Functional analysis of oesophageal clearance from 24 hour ambulatory pH recordings comparing patients with Barrett's oesophagus and healthy controls

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Short title: **A functional model based analysis of oesophageal acid clearance**

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Abstract

Analysis of ambulatory oesophageal pH is problematic due to the complexity of the recorded signals. The investigation typically involves investigating the periods of time acidity falls below an empirically determined threshold. This study aimed to investigate differences in acidity clearance between patients with Barrett's oesophagus and a series of healthy controls using an analytical based model of clearance. For two groups, patients with confirmed Barrett's oesophagus and healthy controls, the periods of acid clearance were extracted from the pH signal curve. The extracted clearances were then averaged and then fitted to an exponential model. The parameters of the fitted models were then compared between the two groups. The results show that the decrease in acidity at the transducer during clearance phase of pH recordings can be accurately modelled by an exponential function as predicted by a formal model of clearance (regression coefficient R^2=0.99 for both healthy controls and patients with Barrett's oesophagus). Patients presenting with confirmed Barrett's oesophagus have a reduced clearance function when compared with healthy controls (P=0.03). This technique may offer an alternative to previous empirical non model based approaches to pH analysis and provide functional information regarding clearance in addition to acidity levels.

Ambulatory oesophageal pH measurements are used to assess the acidity levels in the oesophagus. Typically, a transducer is placed 5 cm above the proximal margin of the lower oesophageal sphincter and the acidity level recorded over a 24-96 hour period (Herbella *et al.* 2009; British Society of Gastroenterology, 1996). Although often cited as the 'gold standard' for determination of oesophageal reflux and diagnosis of gastro oesophageal reflux disease (GORD), analysis is problematic (Haylett *et al* 2003). Problems arise from both the physical nature of the test, the difficulties in analysis and the relationship between the results, symptoms and physiology under investigation (Haylett *et al* 2004). Following a brief review of these problems an analytical model based analysis was developed (Udani *et al* 2007) and used to compare a series of patients with confirmed Barrett's oesophagus and healthy controls. The approach taken focuses on the information derived from the pH curve that relates to the clearance of the acidic contents.

Problems relating to the nature of ambulatory oesophageal pH recordings

The problems regarding measurement and analysis of ambulatory oesophageal pH recordings are widely recognised (Haylett *et al* 2003). The current approach to analysis has been largely based on arbitrary reference points. For example, one of the most common techniques is to use an index based on periods of time the pH fall below 4 (Herbella *et al* 2009; Gerson *et al* 2008). The review of the diagnostic evaluation techniques in the detection and evaluation of gastro-oesophageal reflux disease (GORD) by 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 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. Recent analysis techniques have involved extracting parameters from the pH recordings and combining them with a symptom index (Maine *et al* 2006). However, the ambulatory pH investigation can not measure the volume of reflux and as we do not know whether the oesophagus is collapsed or open it is not possible to know the area of mucosa exposed (Haylett *et al* 2003). Avidan and co-workers 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 (Avidan et al 2002b). 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).

More recently the pH study has been accompanied by multi channel intra luminal impedance measurement which enables both acidic and non acidic content to be detected (Waśko-Czopnik et al 2007) and wireless based pH recording systems (Scarpulla *et al* 2007, Wenner *et al* 2007, Bhat *et al* 2006). However, with increasing information the analysis of these ambulatory studies becomes even more challenging. Although the the issues regarding analysis are yet to be resolved they are starting to be considered.

Symptoms may not always directly correlate with reflux events and at best we can only investigate the probability of symptoms associated with the pH measurements made. As a result a number of symptom correlation indices have been developed. It has been recently shown that a 96 hour study is required to confirm the relationship between symptoms and pH reflux events (Haylett *et al* 2004; Scarpulla *et al* 2006). Furthermore, clinical researchers have, surprisingly, looked at using area

under the pH curve as a measurement (Dinelli *et al* 999;Rebecchi *et al* 2002; Metz *et al* 2006), which for a positive signal and a fixed period of time is directly proportional to the signal mean and alone loses the signal variance and other valuable signal measures. These problems highlight the need to re-examine the pH signal to determine if any further information can be extracted for analysis and comparison between patients groups.

What clinical questions can the technique answer?

In practice ambulatory oesophageal pH investigations are used to investigate patients with symptoms that relate to the diagnosis of gastro-oesophageal reflux disease (GORD). Clinically GORD represents a major problem with the UK spending annually over £400 million on acid suppression medication. Patients present with a range of symptoms, typically heartburn and regurgitation. However, symptoms do not always correlate with the severity of the gastro-oesophageal reflux disease. A reliable test is needed to quantify the physiological processes associated with changes in oesophageal physiology and gastro-oesophageal reflux. Ambulatory pH measurements have enabled a representation of acid reflux to be observed but with considerable limitations.

Where possible the aim of such measurements is to identify normal and pathological disease states and categorise them. Typically the goal is to obtain a numerical parameter that can be used to enable a differential diagnosis. Is the swallowing system and reflux problematic and to what extent? This study aimed to analyse the signals measured during ambulatory oesophageal pH studies and determine if it is possible to obtain measurements based on physiologically meaningful information rather than an arbitrary reference level. The basis of the approach presented was to use an analytical model of oesophageal clearance and fit the recorded data to this model.

Analytical model

A simple exponential based model approach to analysis was developed based on the recently developed model shown in Figure 1 (Udani *et al* 2007). The simple model of GORD was developed to help understand the processes involved in GORD and to identify the principle measurements required to assess oesophageal function. In considering gastro-oesophageal reflux it is essential to consider the factors that effect oesophageal acid exposure at the mucosa i.e. the rate of generation and clearance of the reflux within the distal oesophagus and how the volume of reflux relates to the area of mucosa exposed (Haylett *et al* 2003). Ideally the rate of clearance should equal the reflux rate to ensure minimum exposure i.e.

Acid clearance rate (oesophagus to stomach) $$\mathbf{C} = \frac{dA_o}{dt} \qquad (1)$$

Acid reflux rate (stomach to oesophagus) $$\mathbf{R} = \frac{dA_g}{dt} \qquad (2)$$

Total acid exposure (ideal) $$A_{Tot} = \int_0^t (R - C)dt = 0 \qquad (3)$$

A_o = Volume of oesophageal acid, A_g = Volume of gastric acid, R and C can be expressed in L/Hour

The reflux rate R is a function of a wide range of physical parameters including amongst others: gastro-oesophageal barrier pressure (P_b), gastric pressure (P_g), intra-oesophageal pressure ($P_{o)}$, gastric elasticity (E_g), rate of gastric acid (A_p), rate of gastric acid removal (A_r), acid volume (A_v), number (n_t) and duration of transient lower oesophageal relaxations (T_r). These in turn are functions of parameters such as gastric emptying, which are in turn under hormonal and neural control.

The clearance rate C is a function of swallow efficiency (E_s) and number of swallows (n_s), where the efficiency is a function of the swallow mechanism and the gastric barrier pressure (P_b), gastric pressure (P_g), This is shown schematically in Figure 1. It is also of note that saliva is rich in bicarbonate and has the ability to buffer acid and so the rate of saliva production and its buffering capacity could be considered. However, there in no current evidence that salivary flow is impaired in patients with GORD (Kongara and Soffer, 1999) and therefore, for simplicity it is not considered here.

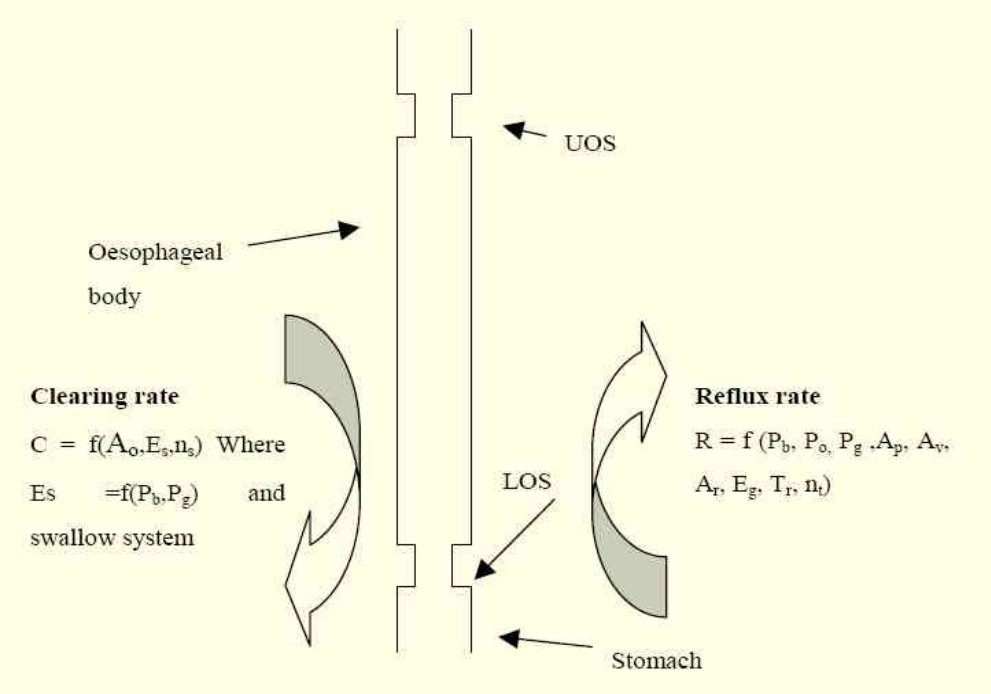

Figure 1 **Modelling GORD.** This schematic highlights the principle factors that effect the volume of acid in the oesophagus. C is the clearance rate and R is the reflux rate (See text for model parameters).

Swallowing efficiency

Swallowing efficiency is itself a function of a wide range of parameters. In addition the efficiency can be examined at different physical scales. At a *macro*scopic level we are looking to find out if oesophageal content has been cleared from the lumen of the oesophagus, where as at a *micro*scopic scale the interest is concerned with potentially damaging content being cleared from the mucosal wall. Although it is not clear how

the mucosa is damaged the evidence suggest that there is a microclimate within the oesophagus and this results in the pattern of damage occurring at the mucosa (Vieth *et al* 2001). Oesophageal folds have also been considered to play a part together with mucin production, i.e. when folded, mucin production will create a positive pressure which may clear any residual material from the folds of the mucosa (Haylett *et al* 2004).

This rate based compartmental model shown in Figure 1 (Udani *et al* 2007) develops the concept of swallow efficiency. This suggests that for a given swallowing efficiency the clearance rate would be a simple exponential function (Figure 2). This earlier work also highlighted that many parameters are unknown preventing us from calculating the volume of acid and therefore the true exposure to the lumen as detailed in Haylett *et al* 2003 i.e. the mucosal area exposed at a given acidity is currently not measurable.

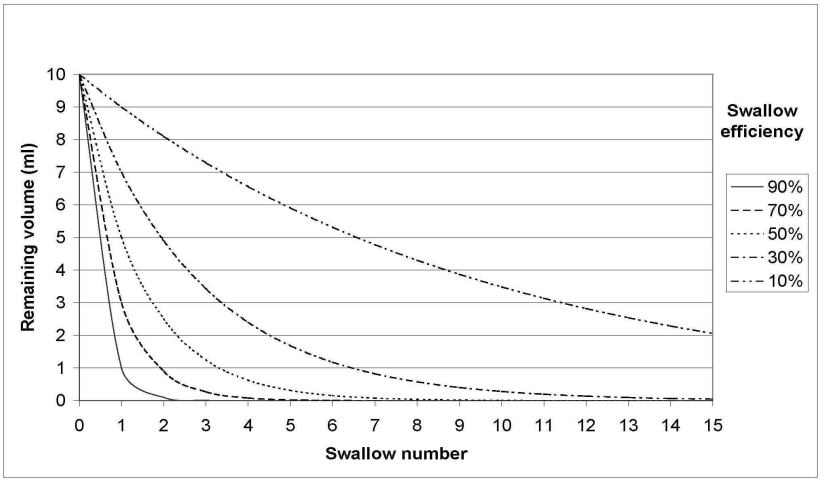

Figure 2. **Reducing swallow efficiency**. This figure shows how reducing swallow efficiency increases the number of swallows required to clear a 10ml bolus

Following an examination of ambulatory pH recordings it can be seen that after the initial reflux event an 'exponential type' increase in pH occurs at the transducer as the oesophagus is presumably cleared and the associated acidity is reduced (See figures 3 and 4). This suggests the decrease in acidity results from an exponential decrease in the proportions of acidic content at the transducer i.e. the increase in pH at the transducer results from the proportion of hydrogen ions detected being reduced in proportion to the volume of acid cleared.

In this work the ascents from the ambulatory oesophageal pH recording were extracted and then fitted by a curve to the basic exponential equation of the form $f(x) = a*exp(-b*x) + c$, where a, b and c are constants. The results of fitting the pH ascents (clearance) to this basic model were then compared between two study groups, namely patients with confirmed Barrett's oesophagus and healthy controls.

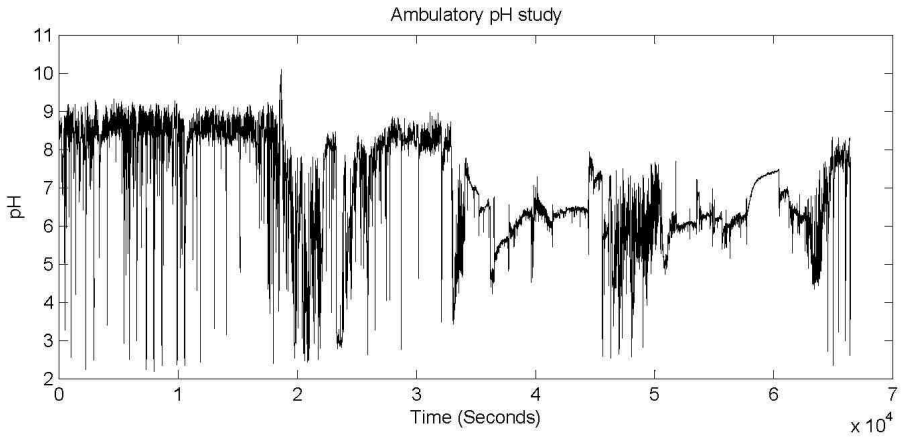

Figure 3. **Ambulatory oesophageal pH study**. This figure shows an example of an ambulatory oesophageal pH study showing the drops in pH associated with typical reflux events.

Methods

Clinical study

The analysis was carried out on a prospective study of controls and patients (Smythe *et al*, 2008) approved by the South Sheffield Research Ethics Committee (Reference number SS99/198) and written informed consent was obtained from each subject before the study commenced. Two groups of subjects were studied : 18 healthy controls (11 males and 7 females) mean age 26 years; range 19-45 years with no history of gastrointestinal disease and a group of 12 patients with Barrett's oesophagus (7 males and 5 females) mean age 58years; range 42 -69 years. Barrett's oesophagus was diagnosed at endoscopy, and histology confirmed intestinal metaplasia in the distal oesophagus. Exclusion criteria included high-grade dysplasia, malignancy, stricture, bleeding, ulcer and previous gastric surgery. The mean length of Barrett's was 5cm (range 3-9 cm). All patients were on long term gastric acid suppression proton pump inhibitor (PPI) therapy, (40mg daily Omeprazole).

Oesophageal ambulatory pH measurement

Oesophageal pH studies were carried out using an antimony pH tip electrode (Konigsberg, Pasadena, USA), placed at 5cm above the LOS. This was connected to a Flexilog 3000 pH/pressure recorder (Oakfield Instruments Ltd., Oxford, England) and the data collected with a 6 second sample rate using the Flexisoft software (Oakfield Instruments Ltd.). All subjects were studied on two occasions. Investigations were carried out on healthy controls without any medication and then repeated after being given 20mg of omeprazole twice daily for 2 days. The Barrett's patients were initially investigated whilst on PPI therapy, and the studies repeated after 5 days without medication.

Modelling and data analysis

For each pH recording continuous segments of increasing pH were extracted from the 24 hour recording. These segments were averaged and the resulting curve fitted to an exponential model of clearance at the transducer of the form f(t) = a*exp(-bt)+c (Figures 3 and 4). In this equation the constant c relates to the final value reached after the clearance. Whereas a relates to the initial value (the average pH drop prior to clearance) and b relates to the time constant of the exponential clearance function and efficiency of clearance swallows i.e.

Clearance *(pH) = pHi*exp(-CR*t) + pHf*

pHi= Initial, pHf = Final value, CR = Clearance Rate constant

The fitting procedure used standard least squares regression for an exponential model MATLAB© (Mathworks Ltd, Boston, USA). The model constants and confidence intervals were evaluated together with the standard goodness of fit statistics and correlation coefficient. These parameters were then statistically compared between the two groups. In addition, the usual signal statistics such as signal mean (directly proportional to the area under the curve for a non negative going signal) the median and standard deviation were also compared between the two groups. Figure 4 shows an example of the fitting process. Figure 6 shows an example of the quality of the fitting process. Statistical analyses involved using the Kolmogorov and Smirnov to test for normality and the parametric student t-test for comparison or means.

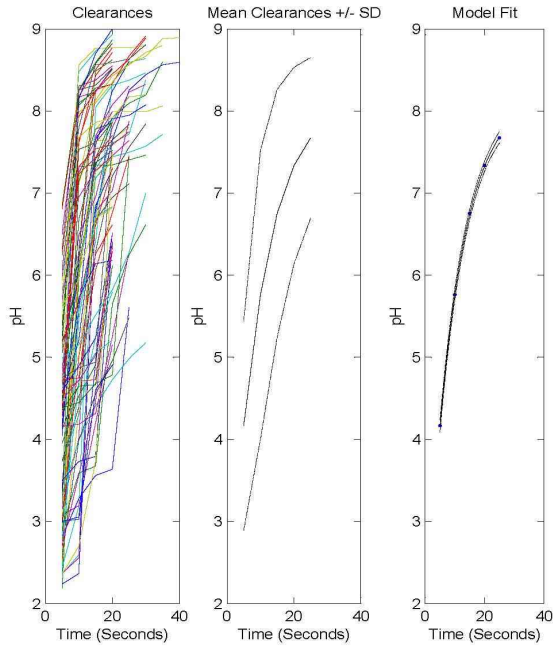

Figure 4a **Example of 24 hour ambulatory pH study Study.** This figure shows an example of a 24 hour ambulatory study carried out during the study. b) **Example of the fitting process.** Clearances are extracted then averaged and c) finally fitted to an exponential model.

Results

The parameters found for the study for the patients are shown in Table 1a together with the regression coefficient. The modelled reflux clearances for both healthy controls and patients with Barrett's Oesophagus had regression coefficients R^2 of 0.99 indicating a good fit to an exponential model. In total the final analysis included 19 investigations on healthy controls and 20 investigations on patients with confirmed Barrett's oesophagus. The analysis excluded corrupt data files, two investigations with only a single reflux event meeting the criteria and a further two studies where the model could not be fitted due to artifacts produced in the recordings.

Table 1a

	Mean coefficients of fitted model parameters and SD			
Group	**R^2**	**A +/-SD**	**B+/-SD**	**C +/-SD**
Controls	0.99	-5.86+/-1.29	0.118+/-0.04	7.07+/-0.90
Barrett's	0.99	-5.42+/-1.38	0.089+/-0.04	6.66+/-0.98
Significance (student-t)	0.47	0.31	0.034	0.180

Table 1b

	Basic signal statistics (+/- SD)			
Group	**mean pH**	**median pH**	**SD pH**	**Clearances**
Controls	6.99+/-0.46	7.2+/-0.46	1.02+/-0.27	32.4+/-19.39
Barrett's	6.11+/-1.52	6.4+/-1.64	1.31+/-0.44	43.4+/-27.46
Significance (student-t)	0.02	0.05	0.02	0.15

* Note: No difference were found in the above parameters between subjects on and off medication therefore were pooled for analysis

Results showed that there was no statistical difference between the parameters examined between the subjects on or off PPI medication following the Kolmogorov and Smirnov test for normality and an appropriate student t-test. The results were therefore pooled and compared between healthy controls and patients with Barrett's oesophagus. Statistically, a difference could be determined between the rate constant b for healthy control (0.118) and the patients with Barrett's oesophagus (0.089), p=0.03, student-t i.e. the patients with Barrett's oesophagus had a reduced rate of clearance (See Figure 5).

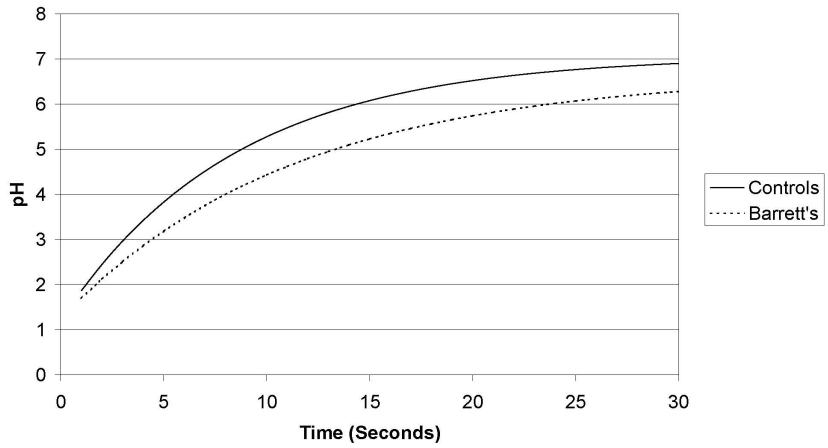

Figure 5. **Comparison of clearance between health controls and patients with Barrett's oesophagus.** Mean clearance function extracted from healthy controls and patients with Barrett's oesophagus.

In addition to the exponential model the basic signal mean and median pH were calculated and compared (Table 2). The results show both the mean and median pH for patients with Barrett's oesophagus was reduced when compared to healthy controls.

Table 2

Number of swallows	
Factors effecting efficiency	Mucosal flexibility and sealing
	Stiffness,
	Contractility,
	Secretions,
	Surface tensions
	Overall barrier pressure (effect of seal at LOS and Gastric pressure)
	Saliva
	Bolus constituency
	Others

Discussion

This work has used a model based approach to the analysis of ambulatory pH data. The technique utilises a simple model of clearance (Udani *et al* 2007) that describes an exponential based pH clearance function. For each study the pH clearances were extracted, averaged and then fitted to an exponential model. The results show that the data for both groups was a good fit exponential model (R2=0.99) . The results also showed a reduced clearance function for the patients with Barrett's oesophagus when compared with healthy controls (P=0.03, Table 1a).

Importantly, the approach taken and the values measured from the curve do not rely on arbitrary cut off values and makes no claims as to the actual exposure at the lumen or the volume of acid. The model, however, does relate to the physiology of the clearance and the overall clearance function i.e. to an extent it quantifies the efficiency of the swallowing system at clearing reflux from the oesophagus. The curve and rate of clearance is related to both number of swallows and the individual efficiency of each swallow. The measurement can not determine factors that make up the overall efficiency and the model shows that these are likely to be the results of a wide variety of parameters (see Table 2). However, it may be possible to use this approach to design a specific investigation to evaluate the clearance efficiency alone, e.g., by swallowing an acidic volume and then monitoring pH for a controlled number of regularly spaced swallows. The results could be used to compute the model and determine a specific value for swallow efficiency.

Although we can not calculate true mucosal exposure (Haylett *et al* 2003), it can be expected to increase with the number of reflux events, and decrease with the number of effective clearances. It would be plausible at this stage to consider the clearance at the transducer to relate to clearance at the mucosa, but without further information this relationship can not be predicted. The question now remains as to whether this technique and approach can be used clinically.

The challenge of describing and diagnosing the spectrum of upper GI disorders is ongoing. It is widely understood that problems are multi-factorial. The technique may offer a new tool to be used to clarify differences in these parameters in the spectrum of upper GI disorders with symptoms that relate to reflux and to form an alternative approach to diagnosis based on functionality.

The model which underpins the analysis is simplistic and may need further development. It is unlikely that the efficiency parameter is linear i.e. we may not expect the same level of efficiency at different volumes in the oesophagus. However, the fit to the simple model was good and the average clearance fitted with a regression coefficient of 0.99 for healthy controls and patients with Barrett's oesophagus (Table 1). The analysis was not totally without problems and where there was no reflux or the signal had no well defined clearances the model could not be computed. The investigations during this study used a six second sample rate. The approach may benefit from an increased sample rate to improve the accuracy of the model fit. For example, Figure 6 shows an example of the quality of fitting at the sampling rate of 8 samples /second.

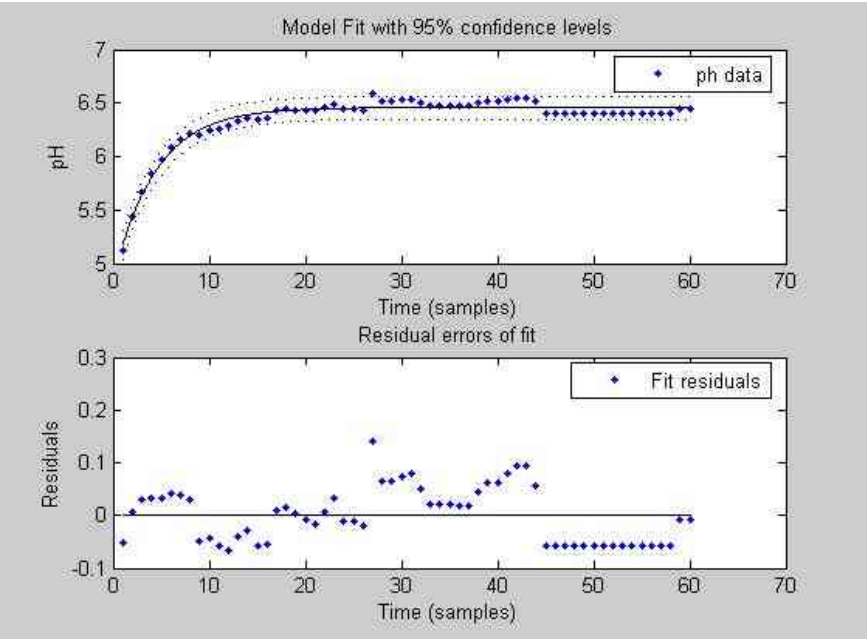

Figure 6. **Fitting with higher sample rate.** An example of fitting the data from an investigation with a higher sample rate showing the quality of fit.

As a result of problems with analysis of oesophageal pH and oesophageal manometry there has been a focus on improving luminal measurement techniques with the introduction of high resolution manometry and luminal impedance measurements. However, critically, any manometry is problematic in that the transducer is not attached to the wall and therefore only measures a radial force should the lumen close enough to constrict the transducer, and therefore is not measuring wall forces at all times. Luminal impedance is being used to investigate none acidic reflux but as with pH measurements the signals are complex and at the moment do not detect volume.

The model based analysis presented here may offer a new tool in addition to these recent approaches. It would be quite possible to implement the analysis developed within this paper into the software. However, for those interested in applying this technique an on-line analysis is being currently being developed by the authors.

Critically, it is recognised that the study and results presented should be considered preliminary and further work is required to clinically evaluate the method. The two groups investigated are small and mean ages are significantly different so any difference in this function may just be a result of age. It has been shown that age can be a factor in oesophageal clearance. However, clearance function may be contributory to the onset of Barrett's oesophagus.

Conclusion

A new approach to the analysis of ambulatory pH recording is presented based on a simple exponential model of oesophageal clearance (Udani et al, 2007). The approach gives a set of parameters which define a transducer pH clearance function (TCF) based on an exponential model of reflux clearance. The clearances can be extracted from ambulatory pH recording of the oesophagus and fitted to the model. In this study the parameters were compared between two groups showing a reduced clearance rate

constant ($p=0.03$) for patients with Barrett's oesophagus when compared with healthy controls.

This technique offers a promising new approach to the analysis of ambulatory oesophageal pH data. It is non arbitrary, being based on an exponential analytical model and may reveal fundamental functional information about the clearance of the acid content from the transducer.

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