Ambulatory oesophageal pH-metry

Position paper of the Working Team on Oesophageal pH-metry by the GISMAD (Gruppo Italiano di Studio sulla Motilità dell'Apparato Digerente)

F. Pace
V. Annese[1]
P. Ceccatelli[2]
L. Fei[3]

In the last three decades, oesophageal pH monitoring has progressed from a physiological research tool to a routine outpatient clinical investigation in patients with suspected gastro-oesophageal reflux disease, one of the most common gastrointestinal disorders. Technological progress has considerably simplified both the procedure and the interpretation of data obtained, and there is currently reasonable consensus as to the parameters that best discriminate between physiological and pathological reflux. There remains a need for internationally agreed definitions and standards with regard to indexes to quantitate the extent and the significance of the relationship between occurrence of symptoms and reflux episodes during the examination. It is felt that national or local normal values are to be used to circumvent different eating habits and other socio-cultural differences which may influence gastro-oesophageal reflux. The reproducibility of the test appears, at present, to be at least good enough to allow classification of the patient as a pathological or physiological refluxer, albeit wide day-to-day variations seem to exist as far as concerns the extent of gastro-oesophageal reflux. Clinical applications of the technique have increased with better knowledge of the protean clinical manifestations of gastro-oesophageal reflux disease, and include the evaluation of "typical" gastro-oesophageal reflux disease patients with negative endoscopy or refractory oesophagitis, the "atypical" manifestations of gastro-oesophageal reflux disease and the pre- and post-operative evaluation of patients undergoing antireflux surgery.

From:
Gastroenterology Department, "L. Sacco" Hospital, Milan; [1] Gastroenterology Department, "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo; [2] Gastroenterology Unit, "San Donato" Hospital, Arezzo; [3] Chair of Digestive Surgery, Second University of Naples, Naples, Italy.

Address for correspondence:
Dr. F. Pace, Ospedale Polo Universitario "L. Sacco", Via G.B. Grassi 74, 20157 Milano, Italy. Fax: +39-02-35799232. E-mail: pace_spm@spm.it

Submitted January 14, 2000. Revised February 25, 2000. Accepted March 14, 2000.

Digest Liver Dis 2000;32:357-64

Key words: gastro-oesophageal reflux disease; oesophageal pH-metry

Introduction

Gastro-oesophageal reflux disease (GORD) is a fairly frequent ailment in which the exposure of the oesophagus to the gastric content may provoke symptoms and/or damage to the oesophageal mucosa which are, at times, very serious [1]. The occasional short-term presence of acid in the oesophageal lumen is considered a physiological event; when this phenomenon, however, increases in terms of frequency, quantity and duration, a picture of pathological gastro-oesophageal reflux presents.

A clinical diagnosis based on the typical symptoms such as heartburn and acid regurgitation is not always sufficient, and further instrumental investigations are necessary for diagnostic confirmation, especially in patients with atypical symptoms [2].
If one also considers that the diagnostic yield of a radiological examination, even if carried out perfectly, is very limited and that at least 50% of patients with GORD do not show oesophagitis at endoscopy [3], it is obvious that an instrumental method able to objectively measure reflux is necessary.
Tuttle and Grossman were the first to use a glass electrode capable of measuring oesophageal pH in order to demonstrate a correlation between oesophagitis and acid reflux [4]; subsequently, the same Authors confirmed that retrosternal heartburn, the most typical symptom of GORD, was present when the pH of the lower third of the oesophagus fell below 4.0 units [5].
Even if Spencer was the first to describe a technique suitable for oesophageal pH monitoring using a glass electrode [6], the pioneer study by De Meester and Johnson [7] contributed above all towards making prolonged oesophageal pH monitoring the most valid technique in the diagnosis of GORD.
The widespread diffusion of this method began at the end of the '70's and since then it has been used more and more frequently, and is now considered a routine out-patient examination. Technological improvements have simplified both the procedure and interpretation of data and, nowadays, there is reasonable consensus concerning the parameters which better distinguish between physiological and pathological gastro-oesophageal reflux. Ambulatory oesophageal 24-h pH-metry is currently the most popular method for the evaluation of patients with suspected GORD, since not only does it represent the most physiological test, but also has the greatest sensitivity and specificity [8].

Technical aspects of ambulatory oesophageal pH-metry

The instrumentation is based on the simple principle of recording pH as an electrochemical measurement; the development of advanced technology, with more and more sophisticated miniaturization of measurement systems, offers the possibility of performing the test in almost physiological, ambulatory conditions which are well accepted by the patients.
One or two electrodes are connected to a solid state memory portable recorder, capable of storing a remarkable amount of data in 24 hours, which are then passed by interface to a computer and processed by means of specific software [9].

pH measurement

Modern methods are based on the electrochemical pH measuring concept, that is the generation of an electric cell where the potential difference produced is proportional to the concentration of hydrogen ions [10]: the electric cell is capable of acting as a pH sensor.
The electrode does not measure the pH directly, but rather an electromotor force determined by the presence of an electrochemical potential in the test solution, with which it interferes. A potential difference (membrane potential) is established between a glass electrode and the solution, which depends on the pH of the solution, and this pH value can be obtained by means of the so-called modified Nerst equation [11 12]; in fact, using glass electrodes, it is calculated that one unit of pH is equivalent to 62 mV of potential difference [13].
Here, it should be recalled that pH represents the negative logarithm in base 10 of hydrogenionic activity; thus, by definition, a neutral solution has a pH of 7.0 units, since the hydrogenionic concentration in pure water is 10^{-7} mol/l; higher concentrations are acid and have a pH less than 7.0 units. A change in one pH unit brings about a ten-fold variation in the hydrogenionic concentration. Furthermore, since the pH scale is logarithmic, the hydrogenionic concentration changes much more when passing from pH 1.0 to pH 2.0 (10^{-1} to 10^{-2} mol/l) than when passing from pH 6.0 to 7.0 (10^{-6} to 10^{-7} mol/l).

Types of electrodes
Many types of electrodes are currently available for the monitoring of oesophageal pH: glass, antimony, radiotelemetric capsules, and ISFET type electrodes, although those most used in clinical practice are either glass or antimony [14 15]. The ideal characteristics of an electrode are good stability, quick response time, sensitivity, reduced calibre, disposable or easily sterilized and low cost [12 16 17].
Glass electrodes are made up of an outside glass covering with a low fusion point and a high electrical conductivity, which depends on the silver sheath covered with silver chloride; a potential difference is produced by means of a circuit achieved with the addition of a reference electrode, generally mercury chloride. The comparison electrode may be internal (combined electrode) or external, or cutaneous (unipolar electrode); the latter, however, may be responsible for interference, due to the fluctuation of skin pH or problems arising from the contact of the electrode with the skin [12]. Glass electrodes are certainly the most valid for measuring the pH of body fluids [18]: they have an almost linear response to pH variations in the range of 1

to 12 units of pH with a nominal error of ±0.05 pH units and a response time in vitro of less than one second for pH variations from 1.0 to 7.0 units [17]. These electrodes are very resistent and have a long life, and indeed, if they are used properly, at least 30-40 examinations can be carried out with them equal to an average life of approximately 800 hours; they can be easily sterilized, although repeated disinfection may make them more rigid and, therefore, less well tolerated by the patient. Glass electrodes with an internal reference are available with an outer diameter of 2.5-3.0 mm, but they are relatively expensive.

"Unipolar" single-crystal antimony electrodes are of the metal/oxide type and, therefore, need a skin reference electrode; "bipolar" antimony electrodes have internal reference and are available in both single- and multi-use forms. Unlike glass electrodes, they are based on the formation of a corrosion potential which determines a limited duration, less than 10 examinations (approximately 140 hours of life) [19]. Response to pH variations is not always linear (hysteresis phenomenon) and requires a few seconds to react when the pH varies from 1.0 to 7.0 or vice versa [17].

The advantages of antimony electrodes are, basically, the smaller diameter (approximately 2 mm), the greater flexibility and the lower cost; their miniaturization also allows the use of probes with more pH sensors without loss of flexibility.

Several studies have shown that, in terms of response times and sensitivity, antimony electrodes are less reliable than glass [17]; however, considering all the characteristics of these two types of electrodes, either can be used for routine clinical oesophageal pH monitoring [7 16].

Also proposed for pH measuring, but no longer used, were radiotelemetry capsule-shaped glass electrodes which are swallowed and fixed with a nylon thread to the cheek. These probes are technically unsuitable, causing problems such as loss of signals and interference with external electromagnetic fields [20].

ISFET (Ion Sensitive Field Effect Transistor) type electrodes comprise a transistor which is sensitive to ionic changes: they have a linear response with a response time of less than 2 seconds for pH variations between 1 and 12. These electrodes have been miniaturized, the dimensions now being similar to those of glass or antimony electrodes. They do not require external (cutaneous) reference and allow recording of pH at more than one site with the same probe. These characteristics are compatible with those of an ideal electrode and, for this reason, may well be the electrodes of the future [21-24].

Recording equipment

The first extended recordings of oesophageal pH were carried out with tracings on paper; these were, therefore, fixed instruments which required hospitalization and walking was limited to the area around the bed.

Today, solid-state memory, portable recorders are available, which directly convert the analogue signal into digital form, allowing computerized management and analysis of the tracing. The recorder contains a voltmeter which through intermittent sampling, measures the electromotive force (EMF) of each electrode. The signal is amplified and transferred to a computer by an analogue-digital interface and software prepared ad hoc transforms the E-potential of the cell into pH values, which are then fed into the RAM memory of the computer. One very useful characteristic of portable digital recorders is the presence of event-markers, enabling specific events, such as retrosternal pain or heartburn, to be recorded directly by the subject during the examination.

Present-day portable recorders are small in size and weight and work off disposable batteries; it is mandatory that the equipment allows a recording of 24 hours at the recommended sample frequency. It is also important that the equipment is supplied with a safety system which ensures that acquired data are not lost in the event the batteries unexpectedly run out and/or after completion of the examination.

Sampling frequency

Sampling frequency, or the number of readings made in a time unit, can usually be programmed in most measuring systems.

The optimal sampling frequency of a signal, which may vary in time, should allow even the briefest pH acid oscillation to be recorded with accuracy.

Sampling every 4-8 seconds (15-8 Hz) can be considered optimal; according to Emde et al. [12], 8 samplings per minute are sufficient for clinical non-research purposes, without significantly reducing the accuracy of the recording.

Methods used in oesophageal pH monitoring

Calibration of the electrodes

Before starting an oesophageal pH monitoring test, the electrodes should be calibrated in vitro. Physiologically, oesophageal pH is close to neutral (pH 7), but during an acid reflux episode it may decrease to values ranging between 1.0 and 2.0 pH units; thus, the system should be calibrated with a solution of pH 1.0 and 7.0, respectively, and at body temperature (37°C), to cover the whole pH scale [25]; some equip-

ment, however, allows automatic correction for the difference between room and body temperature. As pH-metric determinations are carried out over a prolonged period of time, it is also important to check the stability of the system during the 24 hours. The difference between the respective reading values at pH 1.0 and 7.0, before and after the examinations, is called the drift of the calibration; the drift should be contained at 0.3 pH units within 24 hours.
It is also important to determine the stability in time of the electrodes and the recording system. This test can be carried out in vitro leaving the electrodes immersed at a constant temperature in the same buffer solution used for the calibration. This stability check should be carried out at least every 10-15 clinical examinations: the appearance of pH oscillations, of adulterations and significant drift in time, means that the electrodes being used should be eliminated and the working state of the recorder and/or connection systems evaluated.
Calibration should be carried out with the use of reference buffer solutions appropriate for the electrode used. Depending on the type of recorder used, this should be followed by the codification of the patient's data and the time the examination began.

Positioning of the electrode
The pH-metric probe is introduced nasogastrically (the rhinopharynx can be anaesthetized by means of a xylocaine spray) and fixed so that the tip is placed approximately 5 cm above the proximal end of the lower oesophageal sphincter (LOS) [26]. If a cutaneous electrode is being used, this should be positioned on a flat area of the chest once the skin has been well cleansed to ensure good contact: this is particularly important because poor adherence of the cutaneous electrode may cause incorrect measurement of the pH.
Methods of localizing the LOS vary: the use of manometry for this purpose is now accepted as a gold standard, although alternative methods have been reported in the literature [27-31], including pH-metric determination at the gastro-oesophageal inversion point, or that employing fluoroscopy, considering a position of one and a half vertebra above the diaphragm as ideal. Some pH-metry devices also offer automatic evaluation of the position of the LOS using of a solid-state pressure transducer combined with an antimony electrode [32]. Recently, the use of a thin nasogastric probe bearing a latex balloon at its end has been proposed: once the balloon is inflated, the probe is retracted until it meets resistance and thus the distance from the nostrils can be recorded [28].
Dual pH-metry, i.e., the simultaneous recording of pH in the distal oesophagus as well as in the proximal oesophagus or in the hypopharynx has been proposed as a useful tool for the detection of GOR-associated asthma or "reflux laryngitis". However, since correct positioning of the proximal probe and normal values remain to be standardized, "dual" pH-metry should, at present, be regarded as a research tool [29].

Patient preparation and instruction
The patient should always be informed concerning the type of procedure to be used and should sign the necessary consent form. The examination should preferably be carried out in the morning, with the patient having fasted for at least four hours, in order to avoid not only possible vomiting episodes upon introduction of the probe, but also the buffer effect caused by food on gastric secretion.
Prokinetic and antiacid drugs should be suspended 48 hours before the examination, whereas H_2-receptor antagonists and proton pump inhibitors which have a more lasting effect, should be suspended at least 4 and 7 days earlier, respectively. In order to make the examinations as physiological as possible, the patient is allowed to continue his/her normal activity and diet. Some Authors prefer to standardize the procedure, giving a non-acid diet to increase the reproducibility of the test [33]; in normal routine clinical use this approach is not necessary.
It is important that the patient keeps a diary noting mealtimes, night time rest and the appearance of symptoms for an accurate analysis of the data.
Once the probe is in place and the system started, the patient may return home.

Length of the examination
Whilst some studies have shown satisfactory sensitivity and specificty for tests carried out for 3 hours in the post-prandial period or 8 hours including a meal, better diagnostic accuracy is obtained by prolonging the investigation to 22±2 hours. Prolonging the time enables a better evaluation to be made of the correlation symptoms/reflux episodes.

Analysis and reporting of oesophageal pH-metry

Software
Most of the softwares commercially available allow complete evaluation and visualization of oesophageal pH-metry data. However, it is necessary to make sure that the software is suitable to the characteristics of the hardware (computer and printer). The software should be as flexible as possible, and, in particular, it should allow modifications in the sampling frequency, the possibility of indifferently using glass or anti-

mony electrodes and, possibly, the insertion of normal parameters for each Centre.

All the currently used softwares supply a large amount of numerical data in the analysis, some of which are of uncertain significance. It is recommended that the analysis print-out include:

- complete pH/time tracing, possibly with visualisation of the event markers and periods such as meals or supine position;
- evaluation of the percentage of pH<4 during total recording time, periods of upright and supine position, respectively;
- optionals, usually supplied with most softwares, for additional parameters such as total number of refluxes, number of refluxes lasting >5 minutes, longer reflux episodes, area with pH <4, and others.

It is useful if the programme offers the possibility of excluding certain periods of the tracing from the analysis (periods with artefacts) and to analyse others separately (e.g., post-prandial period, administration of a drug). The software should also allow the definition of the minimum duration of the reflux episodes under consideration. With this in mind, it is suggested that reflux episodes lasting <15 seconds should be excluded following, as previously mentioned, a sampling of 8-15 Hz.

Each pH-metry should have at least one event marker for symptoms. Where only one event marker is present, the patient should be recommended to use it for only one symptom, the main one (e.g., heartburn or retrosternal pain). Where no marker is present for position or meals, or if the patient is suspected of not being very accurate, a simple diary should be compiled, synchronizing the patient's hours with that of the data-logger, with requests such as: beginning and end of meal times, time at beginning and end of lying down, possible time taking at which drugs are taken, time at which symptoms appear. Some software implements the calculation of the relationship between symptoms and reflux episodes. Discussion continues in the literature as to which is the optimal "time window", or rather, the length of the period which should be analysed in relation to the symptom in order to consider it correlated to the reflux episode (intervals from 2 to 10 minutes have been suggested) [34]; a good compromise is probably to consider an interval of 5 minutes (two and a half minutes before and two and a half minutes after the appearance of the symptom).

The "symptom index" [35] is calculated according to the formula: No. of symptoms coinciding with reflux/total No. of symptoms x 100. A value of ≥50% is considered indicative of a good correlation. Another useful index for clinical purposes is the "symptom specificity index" [36] which represents the relationship between the No. of reflux episodes coinciding with symptoms/No. of reflux episodes x 100). In this case, values of ≥10% would be positive. Both indexes could be evaluated, even though they suffer from the limitation of having an arbitrary cut-off and of not being validated extensively. It is recommended, however, that they be evaluated especially in patients with normal reflux parameters and the presence of atypical symptoms. At present, none of these parameters, including the new ones such as the binomial formula [37] and the "symptom association probability" [38] have a clear clinical application.

Data analysis

It has already been pointed out that the optimal length of the examination is 22±2 hours [39]. As far as normal values are concerned, when the normal parameters from a single Centre are lacking (obtained with at least 20 normal subjects), it is suggested that normal values obtained through a multicentre study by GISMAD in Italy be used [40]. It should be stressed that the parameter giving the most diagnostic accuracy is the percentage of pH <4 [41]. As previously stated, a reflux episode may be defined as such if it lasts more than 15 seconds, and if pH drops below 4, independently of the duration and the final value of pH observed. In the GISMAD study, the upper normal limits (95%) were 4.8% of total period with pH <4. Use of the "De Meester score" is not recommended, since it is based upon a population different from ours, and taken from a very limited sample numerically, and, moreover, it has not yet been validated.

The labelling of periods with pH >7 as alkaline reflux and the inclusion of such a parameter in the report is not recommended. In fact, investigations carried out with three pH electrodes (oesophagus, fundus and antrum) or with simultaneous bilimetry [42-44] (a spectrophotometric method for the qualitative and semiquantitative assessment of biliary derivatives in the gastric juice or oesophageal fluid) have failed to detect any correlation between the presence of biliary reflux and pH >7. Where the suspicion of duodeno-gastro-oesophageal reflux exists (real reflux with alkaline components), pH-metry should be carried out with simultaneous bilimetry.

Realizing that reflux events may be the cause of atypical symptoms, in particular chest pain, regardless of the overall acid exposure, several schemes have been devised to analyse ambulatory pH data in conjunction with symptoms indicated by the patient with the event marker. As recalled above, there is at present no consensus as to what the optimal "temporal window" might be in the relationship symptoms-reflux event; the commonly used temporal window lies between ±

2 and ± 10 minutes from the onset of the symptom signalled by the patient [45]. The consistency and the significance of the relationship between symptom(s) and reflux events may be quantitatively assessed by different indexes, as reported in the previous paragraph, such as "the symptom sensitivity index", the "symptom specificity index" or the "symptom association probability".

After the procedure, the patient and the physician should be given an analytical report which includes:

- pH/time tracing;
- numerical values of the main parameters analysed with, alongside, the normal values;
- brief description of the methodology and possible limitations of the examination (total length, if less than 24 hours, possible therapy, type of electrode, etc.);
- brief diagnostic conclusions.

Reproducibility

Considerable day-to-day variations in oesophageal acid exposure are known to occur both in healthy volunteers and in patients with GERD [46]. However, despite this finding, several studies examining within-subject variability of pH monitoring results have indicated reasonable reproducibility for the diagnosis of GERD (i.e., classification of a result as normal or abnormal) [47]. As might be expected, the probability of inconsistent diagnoses with a repeat test is greater in patients with borderline results [48]. There is no convincing evidence that standardization of monitoring conditions enhances reproducibility [49] and it is interesting to note that inclusion in the monitoring period of the entire 24-h interval has been shown to increase the reproducibility of oesophageal pH metry [50].

Indications for oesophageal pH-metry

This Working Team considers that the five main indications for oesophageal pH-metry are as follows:

1) the evaluation of patients with typical GORD symptoms (heartburn and regurgitation), but with negative endoscopic examination. The test should be carried out after any antisecretory therapy has been discontinued for a period of ≥7 days;
2) the evaluation of oesophageal acid exposure in patients with typical GORD symptoms and/or endoscopic oesophagitis who are refractory to therapy with proton pump inhibitors. In this case, the examination should preferably be carried out in association with gastric pH-metry and during the assumption of the drug;
3) the evaluation of patients with so-called "atypical" GORD symptoms, such as non-cardiac chest pain, ear, nose and throat (ENT) symptoms or signs of uncertain attribution (especially hoarseness, dysphonia, posterior laryngitis) and respiratory symptoms refractory to appropriate therapy (in particular non-allergic asthma in adult individuals and recurrent pneumonia in infants);
4) pre-operative evaluation of patients requiring antireflux surgery, after having discontinued any anti-reflux therapy for a period of 7 days;
5) post-operative evaluation of patients having undergone antireflux surgery where symptoms or a relapsing oesophagitis are present.

pH-metry safety

No serious side-effects have been described with regard to oesophageal pH-metry, even in infants or especially weak subjects. It is, however, necessary to request written informed consent for the examination. All the equipment currently available adopt a low working electric voltage (6-12 volts) and conform to ISO 9000 standards. In the near future, equipments will have to conform to CE and MDD standards. Whenever equipment has to be modified, for any reason whatever, or even when being set up in a single Centre, it is strongly recommended that these standards be checked.

Disinfection standards

When disposable electrodes are not being used, it is recommended that the catheter be cleaned immediately with organic residue detergent, and then be immersed in a disinfecting solution (e.g., Cidex) and subsequently rinsed. The catheter should be handled with care and strong rubbing avoided, especially those with glass electrodes, because capillary tears could be caused, making it unusable. The extremity of the glass electrodes should be allowed to become dry but should be kept inside a container bathed with the electrolytic fluid supplied by the manufacturer.

References

[1] Heading RC. Epidemiology of oesophageal reflux disease. Scand J Gastroenterol 1989;24(Suppl 168):33-7.

[2] Spechler SJ. Epidemiology and natural history of gastro-oesophageal reflux disease. Digestion 1982;51(Suppl.1):24-9.

[3] Castell DO. pH monitoring versus other tests for GERD. Is this gold standard? In: Richter JE, editor. Ambulatory oesophageal pH monitoring. Practical approach and clinical application. New York: Igaku Shoin; 1991. p. 101-13.

[4] Tuttle SG, Grossman MI. Detection of gastroesophageal reflux by simultaneous measurement of intraluminal pressure and pH. Proceedings of the Society of Experimental Biology and Medicine 1958;98:225-7.

[5] Tuttle SG, Bettarello A, Grossman MI. Gastroesophageal regurgitation. J Am Med Assoc 1961;176:498-500.

[6] Spencer J. Prolonged pH recording in the study of gastroesophageal reflux. Br J Surg 1969;56:9-12.

[7] Johnson LF, De Meester TF. Twenty-four hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 1974;62:325-32.

[8] Mattox HF, Richter JE. Prolonged ambulatory esophageal pH monitoring in the evaluation of GERD. Am J Med 1990;89:345-56.

[9] Fuchs KH, De Meester TR, Albertucci M. Specificity and sensitivity of objective diagnosis of gastroesophageal reflux disease. Surgery 1987;102:575-9.

[10] Fimmel CJ, Etienne A, Cilluffo T, Ritter C, Gasser T, Rey J-P, et al. Long term ambulatory gastric pH monitoring: validation of a new method and effect of H_2 antagonists. Gastroenterology 1985;88:1842-51.

[10] De Meester TR, Johnson LF, Joseph GJ. Patterns of gastroesophageal reflux in health and disease. Ann Surg 1976;184:459-70.

[11] Emde C. Electrochemical aspects of pH electrodes. Dig Dis 1990;8(Suppl 1):18-22.

[12] Emde C, Garner A, Blum AL. Technical aspects of intraluminal pH-metry in man: current status and recommendations. Gut 1987;28:1177-88.

[13] Rovelstad RH, Owen CA, Magrath TB. Factors influencing the continuous recording of in situ pH of gastroduodenal contents. Gastroenterology 1988;83:629-35.

[14] Mela GS, Savarino V, Moretti M, Sumberaz A, Bonifacino G, Zentilin P, et al. Antimony and glass pH electrodes can be used interchangeably in 24-hour studies of gastric acidity. Dig Dis Sci 1990;35:1473-81.

[15] Savarino V, Mela GS, Scalabrini P, Magnolia MR, Percario G, Di Timoteo E, et al. 24-hour comparison between pH values of continuous intraluminal recording and simultaneous gastric aspiration. Scand J Gastroenterol 1987;22:135-40.

[16] Galmiche JP, Scarpignato C. Esophageal pH monitoring. Functional evaluation in esophageal disease. Front Gastrointest Res 1994;22:71-108.

[17] McLauchlan G, Rawlings JM, Lucas ML, Mc Cloy RF, Grean GP, McColl KEL. Electrodes for 24 hour pH monitoring: a comparative study. Gut 1991;32:240-5.

[18] De Caestecker JS, Heading RC. Esophageal pH monitoring. Gastroenterol Clin North Am 1990;19:645-69.

[19] Ask P, Edwall J, Johanson KE. Accuracy and choice of procedures in 24-hour oesophageal pH monitoring with monocrystalline antimony electrodes. Med Biol Eng Comput 1986;24:602-8.

[20] Branicki FJ, Evans DJ, Ogilvie AL, Atkinson M, Hardcastle JD. Ambulatory monitoring of oesophageal pH in reflux oesophagitis using a portable radiotelemetry system. Gut 1982;23:992-8.

[21] Rawlings JM, Lucas ML. Plastic electrodes for measurement of gastrointestinal pH. Gut 1985;26:203-8.

[22] Schepel SJ, Rooij NF, Koning G. In vivo experiments with a pH ISFET electrode. Med Biol Eng Comput 1984;22:6-24.

[23] Duroux PH, Emde C, Bauerfeind P, Francis C, Grisel A, Thybaud L, et al. The ion sensitive field effect transistor (ISFET) pH electrode: a new sensor for long term ambulatory pH monitoring. Gut 1991;32:240-5.

[24] Weusten BL, Akkermans LM, vanBerge-Henegouwen GP, Smout AJ. Spatiotemporal characteristics of physiological gastroesophageal reflux. Am J Physiol 1994;266:G357-62.

[25] Mela GS, Savarino V. Measuring acid gastroesophageal reflux. Dig Dis Sci 1990;35:282-3.

[26] Anggiansah A, Sumboonnanonda K, Wang J, Linsell J, Hale P, Owen WJ. Significantly reduced acid detection at 10 centimeters compared to 5 centimeters above lower esophageal sphincter in patients with acid reflux. Am J Gastroenterol 1993;88:842-6.

[27] Klauser AG, Heinrich C, Schindlbeck NF, Muller-Lissner SA. Is long term esophageal pH monitoring of clinical value? Am J Gastroenterol 1989;84:362-8.

[28] Anggiansah A, Bright N, McCullagh M. Alternative method of positioning pH probe for oesophageal pH monitoring. Gut 1992;33:111-4.

[29] Wo JM, Hunter JG, Waring JP. Dual-channel ambulatory esophageal pH monitoring. A useful tool? Dig Dis Sci 1997;42:2222-6.

[30] Klauser AG, Schindlbeck NE, Müller-Lissner SA. Esophageal 24-hour pH monitoring: is prior manometry necessary for correct positioning of the electrode? Am J Gastroenterol 1990;85:1463-7.

[31] Mattox HE, Richter JE, Sinclair JW, Price JE, Case LD. Gastroesophageal pH step-up inaccurately locates proximal border of lower esophageal sphincter. Dig Dis Sci 1992;37:1185-91.

[32] Singh S, Price JE, Richter JE. The LES locator: accurate placement of an electrode for 24-hour pH measurement with a combined solid-state pressure transducer. Am J Gastroenterol 1992;87:967-70.

[33] Fink S, McCallum RW. The role of prolonged oesophageal pH monitoring in the diagnosis of gastroesophageal reflux. J Am Med Assoc 1984;252:1160-7.

[34] Weusten BLAM, Smout AJ. Symptom analysis in 24-hour esophageal pH monitoring. In: Richter JE, editor. Ambulatory esophageal pH monitoring. Baltimore: Williams & Wilkins; 1997. p. 97-105.

[35] Ward BW, Wu WC, Richter JE, Lui KW, Castell DO. Ambulatory 24-hour esophageal pH monitoring. Technoloy searching for a clinical application. J Clin Gastroenterol 1986;8:59-67.

[36] Breumelhof R, Smout AJ. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. Am J Gastroenterol 1991;86:160-4.

[37] Ghillebert G, Janssens J,Vantrappen G, Nevens F, Piessens J. Ambulatory 24-hour intra-esophageal pH and pressure recordings vs provocation tests in the diagnosis of chest pain of esophageal origin. Gut 1990;31:738-44.

[38] Weusten BLAM, Roelofs JMM, Akkermans LMA, Van Berge-Henegouwen GP, Smout AJ. The symptom association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology 1994;107:1741-5.

[39] Schan CA. What are the optimal length and setting for esophageal pH testing? In: Richter JE, editor. Ambulatory esophageal pH monitoring. Baltimore: Williams & Wilkins; 1997. p. 49-55.

[40] Baldi F, Ferrarini F, Longanesi AM, Bersani G & GISMAD. Ambulatory 24-hour oesophageal pH-monitoring in normal subjects: a multicenter study in Italy. Ital J Gastroenterol 1991;23:447-80.

[41] Bremmer RM, DeMeester TR, Stein JH. Ambulatory 24-hour esophageal pH monitoring-What is abnormal ? In: Richter JE, editor. Ambulatory esophageal pH monitoring. Baltimore: Williams & Wilkins; 1997. p. 77-96.

[42] Mattioli S, PilottiV, Felice V. Ambulatory 24-hour pH monitoring of the esophagus, fundus and antrum. Dig Dis Sci 1990;35:929-38.

[43] Bechi P, Paucciani F, Baldini F, Cosi F, Falciai R, Mazzauti R, et al. Long-term ambulatory enterogastric reflux monitoring: validation of a new fiberoptic technique. Dig Dis Sci 1993;38:1297-306.

[44] Vaezi MF, Richter JE. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. Gastroenterology 1996;111:1192-9.

[45] Kahrilas PJ, Quigley EMM. Clinical esophageal pH recording: a technical review for practice guideline development. Gastroenterology 1996;110:1982-96.

[46] Weiner GJ, Morgan TM, Copper JB. Ambulatory 24-h pH monitoring: reproducibility and variability of pH parameters. Dig Dis Sci 1988;33:1138-41.

[47] Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA, et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity and reproducibility. Am J Gastroenterol 1992;87:1102-11.

[48] Murphy DW, Yuan Y, Castell DO. Does the intraesophageal probe accurately detect acid reflux? Simultaneous recording with two pH probes in humans. Dig Dis Sci 1980;34:649-56.

[49] Trimble KC, Douglas S, Heading RC. Twenty-four esophageal pH monitoring: technique and application. The Gastroenterologist 1995;3:187-98.

[50] Johnsson F, Joelsson B. Reproducibilty of ambulatory oesophageal pH monitoring. Gut 1988;29:886-9.