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A pH-mucosa area unit of measure to consider morphology of the oesophagus when evaluating oesophagitis

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Abstract

Gastro-oesophageal pH measurements are routinely carried out to quantify and determine if levels of acid reflux are responsible for symptoms. Although considered the ‘gold standard’, evidence suggests that pH measurements do not correlate well with the degree of oesophagitis seen during endoscopy. In this study the current measure of pH was critically examined taking into account both the effects of changes in luminal diameter and endoscopy observations. The oesophageal lumen diameter was investigated using a barium swallow for 25 patients presenting with oesophageal disorders. For each subject the widest luminal diameter was measured for a series of five controlled swallows. The results showed that the lumen diameter varied widely from 0.9 to 3.8 cm. An alternative approach to the current measurement of pH was explored. In this approach the exposure not only included the luminal pH and time exposed but also the area of mucosa exposed as a result of differing luminal diameters. Although it is currently not possible to assess the diameter or morphology of the oesophageal lumen during a pH study, the analysis highlighted that the current measure of pH exposure time does not include the area of mucosa exposed. These results may explain, to some extent, the poor correlation between pH measurements and degree of oesophagitis seen during endoscopy.

Keywords: oesophagus, lumen, reflux, GORD, pH, acid, exposure units

1. Introduction

Ambulatory 24 h pH examinations are frequently used to investigate the levels of gastro-oesophageal acid reflux (British Society of Gastroenterology 1996, Stendal 1997). However, as with many gastro-oesophageal measurements, interpretation of the data represents a major challenge (Haylett *et al* 1998) and there is still some debate as to the interpretation and value of these results (Kahrilas and Quigley 1996). A recent review of the diagnostic evaluation techniques in the detection and evaluation of gastro-oesophageal reflux disease (GORD) (Younes and Johnson 1999) highlighted the following problems: (a) 25% of patients with proven oesophagitis at endoscopy have 24 h ambulatory pH data within the 'normal' range; (b) there is an overlap between patients with symptomatic reflux and controls with no oesophagitis; (c) there is controversy regarding reproducibility of 24 h pH monitoring; (d) data analysis still presents many problems. Despite these difficulties 24 h ambulatory pH monitoring is regarded as the 'gold standard' for determining the exposure of the oesophagus to abnormal amounts of acid in GORD (Hampton *et al* 1992) and for investigating the relationship between these events and reported symptoms.

Although reflux oesophagitis is considered a multifactorial disease, it is not clear which factors determine the severity of mucosal damage in GORD (Castell 1993, Richter 1999). Avidan and co-workers examined the relationship between acid reflux and severity of oesophageal mucosa injury (Avidan *et al* 2002b). Their study of 644 outpatients with symptomatic GORD revealed either no or only a weak correlation between parameters measured by 24 h pH monitoring and grade of erosive oesophagitis. One of the strongest influences on oesophageal injury has been found to be the presence of a hiatus hernia (Jones *et al* 2001, Avidan *et al* 2001, 2002a).

Figure 1 shows an example of a 24 h ambulatory oesophageal pH study. The principal features extracted from ambulatory pH measurements are reflux episodes with the pH value measured generally described as 'acid exposure'. Reflux episodes are typically defined as the periods when the pH at the sensor falls below 4. From these reflux episodes, features such as the number of episodes and the total percentage exposure time are calculated, see table 1. Alternative features have also been used including area under the curve with pH less than 4 (Dinelli *et al* 1999) and area under the hydrogen ion activity curve (Rebecchi *et al* 2002). These features are used to give a measure of acid exposure within the lumen. However, none of these features takes into account the dimensions of the lumen geometry, i.e. lumen diameter, distension of the lumen, volume of acid or mucosal folding.

The aim of this study was to measure the maximum diameter of the oesophagus in the distal region of the oesophagus during a series of 5 ml swallows of barium. The results were then considered with reference to the measurement of the intraoesophageal pH.

2. Materials and methods

The maximum diameter of the lumen in the distal region of the oesophagus was measured during routine fluoromanometry (combined manometry and barium swallow). The fluoromanometry system, developed at the Manchester Royal Infirmary, permitted a consecutive frame by frame review of the barium swallow and measurement of lumen diameter (Haylett *et al* 1997). The results of 25 patients (14 females and 11 males, aged between 20 and 71, with a mean age of 49 years, median = 53, SD = 14), with symptoms indicating an oesophageal disorder, were scrutinized with particular reference to the maximal width of the distal lumen.

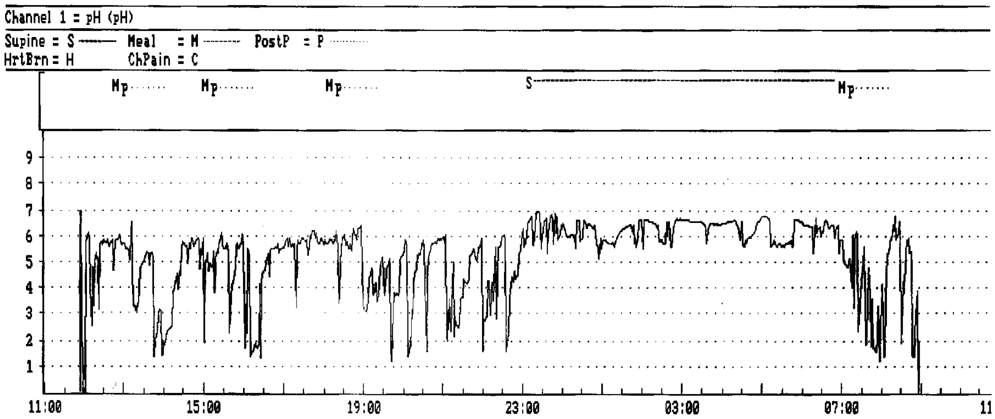


Figure 1. An example of a 24 h oesophageal pH recording.

Table 1. Examples of features extracted from 24 h ambulatory oesophageal pH recording.

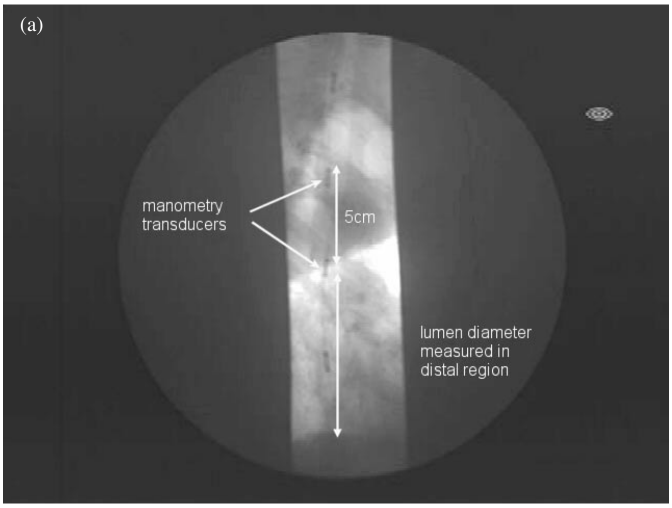
Features
Percentage time of upright reflux
Number of upright reflux episodes > 12 s
Number of upright reflux episodes > 5 min
Percentage time of supine reflux
Number of supine reflux episodes > 12 s
Number of supine reflux episodes > 5 min

Each patient underwent five controlled swallows, the minimum required for an accurate assessment of motility (Devault *et al* 1987), of 5 ml E-Z-HD barium sulphate (E-Z-M Inc., USA), mixed to a standard dilution of 98% w/w. The swallows were carried out in the erect position, at intervals of greater than 30 s, allowing the swallow reflex to recover. More rapid swallows may inhibit primary peristalsis and be misinterpreted as an abnormality (Ask and Tibbling 1980). The maximum diameter in the distal region was measured, i.e. the widest region of barium below the third manometry pressure transducer (see figure 2(a)). This is the region where oesophagitis is commonly seen during endoscopy. The diameter was measured for each swallow using a screen-based digital ruler. This digital ruler was calibrated using the distance between the manometry sensors (5 cm). It is of note that the radiology shows a single plane and the measurement should be regarded as an estimate as the lumen may be elliptical or deformed. In addition, to determine if the success of the swallow affected the lumen diameter, each swallow was classified as *successful* where all the barium was removed from the oesophagus at the end of the swallow, or *failed* where there was residual barium at the end of the swallow. The mean and standard deviations were computed and the difference in luminal diameter was compared between successful and failed swallows using the standard two-tailed Student t test.

3. Results

3.1. Oesophageal diameter

The results showed marked differences in the morphology of the distal oesophagus with the maximum distal lumen diameter during a swallow varying from 0.9 to 3.8 cm (see table 2).



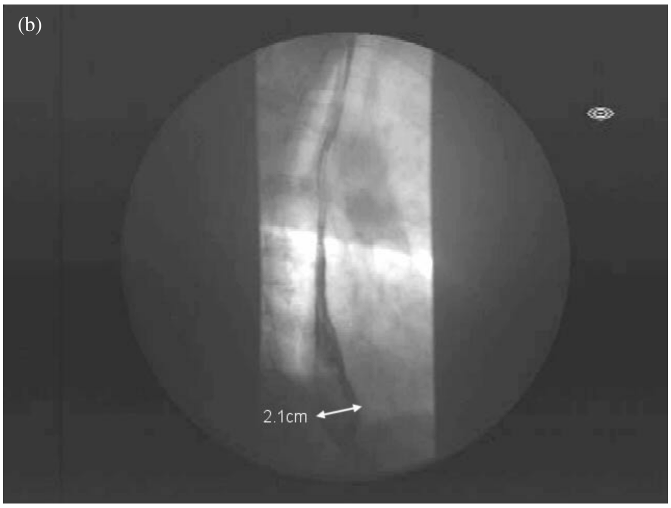


Figure 2. Distal oesophageal morphology during swallowing. (a) Catheter and manometry transducers used for calibration of digital ruler. (b) Normal swallow. (c) Failed swallow with highly dilated lumen. (d) Successful swallow with little evidence of dilation.

No significant difference (Student t, $p > 0.05$) in maximum width was observed between the *successful* or *failed* swallows (see table 2).

Figure 2 shows three examples of different morphologies observed. Figure 2(b) shows a normal swallow where the barium is being cleared from the distal oesophagus by the peristaltic wave. The lumen can be seen to be squeezed closed at both the lower oesophageal sphincter and proximally to the barium column which has a maximum diameter of 2.1 cm. Figure 2(c) shows an oesophagus that is widely distended (diameter 3.8 cm) as a result of failure of peristalsis and failure of the lower oesophageal sphincter (LOS) to open and allow passage of the barium. In this case the patient was diagnosed as having achalasia. Figure 2(d) shows an unusual example of an abnormal swallow, where the patient's oesophagus appeared

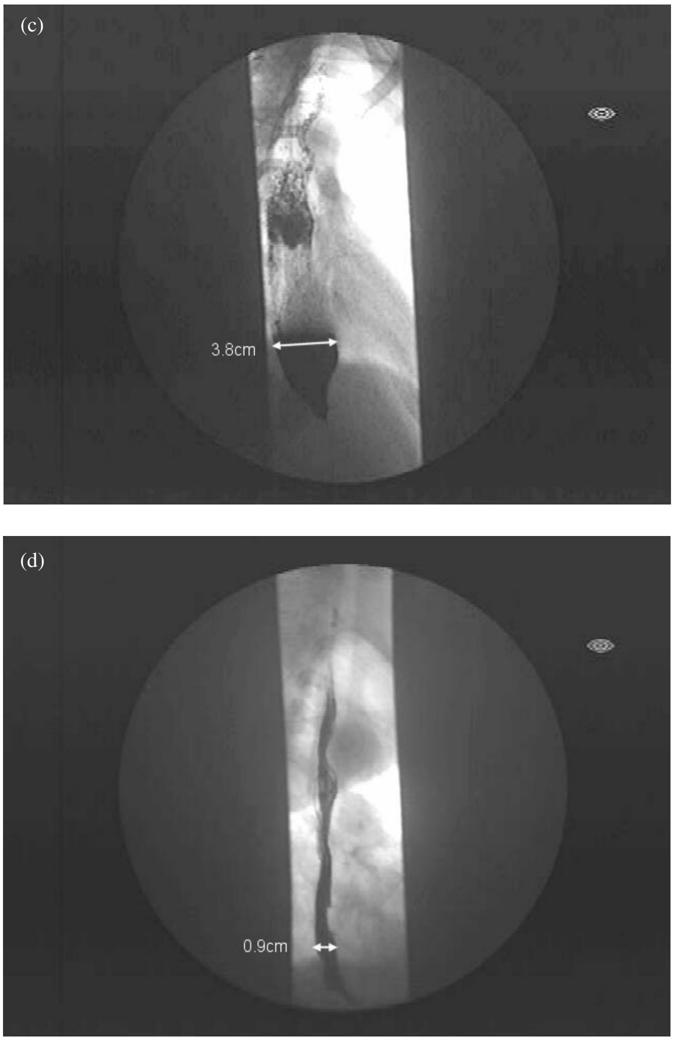


Figure 2. (Continued.)

inelastic. Despite this narrow oesophageal lumen diameter of only 0.9 cm the barium was cleared successfully.

3.2. Calculation of exposure units

The pH level measured at the probe (typically 5 cm above the LOS) is usually described as ‘acid exposure’. Typically, analysing this measurement involves calculating the percentage of time during the investigation that this value falls below pH 4, with the patient in the upright or supine position. These values, together with the total percentage time of reflux and duration of longest episode, are recorded and compared with reference values. However, these values take no account of the dimensions of the lumen geometry, i.e. lumen diameter, distension of the lumen, volume of acid or mucosal folding. The lumen can, however, vary in diameter from a few millimetres with the lumen fully collapsed around the pH sensor, to several centimetres

Table 2. Maximum distal width.

Maximum distal lumen width (cm)	Successful swallows (80)	Failed swallows (42)	
Mean[a]	1.66 ± 0.35	1.69 ± 0.57	No significant difference
Maximum	2.6	3.8	
Minimum	0.9	1.0	

[a] Error shown at 1 standard deviation.

where the lumen and the mucosa are fully distended. These changes are dynamic and rapidly changing as a result of swallows and the content of the oesophagus. Figures 2(b)–(d) show examples of how the lumen can have different morphologies during a swallow. Figures 2(b) and 3 show examples where, as the peristaltic wave approached the LOS, the lumen was seen to balloon, with the maximum distension proximal to the LOS with the lumen still closed (and likely to still have folds) at the most distal oesophagus. It is of note that the effects of folding are often seen in oesophagitis during endoscopy as linear patterns of erosion, or erythma. Endoscopic examples of oesophagitis are illustrated in figures 4(b), (c) and compared with a normal oesophagus (figure 4(a)). In addition these vertical folds, typically five or six, can be seen during double contrast radiology studies (Stiennon 1995).

Ideally, analyses of reflux should take into account simultaneously both the pH and the area exposed. Using both these parameters allows a new unit of exposure, relating pH value to the area exposed at that pH, to be defined. Ideally the measure should scale to both an increase in acidity and the area of mucosa exposed. As an increase in acidity is measured by a reduction in pH, using the inverse of pH (pH^{-1}) allows the unit to scale proportionally with both the pH and area of mucosa exposed (*AE*), i.e. increasing acidity (lowering pH) and increasing area exposed will increase the exposure as measured in exposure units (*EU*s), where

$$EU = \mathrm{pH}^{-1} \times AE\ (\mathrm{cm}^2).$$

The exposure as measured in *EU*s ($\mathrm{cm}^2\ \mathrm{pH}^{-1}$) is likely to be a complex function depending on the mechanical properties of the mucosa, the morphology of the lumen walls and the dynamics of the oesophagus. Parameters that may affect exposure include lumen diameter (or bore); oesophageal wall thickness and elasticity; mucosal folding; mucosal thickness and homogeneity; effects of mucosal alkaline secretions including buffering and positive secretion pressure (these secretions may fill the folds thus ensuring there is no dead volume for any acid to fill); viscosity of the acid reflux; surface tension; volume of oesophageal content and the overall swallow efficiency.

Figure 3 shows that the lumen width can vary widely at different distances from the LOS. Using the defined unit of exposure (*EU*) the differing acid exposure at the mucosa can be estimated in the two extremes. Assuming that the same pH level (pH = 4) is measured by a cylindrical sensor 0.5 cm in length and 0.3 cm diameter (area of a cylinder wall $= \pi dl$, where d = diameter and l = length of cylinder) with the lumen collapsed, i.e. equal to the diameter of the catheter, the total exposure in the collapsed state would be

$$= \mathrm{pH}^{-1} \times AE = \tfrac{1}{4}(0.5\,\mathrm{cm} \times \pi(0.3\,\mathrm{cm})) = 0.12 EU$$

whereas with the lumen dilated, for example 3 cm, the exposure at the mucosa would be

$$= \mathrm{pH}^{-1} \times AE = \tfrac{1}{4}(0.5\,\mathrm{cm} \times \pi(3.0\,\mathrm{cm})) = 1.2 EU.$$

The dimensions of the pH transducer here are only given as an example and would be dependent on the manufacturer and type of pH sensor used.

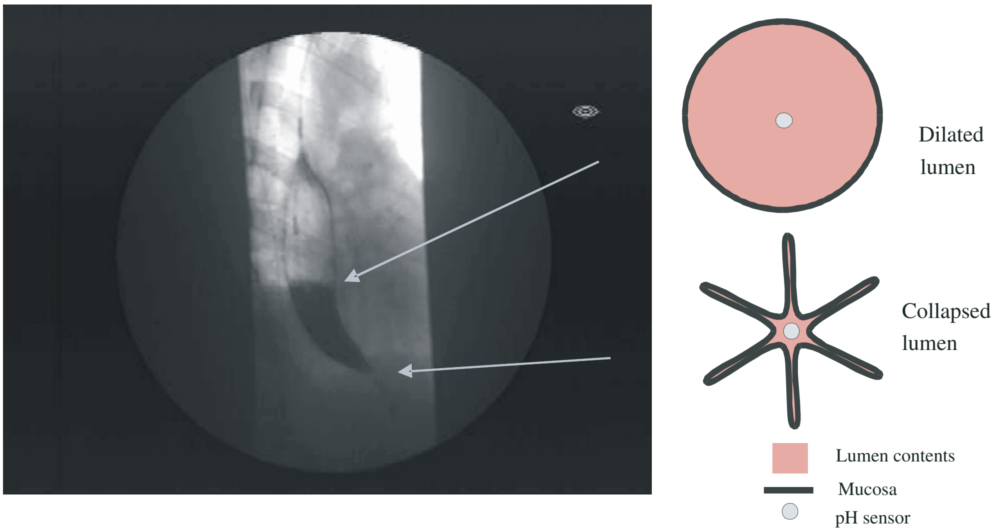
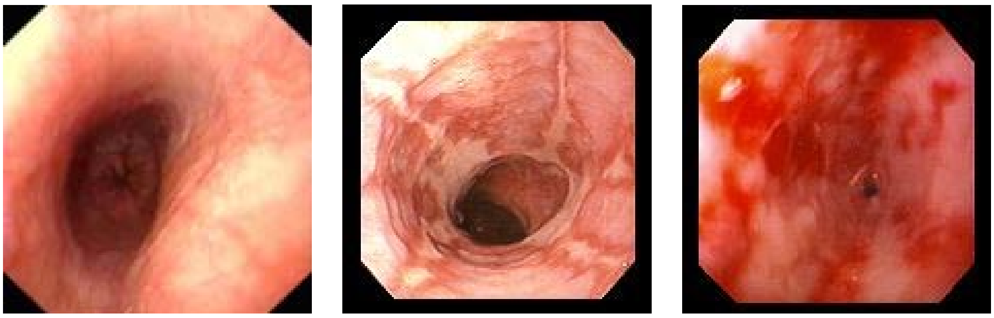


Figure 3. Mucosal morphology. Demonstration of different morphologies of the mucosal wall. Where the oesophagus is dilated, the folds are removed. If the lumen is stretched the oesophageal wall thickness will be reduced. Where the wall is collapsed, the mucosa forms folds, the lumen cross section is reduced and there may be regions that the luminal acid cannot reach. Acid may also be removed by the collapse of the mucosal wall on itself thus squeezing any remaining acid from the folds.



(a) (b) (c)

Figure 4. Lumen folds and oesophagitis. An endoscopic view of (a) normal oesophagus and examples of oesophagitis (b) and (c) with linear longitudinal erosion associated with folding of the mucosa (Martin and Lyons 2002).

In practice, we may be interested in either acid exposure (EU_{acid}) for pH values below 7 or alkali exposure (EU_{alk}) for pH values above 7. Alternatively exposure above or below a predetermined pH level such as 4 ($EU_{<4}$), as is currently the case, could also be used.

The EU described here is an instantaneous value. Measurement of the total acid exposure (EU_{acid}) for a period of investigation involves computing the area under the EU curve for any period of interest to give the total exposure, i.e.

$$\text{Total acid exposure } (\text{cm}^2\,\text{pH}^{-1}) = \int_{t=T_1}^{t=T_2} EU_{\text{acid}}\,\mathrm{d}t.$$

Where a modern pH recorder takes a series of n regular samples at a fixed frequency with period t_s and the area exposed (AE) is known at each sample time, the above formula can be evaluated as the sum of the instantaneous values multiplied by the sample period t_s, i.e.

$$\text{Total acid exposure } (\text{cm}^2\ \text{pH}^{-1}) = \sum_{1}^{n} \frac{AE \times t_s}{\text{pH}}.$$

Rebecchi and co-workers have suggested that hydrogen ion activity (AH^+) represents 'true acid exposure' (Rebecchi *et al* 2002). Their results show that the area under the AH^+ curve, where $\text{AH}^+ = 1000 \times 10^{-\text{pH}}$ mmol l^{-1}, is more sensitive at discriminating negative or positive patient with or without oesophagitis than previous measures. Treating this measurement in a similar manner to the *EU* and including the area exposed gives an alternative measure of total acid exposure EU_{AH^+}, i.e.

$$\text{Total acid exposure } (\text{cm}^2\ \text{pH}^+) = \int_{t=T_1}^{t=T_2} EU_{\text{AH}^+}\, \text{d}t.$$

3.3. Practical problems

In practice, mucosal exposure can only be estimated for the length of the lumen monitored by the pH transducer and then only if the lumen diameter is known. With the highly dynamic nature of the oesophagus, any final exposure is a function of the instantaneous diameter and morphology of the lumen during the pH study and also the volume of reflux within the lumen, i.e. for a given volume of reflux the vertical height exposed will depend on the cross section area of the lumen and the volume of reflux.

Lower grades of oesophagitis present as linear lines of erosion suggesting that the lumen is collapsed during any reflux, while higher grades of oesophagitis present wider areas of erythma and erosions suggesting that the lumen is open. Relating any measured pH to the area exposed would require knowledge of the area exposed, i.e. we need to be able to monitor the instantaneous lumen morphology. It is therefore unlikely that it is possible to calculate this value accurately using the present measurement techniques as these do not give us any clues to the state of the lumen during a pH study. However, it may be possible to estimate the maximum exposure at the level of the transducer by combining the measurement of pH and maximum diameter of the lumen seen during fluoroscopy.

The estimations of EU given as examples assume uniform exposure at the level of the transducer. The evidence from oesophagitis and pathological studies shows that the exposure is non-uniform and localized as a result of the formation of folds (Vieth *et al* 2001). With differing regions at the same level having different exposures, a local measure of exposure is required. This would require the EU to be expressed in terms of a unit area. In practice, the area chosen should reflect the minimum area of interest, for example, pH^{-1} per mm^2. However, with only a single transducer located in the centre of the lumen it is unlikely to be possible to estimate these local exposure levels.

4. Discussion

During a standard 24 h ambulatory pH investigation the degree of oesophageal distension at the pH sensor is unknown. However, the results of this study show that the lumen diameter can vary widely from 0.9 to 3.8 cm (mean 1.67). Evidence for oesophageal mucosal folding resulting from a collapsed or a narrow lumen diameter is seen both during radiology and endoscopy and from the linear areas of erthyma and erosion in oesophagitis (see figure 4). In addition, these areas of erythma at the tips of the folds have been recently validated as being indicative of acid/peptic mucosal injury with correlated histomorphological changes

Table 3. Possible effects of oesophageal morphology, which may modify the true lumen exposure and effect of acid reflux.

Open and distended oesophagus
No mucosal folding
Extended acid exposure, proportional to radius
Reduction in wall thickness resulting from stretching
Reduced effect of mucosal secretions
Collapsed oesophagus
Mucosal folding
Mucosal wall at maximum thickness
Minimum acid exposure
Increased effect of mucosal secretions

(Vieth *et al* 2001). Both mucosal folding and changes in the morphology and mechanical properties of the oesophageal wall may alter the area of mucosa exposed to luminal acid content. This is also supported by evidence of a variable pH 'micro environment' where quite different pH values have been recorded from two electrodes positioned at the same height (Murphy *et al* 1989). If this is the case, this suggests that the present measurement of luminal pH may not reflect the area of mucosa exposed to acid. Twenty four hour ambulatory pH measurements may therefore give only an approximation of lumen acid to mucosa contact and be the reason why there is a poor correlation with acid exposure as presently measured and oesophagitis (Younes and Johnson 1999).

Although the success of a swallow may primarily depend on the quality of peristalsis, it may also be dependent on oesophageal flexibility and the ability of the lumen to close completely. If the lumen closes completely the clearance is more likely to be complete, however, where the lumen fails to close or stay closed a volume of fluid will remain in the lumen (Kahrilas *et al* 1988). The final distribution of any residue will be a function of lumen irregularities. The situation is made more complex in the oesophagus where the dynamics between muscle wall, mucosa and oesophageal content may be difficult to establish. However, in considering acid exposure of the oesophagus in relationship to content and morphology it may be useful to consider the following points:

- *Minimum exposure*. The minimum exposure with the wall in the collapsed state and no acid within the folds, i.e. the minimum exposure for a given pH where a film of acid coats the sensor.
- *Full exposure*. The maximum exposure that will occur if the folds are all open and the mucosa is completely in contact with acid.
- *Extended exposure*. The exposure that will occur when the luminal volume is sufficient to cause the wall to distend, thereby reducing the mucosa thickness.

In this study a new exposure unit (*EU*) has been defined which takes into account both the pH and the area of mucosa exposed. By considering this measure and examining the effects of morphology it can be seen that for a given pH level, measured within the lumen, quite different physiological conditions may exist. Table 3 highlights possible effects relating to the difference in exposure between a collapsed and open lumen.

If these effects are significant, where distension and bolus hold-ups occur at the distal oesophagus, it may be possible to hypothesize the aetiology of the proximal progression of both oesophagitis and failure in motility. Where acid is not cleared, it can be seen that maximal exposure occurs at the widest part of the acid filled distal lumen (see figures 2(c) and 3). As the mucosa is eroded, peristalsis may be further impaired at this level in the oesophagus.

This damage may lead to an increase in distension, poorer efficiency of swallowing, greater volume and retention of reflux which in turn contributes to the height and effect of any acid reflux. An additional factor may be the change in lumen properties resulting directly from the oesophagitis, with recent studies showing that rigidity increases with oesophagitis (Utkin *et al* 1990). The following formula has been proposed to show how the number of mucosal folds depends on the lumen diameter (Stiennon 1995). This formula also shows that any pathological reduction in the elasticity or increase in the thickness of the mucosa will reduce the number of folds.

$$N_{\mathrm{f}} = \frac{\pi E(r-t)}{(-t/E) + \sqrt{2rt - t^2}}$$

where N_{f} is the number of folds, E is the mucosal elasticity, r is the lumen radius and t is the mucosal thickness before contraction (Stiennon 1995).

The importance of the effect of oesophageal morphology on mucosal exposure to acid can only be speculative at the present time. However, the earlier calculations give an order of difference in exposures that may occur within the oesophagus and recent results using neural networks have shown that different patient groups can be identified from the standard pH features (Haylett *et al* 2003b). The exclusion of luminal morphology along with other variables when considering pH measurements may account for the reported difficulties in correlating lumen pH with oesophagitis. The importance of changes in morphology on oesophageal damage is illustrated by the strongest influence on oesophageal injury found to be the presence of a hiatus hernia (Avidan *et al* 2001, 2002a, 2002b) which substantially changes the morphology of the distal oesophagus. In addition, evidence for a relationship between oesophageal morphology and oesophagitis has been presented by Chen and co-workers in a study examining the relationship between oesophageal calibre and oesophagitis. The results of their study showed that the oesophageal diameter is significantly wider in patients with oesophagitis (Chen *et al* 1999).

It is routine to carry out pH monitoring for the investigation of gastro-oesophageal reflux. This is partly due to the relative ease of the transnasal intubation which requires no anaesthetic. However, the simple analysis presented here, although from a theoretical standpoint, highlights many problems that have not been considered or addressed in the literature.

The analysis presented here challenges us to examine the issues regarding the measurement of exposure in more detail. It may be necessary to consider the development of new systems of measurements that enable us to measure or estimate the mucosal area exposed and any changes in lumen morphology. Recent suggestions have included: combining pH measurement with ultrasound; combining pH with real time endoscopy and investigating new designs of pH transducer (Haylett *et al* 2003a). By combining these modalities it may be possible to incorporate pH and measurement of luminal dimensions during an ambulatory investigation. Our current focus is on the development of a small bore fibrescope with an integrated pH sensor. With the advent of mini digital video recorders, it is now possible to record video in an ambulatory setting. Combining ambulatory endoscopy of the oesophageal lumen at the site of the pH transducer and using visual landmarks may enable the assessment of lumen dimensions and give us a better assessment of reflux. However, the development of these techniques presents many new challenges

The value of the analysis and the unit presented is that it highlights problems of the current measure of pH using only the value at the catheter. The analysis shows that the same reading at the pH transducer can give quite different levels of exposure at the mucosa. The current measures of pH exposure which are based on the time exposed and not the area exposed are therefore likely to be nonlinear. It is likely that these important points will require addressing before it is possible to understand the relationship between acid exposure and oesophagitis.

Our current clinical research involves looking more closely at the diameter observed during fluoroscopy and the measurements taken during pH studies while also looking at the relationship between these measurements, oesophageal symptoms and oesophagitis. For example, for a given volume of reflux, the orad migration of refluxed material would be greater for a narrow lumen compared to a wide lumen and hence may give rise to different symptoms. Although we do not currently have an instantaneous measure of the lumen diameter, it may be possible to combine the maximum diameter observed during fluoromanometry with the pH recording; this may give a better estimate of exposure than pH alone.

In conclusion, current measurements of acid exposure take no account of the area of mucosa exposed to luminal content. The results of this study show that the oesophageal luminal diameters vary widely during swallowing. In the author's opinion, these results, together with evidence of mucosal folding seen during endoscopy and radiology, suggest that variations in lumen morphology may need to be considered when investigating the relationship between measurements of acid reflux and oesophagitis. A new exposure unit (*EU*) has been introduced in this study taking into account the area of mucosa exposed. However, it is not possible to calculate *EU*s during 24 h pH studies without knowledge of the oesophageal morphology. It would seem likely that new methodologies and further research will be required to quantify and determine a direct relationship between oesophageal pH measurements and oesophagitis.

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