptoms or mucosal damage.1 GORD patients do not necessarily have more TLOSRs than healthy controls.2 Rather, structural degradation and instability of the gastro-oesophageal junction increase the likelihood of reflux during TLOSRs and at other times (e.g. on straining).3,4 It is likely that the same changes allow greater volumes of gastric contents to pass the reflux barrier and to extend further into the oesophagus.5 Once reflux has occurred, ineffectiv motility and clearance are also important because prolonged exposure to acid and other noxious substances in refluxate (e.g. bile salts, pepsin) increase the risk of erosive reflux disease (ERD). Barrett’s columnar lined oesophagus (CLO) and other complications.6,7 Whether reflux triggers patient symptoms depends on a dynamic interaction between several factors, including patient age and sex, dietary factors, the volume, composition and distribution of the refluxate, mucosal disease, visceral sensitivity, and central factors including stress and patient vigilance (see box).8–20

Oesophageal pH testing was popularised by Johnson and DeMeester in the belief that GORD was not a symptom driven condition, but should be diagnosed by measurement of objective pathology.21 On this basis, the condition was conceived as a continuous spectrum of disease because oesophageal acid exposure is associated with the severity of symptoms and oesophagitis.22 Nevertheless, the relationship between reflux events, acid exposure, endoscopic findings and symptoms is not straightforward.23 For example, patients with Barrett’s CLO often have high levels of acid exposure but few symptoms because the metaplastic, columnar lining of the oesophagus is relatively insensitive to acid.24 Conversely, severe symptoms and a relatively poor response to acid suppression are often reported by patients with normal or near-normal acid exposure and without mucosal injury on conventional endoscopy.24,25

Ambulatory 24 h pH monitoring remains the standard investigation of GORD;26 however, it seems obvious that the value of pH studies is limited in patients in whom symptoms are not due to acid reflux. Multi-channel intraluminal impedance (MII) detects and follows the movement of oesophageal contents and can distinguish fluid and gas within the lumen.27 Combined pH and impedance monitoring has shown that proton pump inhibitors (PPIs) reduce acid reflux but have no effect on the number of reflux events per se.28 Moreover, clinical studies have found that weakly acid or non-acid reflux is a common cause of persistent symptoms in patients on PPI treatment,29 including those with atypical symptoms and chronic cough.30–33 These findings led to rapid adoption of this technique in clinical practice; however, the analysis of MII data is time consuming and its place in the routine investigation of GORD is still being defined.

In this edition of Gut, Emerenziani and colleagues (see page 443) compare the findings of combined pH and impedance monitoring in patients with “endoscopy negative reflux disease” (ENRD), to those with ERD and healthy controls.14 Overall, and consistent with previous studies,29,32 about 80% of patient reports of heartburn and regurgitation were related to acid reflux. Moreover, the frequency of acid reflux as a proportion of all the reflux events was twice as high in patients than controls, adding to the evidence that increased gastric acid production, abnormal distribution of secretions or delayed gastric emptying play an important role in GORD.7,30 Oesophageal acid exposure was lower in ENRD than ERD; in contrast, the percentage association of reflux events with symptoms (symptom index) was higher for both acid and weakly acid reflux. On detailed analysis it was found that only a small proportion of symptoms (12%) were triggered by weakly acid reflux in ERD patients; however, this was significantly higher in ENRD patients (22%), especially in the subgroup with physiological oesophageal acid exposure (32%). In addition, and independent of acid content, the presence of gas in the refluxate (i.e. mixed reflux) increased the likelihood that symptoms were reported in ENRD patients, almost certainly because of increased refluxate volume and oesophageal distension. The importance of these findings is not to suggest that the acquisition of more and more complex information about oesophageal contents improves the diagnostic yield of GORD. Rather it is to emphasise that patients with a sensitive oesophagus can experience typical reflux symptoms in response to chemical or mechanical stimulation in the clinical setting, and that a high symptom index is a surrogate marker for visceral hypersensitivity and/or abnormal central processing of visceral sensations. As explained below, this insight may be of value in interpreting reflux studies and predicting the outcome of treatment.

Before recommending that combined pH and impedance replace conventional pH monitoring, technical factors that affect published comparison should be considered. Firstly, the use of antimony pH electrodes rather than “reference standard” glass electrodes in most studies (and most commercial catheters) could bias results. In clinical practice the diagnostic agreement between these systems is acceptable;34,35 however, pH measurements acquired by antimony electrodes (with external reference) drift upwards over time due to oxidation in acid environments.36–38 As a consequence, antimony electrodes may register less “acid reflux” events than glass electrodes, especially when gastric pH is elevated in the post-prandial period and on PPI treatment. Secondly, the recording characteristics and signal processing of pH and MII systems are fundamentally different. The former provides a continuous assessment of oesophageal acid exposure. Each pH measurement represents the mean acid exposure over a period of time (typically 6 s), with reflux events recorded after two consecutive readings under pH 4 (i.e. 12 s). The latter detects discrete acid and non-acid reflux events, but does not provide an assessment of “refluxate exposure” because current MII techniques are insensitive to volume change.29 In addition, impedance measurements are acquired at 50 Hz and reflux events are identified by a characteristic distal to proximal impedance fall
Factors associated with patient reports of reflux events

- Patient demographics\textsuperscript{5-11}
  - age
  - sex
  - ethnicity
- Refluxate composition (chemical stimulation)\textsuperscript{13, 14}
  - acid/pH
  - bile salts/pepsin (more relevant for mucosal injury)
  - liquid/gas (interacts with volume and distribution)
- Refluxate volume/distribution (mechanical stimulation)\textsuperscript{5, 6}
  - Oesophageal sensitivity increases distal to proximal (laryngo-pharyngeal structures very sensitive)
- Endoscopic findings\textsuperscript{14, 15}
  - Increased in ENRD and functional heartburn
  - Decreased in Barrett’s CLO
- Peripheral visceral sensitisation\textsuperscript{14, 13, 20}
  - Previous acid exposure
  - Inflammation
  - Dietary fat
  - Alcohol
- Central factors\textsuperscript{18, 19}
  - Acute stress
  - Somatisation
  - Vigilance
  - Psychiatric morbidity

(liquid) or rise (gas).\textsuperscript{40} Semi-automatic MII analysis software identifies reflux events, typically by an impedance fall >50% from baseline to <1000 Ω; however, findings must be checked manually and the baseline is routinely adjusted to increase sensitivity. A similar approach to pH data would allow rapid falls in pH that do not reach the pH 4 threshold to be counted as reflux events, an approach that identifies many symptom-associated reflux events currently detected “only” by MII, especially weakly acid reflux in patients on PPI treatment.\textsuperscript{28} Studies are needed that compare a similarly rigorous analysis of pH and MII data.

A further limitation of many studies is that reflux symptoms are not assessed independently of the pH and impedance measurements by validated questionnaire. The relationship between oesophageal acid exposure, symptom–reflux association and overall symptom severity is not clear. Patients with ERD or Barrett’s CLO and severe, prolonged oesophageal acid exposure often describe long periods of burning chest and epigastric discomfort, information that cannot be easily recorded by data loggers (especially at night), resulting in a low symptom index. In contrast, patients with ENRD and mild acid exposure more often experience discrete symptoms with reflux events, resulting in a high symptom index. This issue and the high day-to-day variability of symptoms probably explain why symptom–reflux association tests do not reliably predict the response to PPI treatment in unselected patients.\textsuperscript{29} An alternative approach is to consider the severity of oesophageal acid exposure and association of reflux events and symptoms (e.g. symptom index) as independent factors affecting overall symptom severity. Accordingly, pH monitoring provides a direct assessment of disease severity in terms of acid exposure, whereas symptom index (assessed by pH and/or MII monitoring) provides an assessment of visceral sensitivity to reflux events (fig 1). This approach is supported by a recent analysis of reflux and symptom events during 96 h wireless pH monitoring.\textsuperscript{41} As expected, symptom severity off treatment increased with oesophageal acid exposure (fig 2A). Almost all patients improved to some extent on high dose PPI treatment; however, the response was invertedly correlated to symptom index (fig 2B). Thus, independent of oesophageal acid exposure, patients with a high symptom index (i.e. visceral hypersensitivity) were more likely to experience persistent symptoms on treatment due to weak acid and/or mechanical distension by persistent reflux episodes.\textsuperscript{42} These observations explain the paradox that patients with severe oesophageal acid exposure and mucosal disease often have a low symptom index but respond well to acid suppression, whereas patients with ENRD and functional heartburn with a high symptom index often continue to experience symptoms on treatment. Classification of patients on this basis is consistent with the shift in conceptual framework from GORD as a continuous spectrum of disease, to ENRD, ERD and Barrett’s CLO as different pathophysiological responses to acid exposure.\textsuperscript{13} At the same time it allows for some movement between ENRD and ERD observed in large longitudinal trials,\textsuperscript{20, 42} as oesophageal acid exposure and visceral sensitivity vary over time with age, weight, stress and other factors.

In summary, research with combined pH and MII monitoring is slowly “making sense” of oesophageal contents and the occurrence of reflux symptoms; however, in clinical practice it is not clear whether this technique should be used routinely or reserved for special indications. Current guidelines advise a “treat and test” approach with further investigation by endoscopy and physiological measurement reserved for patients that fail to respond to acid suppression.\textsuperscript{43} A small number (~2%) of patients (higher in Asian populations) have persistent acid reflux on treatment due to mutations in the cytochrome enzymes that metabolise PPIs.\textsuperscript{44}
commonly, persistent symptoms are reported by patients with hiatal hernia due to regurgitation of large volumes of gastric content and those with ENRD and functional heartburn due to hypersensitivity to ongoing reflux. Physiological studies are rarely needed to confirm the diagnosis in the former group unless fundoplication surgery is under consideration. In contrast, patients with no endoscopic findings often require investigation as “atypical” symptoms are common in these individuals and, conversely, reflux is not necessarily the cause of “typical” symptoms. The combined pH and MII technique is ideal for this indication; however, detailed assessment of the refluxate as described by Emerenziani and colleagues is not usually required as symptoms are not specific for oesophageal contents. Alternatively, applying the approach described above, pH studies alone may be adequate to detect oesophageal hypersensitivity if the recording is examined in detail to detect weakly acid reflux (pH 4–5), thus increasing the sensitivity of conventional symptom–reflux assessment. Indeed prolonged pH monitoring by wireless pH measurement may be preferable, especially in patients with intermittent symptoms. A study directly comparing the diagnostic yield of 24 h combined pH–impedance and 48 h wireless pH measurement is currently in progress.

Ultimately, the goal of investigation is to improve patient care. Previously, GORD treatment was directed towards healing mucosal injury. More recently, there has been a shift to controlling symptoms. Patients with ENRD with an incomplete response to PPIs have a form of functional bowel disease and, in common with these conditions, effective treatment can be directed not only at reducing the stimulus by acid suppression, but also at reducing visceral hypersensitivity. For those with ERD the aim will be “complete remission” of symptoms and mucosal disease, whereas in Barrett’s CLO the priority is to prevent progression to dysplasia and malignancy. This change of focus and the improved ability to identify the causes of symptoms and disease using modern physiological measurement will benefit patients by directing effective treatment on an individual basis.

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Figure 2 Results from 20 patients with reflux symptoms assessed over 96 h by a wireless pH monitoring (prolonged measurement significantly improved diagnostic reproducibility). (A) The symptom load suffered by GORD patients was related to the severity of oesophageal acid exposure. No similar correlation with symptom index was observed. (B) The response to treatment with high dose PPIs was inversely related to the symptom index: patients who sensed a large proportion of reflux events responded poorly.
The significance of the gut barrier in disease

Jon Meddings

In the paper by Wapenaar et al (see page 463) the authors have taken a fascinating approach to identifying shared mechanisms involved in the genesis of either coeliac disease or inflammatory bowel disease (IBD).1 They argue that these two prototypical inflammatory diseases of the intestinal mucosa there exists reasonable evidence for a defect in barrier function that appears to be required before the development of disease. Furthermore, as both diseases have strong genetic components they speculated that these syndromes might share common genetic defects in the control of intestinal barrier function. They used a genetic association analysis approach and through this identified two adapter protein coding genes that were associated with coeliac disease in patients from both Great Britain and The Netherlands. They went on to demonstrate that one of these genes was also associated with ulcerative colitis in a Dutch patient cohort.

These observations are important not only for the conclusions reached in the paper but also in the broader context. Until recently, it was believed that IBD, such as Crohn’s disease, represented dysregulation of the adaptive immune system. Over the past decade, however, there has been increasing recognition of the importance of both epithelial barrier function and innate immunity in the genesis of intestinal inflammation. In the broadest sense these two factors could be argued to be different aspects of the same basic system. Within the gastrointestinal tract there is significant exposure to foreign compounds that can drive systemic inflammation through a variety of mechanisms. The gut has a tremendous number of defence mechanisms that have evolved to manage this ever-changing threat (fig 1). In general terms these include the ability to manage commensal flora in preference to pathogenic organisms, the secretion of toxic molecules such as defensins, the scavenging and binding of luminal organisms by specifically formulated mucins, the presence of regulated tight and adherens junctions between epithelial cells that regulate the passage of potentially pro-inflammatory molecules and the presence of both intra- and extracellular pattern recognition molecules that can regulate immunological responsiveness to environmental stimuli. Finally, the adaptive immune system, which sits on top of this large defensive system, can fine tune the responses to a wide variety of environmental agents. It is an amazingly complex system that in most of us functions extremely well.

Given the complexity of this defensive system, however, it is not at all surprising that defects in many of these important systems could ultimately lead to inflammatory disease. Furthermore, as the mucosal immune system is “educated” primarily in the gut and these cells subsequently migrate elsewhere, it is perhaps not surprising that defects in these systems may lead to inflammatory disease that can be expressed at sites distant to the intestine. This is becoming increasingly apparent in human disease and in animal models of disease.

It is beyond the scope of this commentary to review each aspect of mucosal defence exhaustively and there have been excellent reviews recently.2 I would, however, like to discuss one aspect of gut barrier function; that being abnormal epithelial permeability and disease. The genetic abnormalities described in this paper would appear to fit most closely with this system.

Abnormal permeability refers to a measurable increase in flux of small water-soluble compounds across the paracellular pathway of the small intestine. The rate of movement across this pathway is regulated primarily by the functional state of the tight and adherens junction. These, in turn, are controlled by a complex array of intracellular proteins within the enterocyte as well as the protein composition of the junctions themselves. Increased permeability can be observed as a result of action by inflammatory cytokines (such as tumour necrosis factor α, IL17 or IFN-γ), bacterial interactions with the enterocyte, migration of inflammatory cells across the epithelium, nutrient transporter activation, noxious environmental agents or it may exist de novo, without apparent cause.3,4 In the latter case this may be secondary to an alteration in the protein composition of the junctions or presumably their regulatory systems. In the paper by Wapenaar et al,1 in this issue of Gut, it