Authors' affiliations

S L Preston, Department of Gastroenterology, Concord Repatriation General Hospital, Sydney, Australia, and Histopathology Unit, Cancer Research UK, London, UK

J A Jankowski, Department of Clinical Pharmacology, University of Oxford, Oxford, UK, Digestive Diseases Centre, University Hospitals of Leicester, Leicester, UK, and Histopathology Unit, Cancer Research UK, London, UK

Correspondence to: Professor J A Jankowski, Department of Clinical Pharmacology, University of Oxford, Woodstock Rd, Oxford OX2 6HE, UK; janusz.jankowski@clinpharm.ox.ac.uk

Conflict of interest: None declared.

REFERENCES

- Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;**83**:2049–53.
- Prach AT, MacDonald TA, Hopwood DA, et al. Increasing incidence of Barrett's oesophagus: education, enthusiasm, or epidemiology? *Lancet* 1997;**350**:933.
- Falk GW. Barrett's esophagus. *Gastroenterology* 2002;**122**:1569–91.
- Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988;**319**:525–32.
- Jankowski JA, Wright NA, Meltzer SJ, et al. Molecular evolution of the metaplasia-dysplasia-adenocarcinoma sequence in the esophagus. *Am J Pathol* 1999;**154**:965–73.
- Bond JH. Clinical evidence for the adenoma-carcinoma sequence, and the management of patients with colorectal adenomas. *Semin Gastrointest Dis* 2000;**11**:176–84.
- Winawer SJ, Zaubler AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993;**329**:1977–81.
- Jankowski J, Moayyedi P. Re: Cost-effectiveness of aspirin chemoprevention for Barrett's esophagus. *J Natl Cancer Inst* 2004;**96**:885–7.
- Montgomery E, Goldblum JR, Greenson JK, et al. Dysplasia as a predictive marker for invasive carcinoma in Barrett esophagus: a follow-up study based on 138 cases from a diagnostic variability study. *Hum Pathol* 2001;**32**:379–88.
- Reid BJ, Haggitt RC, Rubin CE, et al. Observer variation in the diagnosis of dysplasia in Barrett's esophagus. *Hum Pathol* 1988;**19**:166–78.
- Murray L, Sedo A, Scott M, et al. TP53 and progression from Barrett's metaplasia to oesophageal adenocarcinoma in a UK population cohort. *Gut* 2006;**55**:1390–7.
- Coggi G, Bosari S, Roncalli M, et al. p53 protein accumulation and p53 gene mutation in esophageal carcinoma. A molecular and immunohistochemical study with clinicopathologic correlations. *Cancer* 1997;**79**:425–32.
- Ransohoff DF. Rules of evidence for cancer molecular-marker discovery and validation. *Nat Rev Cancer* 2004;**4**:309–14.
- Sharma P, McQuaid K, Dent J, et al. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. *Gastroenterology* 2004;**127**:310–30.
- Pepe MS, Etzioni R, Feng Z, et al. Phases of biomarker development for early detection of cancer. *J Natl Cancer Inst* 2001;**93**:1054–61.
- Barrett MT, Sanchez CA, Prevo LJ, et al. Evolution of neoplastic cell lineages in Barrett oesophagus. *Nat Genet* 1999;**22**:106–9.
- Prevo LJ, Sanchez CA, Galipeau PC, et al. p53-mutant clones and field effects in Barrett's esophagus. *Cancer Res* 1999;**59**:4784–7.
- Reid BJ, Prevo LJ, Galipeau PC, et al. Predictors of progression in Barrett's esophagus II: baseline 17p (p53) loss of heterozygosity identifies a patient subset at increased risk for neoplastic progression. *Am J Gastroenterol* 2001;**96**:2839–48.
- Eads CA, Lord RV, Kurumboor SK, et al. Fields of aberrant CpG island hypermethylation in Barrett's esophagus and associated adenocarcinoma. *Cancer Res* 2000;**60**:5021–6.
- Wong DJ, Paulson TG, Prevo LJ, et al. p16(INK4a) lesions are common, early abnormalities that undergo clonal expansion in Barrett's metaplastic epithelium. *Cancer Res* 2001;**61**:8284–9.
- Bani-Hani K, Martin IG, Hardie U, et al. Prospective study of cyclin D1 overexpression in Barrett's esophagus: association with increased risk of adenocarcinoma. *J Natl Cancer Inst* 2000;**92**:1316–21.
- Arber N, Lightdale C, Rotterdam H, et al. Increased expression of the cyclin D1 gene in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 1996;**5**:457–9.
- Reid BJ, Blount PL, Rubin CE, et al. Flow-cytometric and histological progression to malignancy in Barrett's esophagus: prospective endoscopic surveillance of a cohort. *Gastroenterology* 1992;**102**:1212–19.
- Fennerty MB, Sampliner RE, Way D, et al. Discordance between flow cytometric abnormalities and dysplasia in Barrett's esophagus. *Gastroenterology* 1989;**97**:815–20.
- Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 2001;**120**:1607–19.
- Dulai GS, Guha S, Kahn KL, et al. Preoperative prevalence of Barrett's esophagus in esophageal adenocarcinoma: a systematic review. *Gastroenterology* 2002;**122**:26–33.
- Cawley HM, Meltzer SJ, De Benedetti VM, et al. Anti-p53 antibodies in patients with Barrett's esophagus or esophageal carcinoma can predate cancer diagnosis. *Gastroenterology* 1998;**115**:19–27.
- Jankowski JA, Hawk ET. A methodologic analysis of chemoprevention and cancer prevention strategies for gastrointestinal cancer. *Nat Clin Pract Gastroenterol Hepatol* 2006;**3**:101–11.

Oesophagus

Impedance-pH monitoring in proton pump inhibitor resistant patients: ready for clinical application?

J P Galmiche

Impedance-pH monitoring represents a useful tool for studies and clinical research in oesophageal disorders, and may hold promise for the group of patients dissatisfied with their antireflux treatment

Gastro-oesophageal reflux disease (GORD) is a very common disorder in which the reflux of gastric (or gastroduodenal) contents causes troublesome symptoms and/or lesions of the oesophageal mucosa. The harmful effects of acid injury on the oesophageal mucosa have been established for decades by experimental and clinical studies.¹ From a clinical and therapeutic viewpoint, the central role of acid in the pathogenesis of reflux

symptoms and lesions of the oesophagus was most convincingly confirmed by the introduction of acid suppressive therapy; the development of proton pump inhibitors (PPIs) achieved a level of efficacy not previously reached by antacids or H₂ blockers.²

Despite the progress made with PPIs, it has now however become clear that up to 40% of patients with GORD symptoms are either not completely satisfied with their acid suppressive

therapy or may be resistant to PPIs.³ Several reasons may underlie an individual's resistance to his or her PPI regimen. Firstly, it may be that symptoms are not related to acid reflux; this may be the case when atypical and non-specific symptoms are reported and endoscopy does not show mucosal breaks, for example. In addition, acid injury may not be completely eliminated by PPI treatment and acid exposure remains abnormal. The level of acidity necessary to cause symptoms is not precisely defined and is likely to vary from subject to subject or even in the same individual. Several studies have shown that "weakly acidic" or short lasting reflux episodes may cause symptoms similar to those reported in classical GORD despite an overall normal 24 hour oesophageal acid exposure time.^{4,5} In these patients with an apparently hypersensitive oesophagus, an increased dose of PPI (for example, omeprazole twice daily) proved to be effective in the subgroup of individuals with a significant association between symptoms and acid reflux episodes.⁶ In practice, demonstration of such a temporal relationship requires analysis of symptoms and acid events recorded

during 24 hour oesophageal pH monitoring. Different symptom indices and probability calculations are commonly used to express the strength of this association between acid reflux and symptomatic events.⁷⁻⁹

However, despite the significant role of acid in GORD pathogenesis, other components of the reflux material can also exert a deleterious effect on the oesophageal mucosa; they can act either alone or synergistically with acid. These molecules include biliary acids and enzymes such as trypsin, normally present in the duodenum, which can reflux into the stomach and then the oesophagus (duodenogastro-oesophageal reflux (DGOR)).¹ Non-chemical stimuli such as mechanical distension of the oesophagus by the reflux bolus can also trigger symptoms, which are likely to include heartburn and regurgitation. Finally, demonstration of the role of reflux in the pathogenesis of symptoms is frequently a difficult issue. Although 24 hour pH monitoring in patients off therapy may provide some clues, the sensitivity of this technique is relatively poor in non-erosive GORD, and probably does not exceed 60–70% at best.¹⁰ With respect to pH monitoring, the problem is further complicated in patients who continue to report symptoms while receiving acid suppression; the classical threshold of acid exposure (that is, per cent time pH less than 4) may be too stringent for the detection of abnormalities when monitoring patients who continue to receive PPI therapy.¹¹ In fact, an oesophageal pH less than 4 cannot be considered a reliable marker for the detection of reflux episodes in a patient on PPI therapy or in those with spontaneously low gastric acidity, such as frequently fed infants.

Addition of the detection of bilirubin (used as a marker of DGOR) to pH monitoring has been shown to be useful in patients poorly responsive to a once daily dose of a standard PPI.¹² This method is however hampered by the special monitoring conditions required (liquid diet) and limited access to the technique in clinical practice. In summary, neither standard pH monitoring nor bilirubin monitoring can satisfactorily address the situation of the so-called “non-acid reflux”, especially in patients with persistent symptoms on PPI therapy.

What really is “non-acid reflux”? No definition is universally accepted and this terminology actually regroups a number of different conditions with no well defined corresponding clinical entities.¹³ New concepts have recently emerged with the development of a novel technology combining impedance and pH measurement. Impedance is a

parameter which describes resistance to the flow of an electric current between adjacent pairs of electrodes mounted on an oesophageal catheter; when adjacent electrodes are linked by a liquid bolus, conductivity is high and therefore impedance is low. In contrast, when electrodes are separated by gas, such as during a belch, conductivity is low and impedance increases. In recent years several groups have applied this technique to the detection of reflux episodes in both normal volunteers and reflux patients.¹⁴⁻¹⁶ These studies have provided convincing evidence that impedance-pH monitoring can accurately detect and characterise nearly all reflux episodes. Following this technical progress, a tentative classification of non-acid reflux has been proposed by a panel of experts.¹⁷ According to this technology based description system, the term non-acid reflux includes both “weakly acidic reflux” (reflux events that result in an oesophageal pH between 4 and 7, or 6.5 in reference to physiological neutrality) and “weakly alkaline reflux” (reflux detected by a change in impedance level but with pH remaining above the oesophageal value of 7 or 6.5).

In this issue of *Gut*, Mainie and colleagues¹⁸ report on the clinical application of impedance-pH monitoring to patients with symptoms that persist despite acid suppressive therapy (*see page 1398*). This large series of 168 patients was recruited on the basis of therapeutic failure after at least one month of a twice daily PPI regimen. Interestingly, persistent symptoms were categorised as typical (heartburn, regurgitation, or chest pain) or atypical (for example, cough, hoarseness, abdominal discomfort). The primary endpoint of the study was the symptom index (SI), defined as the number of symptoms associated with reflux episodes divided by the total number of symptomatic events. Symptom association probability (SAP) was also determined according to previously described methodology.⁸ Surprisingly, the time windows used to determine whether or not a symptom was reflux related differed for SI (reflux within five minutes prior to symptom occurrence) and SAP (two minute segments with and without reflux). The most original aspect of the work, for which the authors should be complimented, relies on the fact that impedance-pH was monitored in patients on therapy. This experimental design allowed more appropriate analysis of the mechanisms of symptoms occurring during the average 20 hour recording period. As expected,¹¹ very few patients (11%) continued to have abnormal acid exposure while receiving a PPI twice daily and only 17% of the reflux

episodes detected by impedance were acid reflux (with pH below 4). In contrast, more than 80% of reflux episodes were non-acid, as defined previously, the majority of which (90%) being categorised as weakly acidic and rarely, weakly alkaline (10%). It is of note that of the 144 patients who reported symptoms during the monitoring period, nearly half had a negative SI, suggesting a mechanism other than reflux in the pathogenesis of their symptoms. For those with a positive SI, non-acid reflux was the predominant mechanism underlying residual symptoms. Finally, typical GORD symptoms in patients on PPI therapy were more likely to be associated with a positive SI (primarily non-acid) compared with atypical symptoms which were more frequently associated with the absence of reflux.

The results of the study by Mainie and colleagues¹⁸ are consistent with other studies which have already assessed the additional yield of oesophageal impedance monitoring in patients on and off therapy.¹⁴⁻¹⁹⁻²⁰ It has been confirmed that standard 24 hour pH monitoring alone is of limited value in understanding the mechanism of PPI resistance as the large majority of these patients have normal or even low acid exposure values while receiving PPI therapy.¹¹ It is of note that Mainie and colleagues¹⁸ used especially low thresholds to define abnormal acid exposure times in PPI receiving patients. While the addition of impedance to pH monitoring seems of relatively limited clinical value in patients not receiving therapy,¹⁹⁻²⁰ the diagnostic yield of the combined measurement seems to be substantially improved in treated patients.¹⁸⁻¹⁹ The role of weakly acidic reflux episodes in symptom pathogenesis has now been established beyond doubt, both in typical (for example, regurgitation on therapy) and atypical GORD; for example, an association with chronic cough has now been reported in patients either off²¹ or on therapy.¹⁹ However, as for pH monitoring alone, controversies remain regarding the best method of expression of the strength of association between symptoms and reflux episodes; this issue seems particularly relevant as the aim is to best predict therapeutic response to acid suppression.²² It is indeed again surprising to see that the correlation between the SAP and SI results in the Mainie and colleagues study¹⁸ was so poor, a result that is however consistent with our own experiences.¹⁹

The choice of SI rather than SAP, as well as the time window for symptom analysis (two or five minutes) remains largely based on personal and arbitrary

choices; this may be an area of research that deserves further attention. Standardisation of both the technique and parameters and validation of software required for reducing the analysis time are first necessary to further increase clinical application. Finally, the exact role of pH-impedance monitoring will depend on its diagnostic relevance and ability to influence the management of GORD patients, particularly those with predominant extra-oesophageal symptoms. Data from Mainie and colleagues¹⁸ and other groups concerning the outcome of surgery in PPI resistant patients that are carefully selected on the basis of objective impedance-pH analysis is eagerly awaited. Application of this recent technology will be particularly relevant to the pharmacological assessment of new drugs aimed at reduction of transient lower oesophageal relaxations, such as GABA-b agonists and glutamate ligands.^{23–25}

In conclusion, at its present stage of development, impedance-pH monitoring represents a useful tool for studies and clinical research in oesophageal disorders. It is probably too early for it to be considered as ready for routine clinical application but recent studies hold promise, particularly for the group of patients dissatisfied with their anti-reflux treatment. Further studies should more directly measure the impact of results on patient management.

Gut 2006;**55**:1379–1381.

doi: 10.1136/gut.2006.098806

Correspondence to: Professor J P Galmiche, Institut des Maladies de l'Appareil Digestif, University Hospital Hôtel-Dieu, 44093 Nantes, France; jeanpaul.galmiche@chu-nantes.fr

Conflict of interest: None declared.

REFERENCES

- 1 Vaezi MF, Singh S, Richter JE. Role of acid and duodenogastric reflux in esophageal mucosal injury: a review of animal and human studies. *Gastroenterology* 1995;**108**:1897–907.
- 2 Chiba N, De Gara CJ, Wilkinson JM, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology* 1997;**112**:1798–810.
- 3 Fass R, Shapiro M, Dekel R, et al. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease—where next? *Aliment Pharmacol Ther* 2005;**22**:79–94.
- 4 Shi G, Bruley des Varannes S, Scarpignato C, et al. Reflux related symptoms in patients with normal oesophageal exposure to acid. *Gut* 1995;**37**:457–64.
- 5 Trimble KC, Pryde A, Heading RC. Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD. *Gut* 1995;**37**:7–12.
- 6 Watson RGP, Tham TCK, Johnston BT, et al. Double blind cross-over placebo controlled study of omeprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux—the 'sensitive oesophagus'. *Gut* 1997;**40**:587–90.
- 7 Wiener GJ, Richter JE, Copper JB, et al. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. *Am J Gastroenterol* 1988;**83**:358–61.
- 8 Weusten BL, Roelofs JM, Akkermans LM, et al. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology* 1994;**107**:1741–5.
- 9 Bredenoord AJ, Weusten BL, Smout AJ. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. *Gut* 2005;**54**:1810–17.
- 10 Kahrlas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. *Gastroenterology* 1996;**110**:1982–96.
- 11 Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. *Am J Gastroenterol* 2005;**100**:283–9.
- 12 Tack J, Koek G, Demedts I, et al. Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: acid reflux, bile reflux, or both? *Am J Gastroenterol* 2004;**99**:981–8.
- 13 Sifrim D. Acid, weakly acidic and non-acid gastroesophageal reflux: differences, prevalence and clinical relevance. *Eur J Gastroenterol Hepatol* 2004;**16**:823–30.
- 14 Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology* 2001;**120**:1599–606.
- 15 Zerbib F, Bruley des Varannes S, Roman S, et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. *Aliment Pharmacol Ther* 2005;**22**:1011–21.
- 16 Shay S, Tutuian R, Sifrim D, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. *Am J Gastroenterol* 2004;**99**:1037–43.
- 17 Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut* 2004;**53**:1024–31.
- 18 Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. *Gut* 2006;**55**:1398–402.
- 19 Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD. A study in patients off and on therapy. *Am J Gastroenterol* 2006 (in press).
- 20 Bredenoord AJ, Weusten BL, Timmer R, et al. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. *Am J Gastroenterol* 2006;**101**:453–9.
- 21 Sifrim D, Dupont L, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. *Gut* 2005;**54**:449–54.
- 22 Taghavi SA, Ghasedi M, Saberi-Firooz M, et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. *Gut* 2005;**54**:1067–71.
- 23 Koek GH, Sifrim D, Lerut T, et al. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. *Gut* 2003;**52**:1397–402.
- 24 Vela MF, Tutuian R, Katz PO, et al. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. *Aliment Pharmacol Ther* 2003;**17**:243–51.
- 25 Frisby CL, Mattsson JP, Jensen JM, et al. Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate receptor ligands. *Gastroenterology* 2005;**129**:995–1004.

Neurogastroenterology

Hypnosis for non-cardiac chest pain

O S Palsson, W E Whitehead

Hypnosis may be an effective treatment for patients with non-cardiac chest pain that has not responded to acid inhibition

Non-cardiac chest pain (NCCP) is a condition defined by recurrent episodes of substernal chest pain suggestive of coronary artery disease in patients in whom no cardiac cause can be found after a comprehensive evaluation.¹ It is aetiologically heterogeneous,

and the cause in individual patients often remains unclear even after thorough investigation. Patients with NCCP are frequently not reassured by negative investigations and are persistent in their pursuit of further medical evaluations for possible cardiovascular disease. The

consequent impairment in personal and occupational functioning and subjective well being can be substantial. A recent estimate places the annual cost of health care services provided in the USA to treat NCCP at 6.5 billion dollars.²

The most commonly identified cause of NCCP symptoms is gastro-oesophageal reflux disease. Consequently, a therapeutic trial of a proton pump inhibitor is often recommended to confirm the diagnosis and as the firstline treatment.^{3–5} However, a variety of other factors have been suggested as possible causes of NCCP in individual patients, including oesophageal dysmotility, visceral hyperalgesia, musculoskeletal problems, and psychological factors, such as anxiety and somatisation.⁵ When