Computerized 24-hour Ambulatory Esophageal pH Monitoring and Esophagogastroduodenoscopy in the Reflux Patient

A Comparative Study

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Ambulatory 24-hour esophageal pH monitoring and esophagogastroduodenoscopy were performed in 72 patients with symptoms suggestive of gastroesophageal reflux. Additionally, 22 asymptomatic healthy volunteers underwent pH monitoring. In patients with classsic reflux symptoms and endoscopic esophagitis, a mean of 5.41 minutes/hour of reflux below pH 4 was found compared to 0.70 minutes/hour in controls (p < 0.0001). The mean number and duration of reflux events in this group were 1.51 events/hour and 4.0 minutes/event, compared with 0.31 events/hour and 2.26 minutes/event in volunteers (p < 0.001, p < 0.01). A new system for ambulatory esophageal pH monitoring is presented using a pH-sensitive radiotelemetry pill or a pH probe and computerized methods for ambulatory data collection, analysis, and storage. An overall sensitivity of 76% was obtained with a 91% selectivity for detection of acid reflux in 51 patients having classic symptoms of gastroesophageal reflux. Ambulatory pH monitoring was positive for acid reflux in seven of 11 patients with normal endoscopic findings. Conversely, eight of 12 patients with normal pH monitoring had endoscopic esophagitis. In 19 patients presenting with atypical symptoms or previous gastric surgery, endoscopic findings were normal in 15. Nine of these 15 were identified as acid refluxers by pH monitoring. A combined approach using both pH monitoring and endoscopy is warranted for maximal detection and quantification of disease. A clear clinical role for pH monitoring is seen in the early diagnosis of acid reflux, particularly in patients having normal endoscopic findings with nonspecific gastrointestinal complaints or previous gastric operations.

THE DIAGNOSIS AND CHARACTERIZATION of gastroesophageal reflux are greatly facilitated by the use of 24-hour esophageal pH monitoring.[1,2] New ambulatory techniques allowing outpatient assessment provide data on the physiology of reflux during stress of routine activities in the patient's home or work environment.[3]

Esophagoscopy permits detection and quantification of esophagitis, but may not be relied upon to provide adequate information about the actual causative reflux. Studies have shown that increasing amounts of acid reflux may correlate with more profound histologic esophagitis.[4] The ability of distal esophageal pH measurement to diagnose esophageal reflux as the relevant problem in patients with normal endoscopic findings or atypical, nonspecific symptoms, however, remains less clear.

A prospective, comparative evaluation of the roles of endoscopy and 24-hour pH monitoring in the detection of esophageal reflux disease was undertaken. A new computerized method of ambulatory esophageal pH monitoring using a pH-sensitive radiotelemetric capsule or a pH probe is presented along with new microprocessor-based methods of pH data interpretation.[5]

Patients and Methods

Seventy-two patients with symptoms suggestive of gastroesophageal reflux were entered into the study along with a control group consisting of 22 asymptomatic healthy volunteers. Patients ranged in age from 20 to 82 years with a mean of 51.2. Volunteers ranged from 19 to 77 years old with a mean of 25.2 years. Patients and volunteers underwent esophageal manometry and 24-hour ambulatory esophageal pH monitoring. Additionally, esophagogastroduodenoscopy was performed in all patients. The study was approved by the Ethics Committee of the University of Dundee.

Manometry was performed with a triple lumen perfused catheter system and a slow pull-through technique.[6] Esophageal pH was measured using either a pH probe (Russel pH, Auchtermuchty, Scotland) or a radiotelem-

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etry pill (Medici Developments Ltd., London) suspended 5 cm above the manometrically determined high-pressure zone.[7] The radiotelemetry pill has a self-contained NaCl reservoir as a reference electrode, while the pH probe requires an external Ag/AgCl skin electrode for reference. Response times of the probe and pill are 5 seconds and 1 second, respectively, for 95% of a step change between pH 7 and 4.

A portable microprocessor receiving unit was developed for logging of pH data. The unit is worn on a waistbelt during ambulatory testing and receives signals from the radiotelemetry pill via a ferric bar aerial worn against the chest. All subjects underwent pH monitoring in their routine home or work environment for 18 to 24 hours. The portable receiving unit contains an 8 Bit Motorola microprocessor and 32K random access memory for digital data storage. A sampling interval of 10 seconds for recording of esophageal pH was standard although this is an adjustable function. At the conclusion of ambulatory testing, the data are instantaneously transferred to an Apple computer for analysis and permanent disc storage.

An event button coupled with a 16 character dot matrix liquid crystal display allows the patient to indicate specific activities or symptoms such as meals, position (erect or supine), or pain. This button enters an event-specific code into the computer memory simultaneously with esophageal pH and time of day. Thus, precise correlation of pH and selected events is possible without further user input. A segment from a computer-generated plot of pH data is shown with events as indicated by the patient during testing (Fig. 1). An association between postprandial reflux and pain is seen.

Patients were unrestricted as to the number of meals or supine episodes allowed during testing and were encouraged to follow their usual daily activity routine. Instructions were given to avoid food and beverages with high acid content, and a diary was kept by each patient listing all items consumed during testing to verify compliance.

Computer-based analysis schemes were developed for interpretation of esophageal pH data. Two alternative methods were used in all cases. First, an analysis based on individual reflux events was developed. The onset of a reflux event was defined as a drop in esophageal pH to below 4 and its termination when the pH reverted to 4 or above. The frequency and average duration in minutes of these reflux events were reported along with the total time in minutes per hour of esophageal exposure to pH < 4. A separate analysis was performed for erect and supine periods in addition to the total data record, yielding nine parameters.

Second, an analysis based on cumulative esophageal acid exposure reported the per cent of study time that
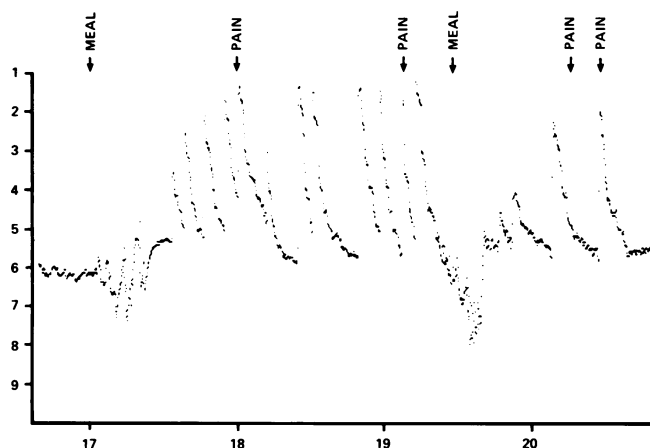

FIG. 1. Segment from 24-hour esophageal pH plot. Note association of postprandial reflux with pain. X-axis = time of day, y-axis = pH.

the distal esophageal pH was below 3, 4, 5, and 6, respectively. This was determined without respect to individual reflux events and thus represents a cumulative acid exposure profile. Separate determinations for erect and supine periods in addition to the total data record yields 12 parameters. Cumulative esophageal acid exposure in individual patients was graphically compared to the mean acid exposure at each pH in controls. An individual record is abnormal if the shaded patient area in Figure 2 crosses the mean plus 3 standard deviations line for controls.

For each analysis method an individual record was considered abnormal (positive for reflux) if any one parameter was greater than 3 standard deviations above the normal mean. Normal values were determined through the study of 22 asymptomatic healthy volunteers using the same pH monitoring system. The mean plus 3 standard deviations was used as an empirical upper limit for normal. The sensitivity was calculated as the
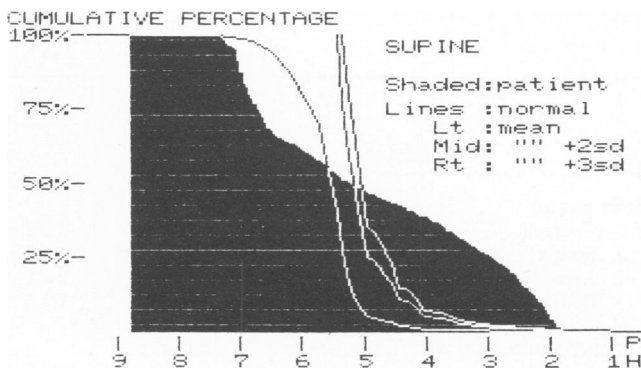

FIG. 2. Computer-generated analysis detailing cumulative esophageal acid exposure for supine position. X-axis = pH, y-axis = per cent study time below designated pH, shaded area = individual patient record, lines = mean, mean plus 2 + 3 standard deviations determined from control population.

TABLE 1. *Acid Reflux Event Analysis (Mean ± SEM)*

Groups (N)		Time pH < 4 (min/hour)	Number of Events (events/hour)	Duration (min/event)
Erect Posture				
Controls	(22)	0.90 ± 0.25	0.53 ± 0.11	1.47 ± 0.17
1. Reflux symptoms plus normal endoscopy	(11)	2.86 ± 0.69*	1.36 ± 0.24*	1.94 ± 0.29
2. Reflux symptoms plus esophagitis	(35)	5.45 ± 1.13†	2.35 ± 0.41‡	2.04 ± 0.17§
3. Reflux symptoms plus stricture	(5)	14.15 ± 5.21*	2.97 ± 0.92§	4.18 ± 0.94*
Supine posture				
Controls	(22)	0.48 ± 0.26	0.06 ± 0.02	2.39 ± 1.16
1. Reflux symptoms plus normal endoscopy	(11)	2.41 ± 1.32§	0.37 ± 0.20§	4.13 ± 1.77
2. Reflux symptoms plus esophagitis	(35)	5.59 ± 1.30†	0.62 ± 0.17‡	7.76 ± 1.72*
3. Reflux symptoms plus stricture	(5)	13.39 ± 5.31*	1.07 ± 0.32*	10.92 ± 5.19§

* p < 0.01, †p < 0.001, ‡p < 0.0001, §p < 0.05.

per cent of patients with classic symptoms of reflux having a positive pH monitoring test, and the selectivity as the per cent of controls with results below the mean plus 3 standard deviations for all parameters. Statistical comparisons were made using the Mann-Whitney U test.

Results

Patients referred for pH monitoring with classic symptoms of gastroesophageal reflux were divided into three groups on the basis of endoscopic findings. Group 1 consisted of 11 patients with endoscopically normal esophageal mucosa. Group 2 included 35 patients with endoscopic esophagitis. Group 3 consisted of five patients with benign distal esophageal strictures. Esophageal mucosal biopsies were performed in 30 cases. Biopsies confirmed gross findings in Groups 2 and 3. Four patients in Group 1 had histologic esophagitis.

Using the analysis based on reflux events, the mean time of esophageal pH < 4 was 2.61 minutes/hour in group 1 and 5.41 minutes/hour in Group 2 compared

with 0.70 minutes/hour in asymptomatic volunteers. Number and duration of reflux events were also increased in Group 1 (0.86 events/hour, 2.56 minutes/event) and Group 2 (1.51 events/hour, 4.0 minutes/event) compared to volunteers (0.31 events/hour, 2.26 minutes/event). Table 1 indicates results with respect to erect and supine position. Of note is an increase in the mean duration of reflux events in the supine position.

Cumulative acid exposure identified 33 of 51 records as abnormal in Groups 1 to 3 by reporting per cent of data below each pH unit from 3 to 6 during the study. The best single band was pH 4, identifying 28 patients as abnormal. Mean percentage of esophageal exposure to pH below 4 was 5.8 in Group 1, compared with 9.6% and 23.4% in Groups 2 and 3, respectively. Volunteers had a mean of 1.6% of total data less than pH 4. Table 2 further details cumulative acid exposure with respect to patient position.

An overall sensitivity of 76% (39 of 51 patients) was obtained by using both the analysis based on reflux events and cumulative pH exposure for Groups 1 to 3.

TABLE 2. *Cumulative Esophageal Acid Exposure (Mean ± SEM)*

Groups (N)		Percentage of Data Below Designated pH			
		pH 6	pH 5	pH 4	pH 3
Erect posture					
Controls	(22)	23.3 ± 3.9	5.5 ± 1.0	2.2 ± 0.4	0.9 ± 0.2
1. Reflux symptoms plus normal endoscopy	(11)	46.6 ± 6.4*	13.8 ± 2.1†	5.8 ± 1.1*	2.5 ± 0.4*
2. Reflux symptoms plus esophagitis	(35)	38.1 ± 3.6*	18.3 ± 2.6‡	9.9 ± 1.9†	4.7 ± 1.1‡
3. Reflux symptoms plus stricture	(5)	63.6 ± 10.6*	39.8 ± 10.7*	24.8 ± 8.8§	15.4 ± 6.6§
Supine posture					
Controls	(22)	81.6 ± 4.5	6.1 ± 2.8	1.0 ± 0.5	0.3 ± 0.1
1. Reflux symptoms plus normal endoscopy	(11)	83.2 ± 8.1	18.2 ± 7.8§	4.7 ± 2.2*	2.7 ± 1.16*
2. Reflux symptoms plus esophagitis	(35)	79.9 ± 4.1	28.9 ± 5.1†	9.5 ± 2.2†	4.4 ± 1.2*
3. Reflux symptoms plus stricture	(5)	72.3 ± 15.9	44.9 ± 12.5*	22.4 ± 8.9§	10.4 ± 4.7§

* p < 0.01, †p < 0.001, ‡p < 0.0001, §p < 0.05.

If patients had endoscopic esophagitis 77% were identified as abnormal, and if stricture was present all were positive on pH monitoring. Notably, seven of the 11 patients with normal endoscopic findings also had positive pH tests. Two of the healthy volunteers had abnormal results using either analysis method, yielding a selectivity of 91%.

Among the 39 positive tests for acid reflux, 10 (26%) were identified on the basis of reflux occurring exclusively while the patient was erect and nine (23%) solely while the patient was supine. Twenty patients (51%) were combined refluxers in that they had a positive study based on acid reflux occurring in both positions. A similar distribution of erect and supine acid reflux was seen in patients with normal endoscopic findings, endoscopic esophagitis and in those with stricture (Table 3).

Eight patients with chief complaint of nonspecific abdominal pain and 13 patients with previous gastroenterologic surgery formed the basis for two additional groups. All eight patients with abnormal pain had undergone routine workup for causes of upper gastrointestinal disease without diagnosis excepting one with cholelithiasis. The 13 patients with previous surgery had either an ulcer operation or an antireflux procedure in the past as outlined in Table 4.

Two of the 11 patients with reflux symptoms and previous gastric operations for peptic ulcer disease had endoscopic esophagitis. One of these had a pH monitoring test positive for acid reflux. The other showing no acid reflux by pH monitoring had a tight esophageal stricture, not previously dilated. Five of the remaining nine patients with normal endoscopic findings had positive pH monitoring tests identifying them as acid refluxers.

Two patients presented with reflux symptoms 6 months and 2 years after antireflux surgery. One had undergone a Belsey Mark IV repair and the other a Nissen fundoplication. Both had endoscopic esophagitis and both had positive pH monitoring tests for acid reflux.

Six of the eight patients with abdominal pain additionally had symptoms of heartburn, regurgitation, or dysphagia. Each of these six had normal endoscopic findings, while four had pH monitoring tests positive for acid reflux. The remaining two patients with no reflux symptoms had endoscopic esophagitis with normal pH monitoring. One of these having cholelithiasis had resolution of symptoms following cholecystectomy.

Discussion

Prolonged monitoring of distal esophageal pH provides an accurate assessment of gastroesophageal acid reflux. It does not, however, assess the response of the distal esophageal mucosa to the reflux. Esophagoscopy allows direct examination of the distal esophagus but fails to clarify the cause of symptoms in the absence of esophagitis.[8] Direct comparison of these techniques in the evaluation of unselected patients presenting with symptomatic esophageal reflux allows a more precise definition of their current clinical roles.

Our results show that there is a stepwise increase in detected acid reflux corresponding to the severity of endoscopic findings. Total time of esophageal exposure to pH < 4 increased from 3.03 minutes/hour in those patients without esophagitis to 5.41 minutes/hour in those with documented esophagitis and reached a maximum of 13.72 minutes/hour in patients with stricture. This was found to be due to both an increased frequency and duration of reflux events. The increased event duration reflects a diminished capacity to clear refluxed acid in the presence of esophagitis and stricture. Cumulative acid exposure similarly demonstrated an increased percentage of study time below pH 3, 4, and 5 in these groups. These findings support previous published observations that a larger percentage of patients have increased acid reflux when esophagitis is present.[1,9]

Endoscopy and pH monitoring prove complimentary

TABLE 3. Correlation of Reflux with Position

Groups (N)		Number of Individuals with Reflux in Designated Posture		
		Erect Alone	Supine Alone	Combined Supine/Erect
Controls	(22)	1	1	0
1. Reflux symptoms + normal endoscopy	(11)	2	2	3
2. Reflux symptoms + esophagitis	(35)	7	6	14
3. Reflux symptoms + stricture	(5)	1	1	3
Totals		11	10	20

TABLE 4. Correlation of Endoscopy and pH Monitoring in Patients with Previous Gastric Operations

Previous Operation	N	Endoscopy Findings	N	pH Monitoring Results	N
Vagotomy (truncal/ drainage or parietal cell)	5	Normal	3	Normal	2
		Esophagitis	2	Acid reflux	3
Vagotomy and antrectomy	5	Normal	5	Normal	2
		Esophagitis	0	Acid reflux	3
Total gastrectomy	1	Esophagitis	1	Normal	1
Antireflux procedure	2	Esophagitis	2	Acid reflux	2

in this study. Of 11 patients with endoscopically normal esophageal mucosa, seven were identified as acid refluxers by pH monitoring. Of the 12 patients with normal pH monitoring results, endoscopy showed esophagitis in eight. These results confirm that each test identifies a different subset of reflux patients. While pH monitoring uniquely detected reflux at an early clinical stage in one group of patients, it missed the diagnosis in a similar number with endoscopically severe disease. Thus from a clinical perspective, neither test alone is found ideal to both detect and quantify existing esophageal reflux disease.

Characterization of patients as erect (26%), supine (23%), or combined (51%) refluxers did not predict severity of endoscopic findings. Eight of nine patients with erect reflux alone had endoscopic esophagitis or stricture compared with seven of the nine supine refluxers. Supine reflux events were of increased duration compared to erect reflux events but occurred less frequently yielding a similar acid exposure below pH 4 (Tables 2, 3). If acid contact time is a significant factor in the production of esophagitis, one would expect the observed similar involvement of esophagitis in this group of patients. Of note is an observed increase in the per cent of data below pH 5 and 6 while patients are in the supine position, but this does not correlate with an increased incidence of esophagitis or stricture in these individuals.

Patients having atypical symptoms and those with previous gastric or esophageal operations often prove difficult to diagnose. Fifteen of the 21 patients in these groups had normal endoscopic findings; of these, nine were diagnosed as acid refluxers by pH monitoring. Ambulatory esophageal pH monitoring can thus make a substantial contribution to the clinical management of these complicated patients, particularly in the absence of endoscopically identifiable pathology.

These results support the current understanding of reflux pathophysiology. First, a multifactorial etiology for esophagitis is postulated and the detected acid reflux may only be serving as a marker for another more injurious agent in the refluxate.[10,11] Second, reflux most likely occurs in the absence of esophagitis for varying periods of time in different individuals depending on mucosal protective factors and esophageal clearing capacity.[8,12] Identification of patients at an early clinical stage through pH monitoring is advantageous in the prevention of esophagitis and its complications. Additionally, esophagitis may be the key factor in a self-perpetuating cycle of esophageal injury leading to further reflux.[12] Thus, detection of reflux prior to the appearance of esophagitis may allow improved control of the disease process.

The complementary roles of endoscopy and pH monitoring are emphasized by this study. Early identification of reflux and clarification of the role of reflux in the complicated patient with atypical symptoms or previous surgery represent two important contributions of pH monitoring to clinical management. Additionally, the quantitation of acid reflux is useful in that it appears to correlate with severity of disease. Endoscopy remains an essential adjunct for diagnosis since a subset of patients present with esophagitis in the face of normal pH monitoring.

Computerized radiotelemetry represents a significant technical advance in the performance of ambulatory esophageal pH monitoring. The analytic methods devised allow for instantaneous interpretation of 24-hour esophageal pH data with 76% sensitivity and 91% selectivity. Microprocessor-controlled data collection and analysis in combination with radiotelemetric monitoring techniques greatly facilitate its clinical use.

Acknowledgments

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