*Alimentary tract and pancreas*

# Daytime gastro-oesophageal reflux is important in oesophagitis

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SUMMARY    Fifty two patients were studied to investigate the patterns of gastro-oesophageal reflux during ambulatory pH monitoring and the relationship of reflux to presence and severity of oesophagitis. Twenty nine had evidence of oesophagitis which was graded according to severity. Acid exposure (pH<4) was calculated in each case for the total study period, the recumbent and upright periods, and the three hour period after the evening meal. Exposure in the upright period correlated closest ($r=0.92$: $p<0.001$) with that during the total period. Recumbent exposure correlated with both upright and postprandial exposure ($p<0.001$). Acid exposure during all four periods correlated significantly with the severity of oesophagitis, but postprandial acid exposure correlated best and recumbent acid exposure least well. Although acid clearance in the total, recumbent and upright periods correlated with oesophagitis, postprandial clearance showed the closest relationship. Thus the magnitude of daytime reflux, especially postprandial reflux and acid clearance, is more closely related than nocturnal reflux to oesophagitis. The results do not support the contention that night time reflux is inherently more injurious than daytime reflux to the oesophageal mucosa.

Since Spencer first described prolonged monitoring of distal oesophageal pH in 1969,[1] it has become possible to define patterns of gastro-oesophageal reflux. Some postprandial reflux occurs in normal subjects[1-5] but night time reflux is said to predominate in patients with reflux oesophagitis.[4,6,7] Consequently it has been argued that night time reflux is the most important factor in the development of oesophagitis.[7,8] We have previously reported observations in patients with oesophagitis undergoing 15 hour intraoesophageal pH recording which did not accord with this view[9] and have now undertaken ambulatory intraoesophageal pH studies in 52 patients to investigate the relationships between the pattern and magnitude of reflux, oesophageal acid clearance and the presence of oesophagitis.

## Methods

### PATIENTS
Fifty two patients were studied. All were referred for investigation of possible oesophageal disease; 25 had heartburn and four had other dyspeptic symptoms suggestive of gastro-oesophageal reflux, and 23 had recurrent chest pain, which had initially been considered cardiac. They were referred after cardiological investigation proved negative. All patients underwent upper gastrointestinal endoscopy, two or more endoscopically guided pinch biopsies being taken from at least 2·5 cm above the gastro-oesophageal mucosal junction[10] in patients with either a normal appearing or minimally abnormal oesophagus. The severity of oesophagitis was graded endoscopically (Table 1), based on the system of Little *et al*,[11] modified according to Savary.[12] In an attempt to avoid misinterpretation of mild endoscopic abnormality, however, biopsy evidence of oesophagitis (epithelial reactive changes plus polymorphonuclear leucocyte infiltration) was required

Table 1   *Grading system for oesophagitis*

| Grade | Criteria |
|-------|----------|
| O | Normal endoscopy and normal biopsy. |
| I | Two or more erythematous streaks extending upwards from cardia or lesser or equivocal endoscopic abnormality when supported by biopsies demonstrating oesophagitis. |
| II | Non-confluent ulceration or diffuse friability and contact bleeding. |
| III | Confluent ulceration or benign stricture* or Barrett's oesophagus. |

*Strictures were dilated at time of endoscopy.

in these cases. In addition, we elected to categorise stricture, Barrett's oesophagus or circumferential ulceration as a single 'severe' grade. Barrett's oesophagus was diagnosed if the gastro-oesophageal mucosal junction identified and located at endoscopy extended 3 cm or more above the lower oesophageal sphincter located by manometry,[14] or if a chronic peptic ulcer was present in gastric type epithelium above the lower oesophageal sphincter.

All patients underwent 23 hour ambulatory intra-oesophageal pH recordings using a glass pH electrode with incorporated potassium chloride reference electrode (Ingold electrode, No. 440, Pye-Unicam, UK), which was passed by the naso-oesophageal route and positioned with the tip 5 cm above the lower end of the lower oesophageal sphincter (previously located manometrically). Output from the pH probe was recorded on a modified Holter cassette recorder, which the patient carried on a belt. Before and after each recording, the pH probe was standardised against buffer solutions at pH2, 4, 5, and 7. A pH drift of >1 pH unit leading to rejection of the recording occurred in only two patients not included in this report.

If they wished, patients were allowed to go home for the period of pH recording, although some preferred to remain in the hospital. All were encouraged to be freely ambulant during the day, without restrictions on activities, food or drink consumption. Patients kept a record of the time of food or drink consumption, posture changes, and symptoms experienced on a diary card. Where acidic beverages were consumed, these records enabled us to verify that only brief falls in oesophageal pH occurred during ingestion, making negligible impact on the measurement of acid contact time. By not rigidly defining the nature of food intake we hoped to observe the patients' usual patterns of postprandial reflux.

The cassette recording was analysed on a replay machine (Oxford Tape Replay, Oxford Instruments, Abingdon, Oxford), and the oesophageal acid

exposure calculated as the period of time during which the pH was below 4. This value was then expressed as the percentage of the total time of the study (23 hours). Acid exposure was similarly calculated for the period of recumbency (in practice the night time), for the upright period (in practice the day time), and for the three hour period after the evening meal during which the patient remained ambulant or sitting (postprandial acid exposure).

Acid clearance times were also calculated for each patient. A reflux episode was defined as any fall in pH to below 4, and its duration as the time taken for the pH to rise again to 4. Acid clearance times were thus calculated as time pH was <4 divided by the number of reflux episodes, and measurements were derived separately for the total (23 hour), upright, postprandial and recumbent periods of study. Because it could be argued that calculation of acid clearance during the postprandial period might be subject to error had the patient consumed acid foodstuffs (resulting in brief falls in intraoesophageal pH), clearance was also calculated for the 60–180 minutes period after the start of the evening meal to exclude the period of eating. The duration of the longest reflux episode and the number of reflux episodes lasting more than five minutes were also measured.

STATISTICAL ANALYSIS

Linear regression analysis was used for comparisons of acid exposure during the different time periods; Spearman Rank correlation was used for analysis of the relationships between acid exposure times and oesophagitis, and between acid clearance and oesophagitis. Kruskal-Wallis one way analysis of variance by ranks was used to compare reflux frequency or acid clearance between groups of patients.

Results

Oesophageal acid exposure during the recumbent, upright and postprandial periods of recording correlated significantly (p<0·001) with acid exposure during the total 23 hour recording period (r=0·69, 0·92 and 0·76 respectively [Figs 1a–b; Fig. 2a]). Correlations were also observed between recumbent and upright acid exposure (r=0·52; p<0·001) (Fig. 2b) and between recumbent and postprandial acid exposure (r=0·49; p<0·001).

Oesophagitis was detected in 29 patients, being grade I in 14 patients, grade II in nine patients, and grade III in six patients. Twenty of these patients had reflux symptoms. Applying rank correlations to the results from all 52 patients, significant correlations were observed between the severity of oesophagitis and oesophageal acid exposure in all four periods of measurement (Table 2, left hand column). Similar
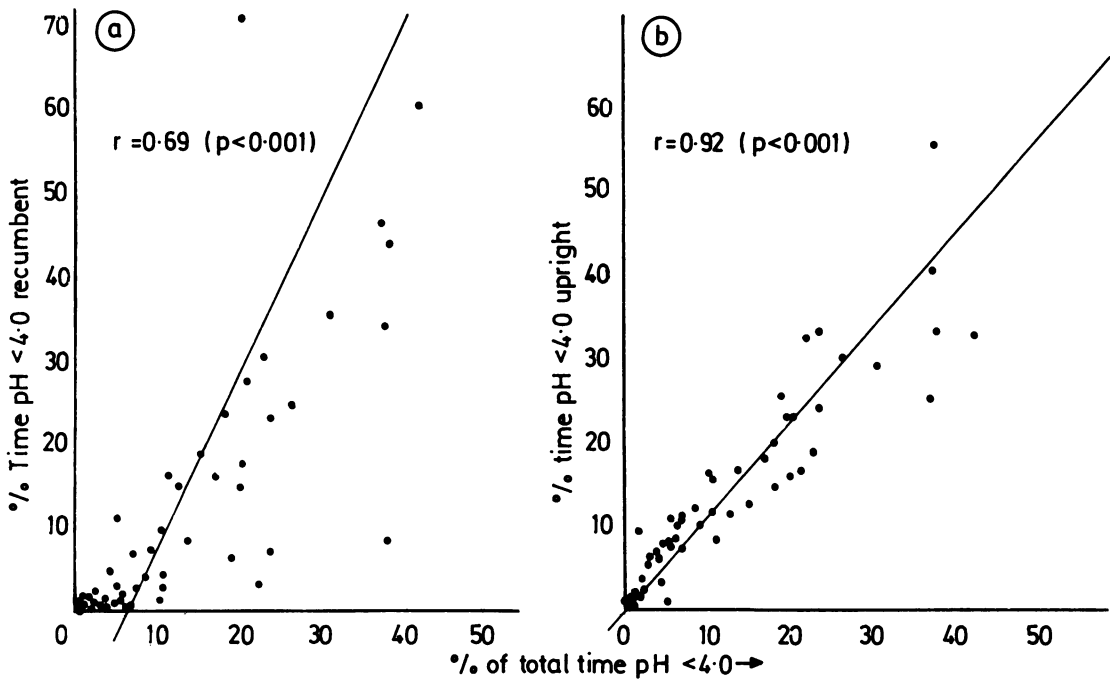
Fig. 1(a)    *Acid exposure in the recumbent position is compared with acid exposure for the total recording period.* (b) *Upright acid exposure is plotted against total acid exposure. Acid exposure is expressed as the percentage of time during each period that pH was less than 4.*
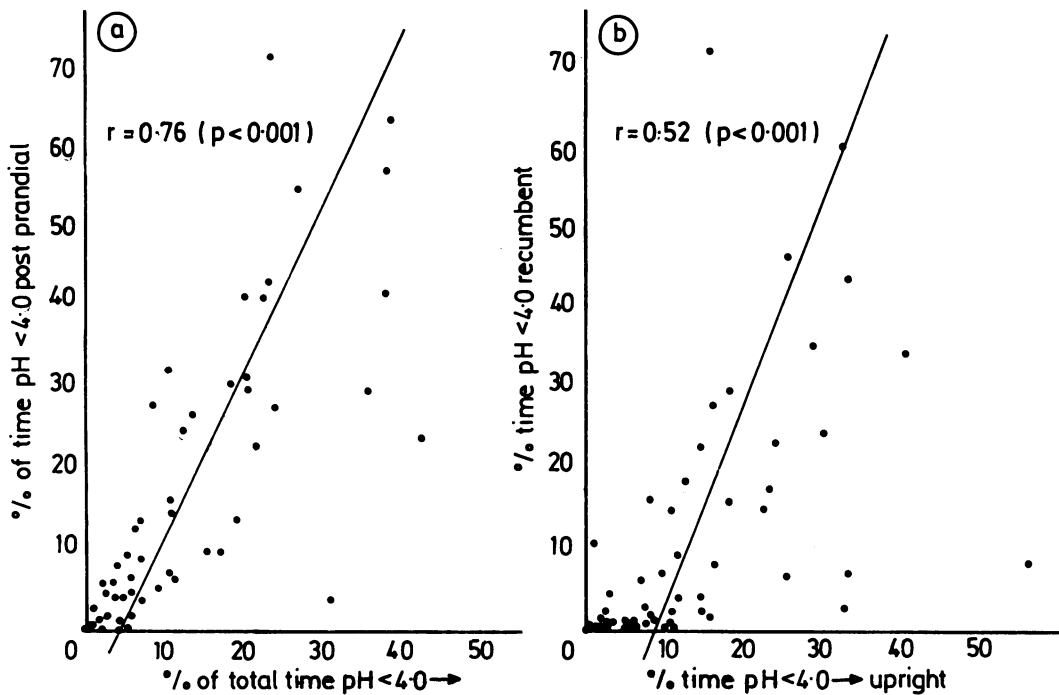


Fig. 2(a)    *Three hours of postprandial acid exposure is compared with acid exposure for the total recording period.* (b) *Recumbent acid exposure is plotted against upright acid exposure.*
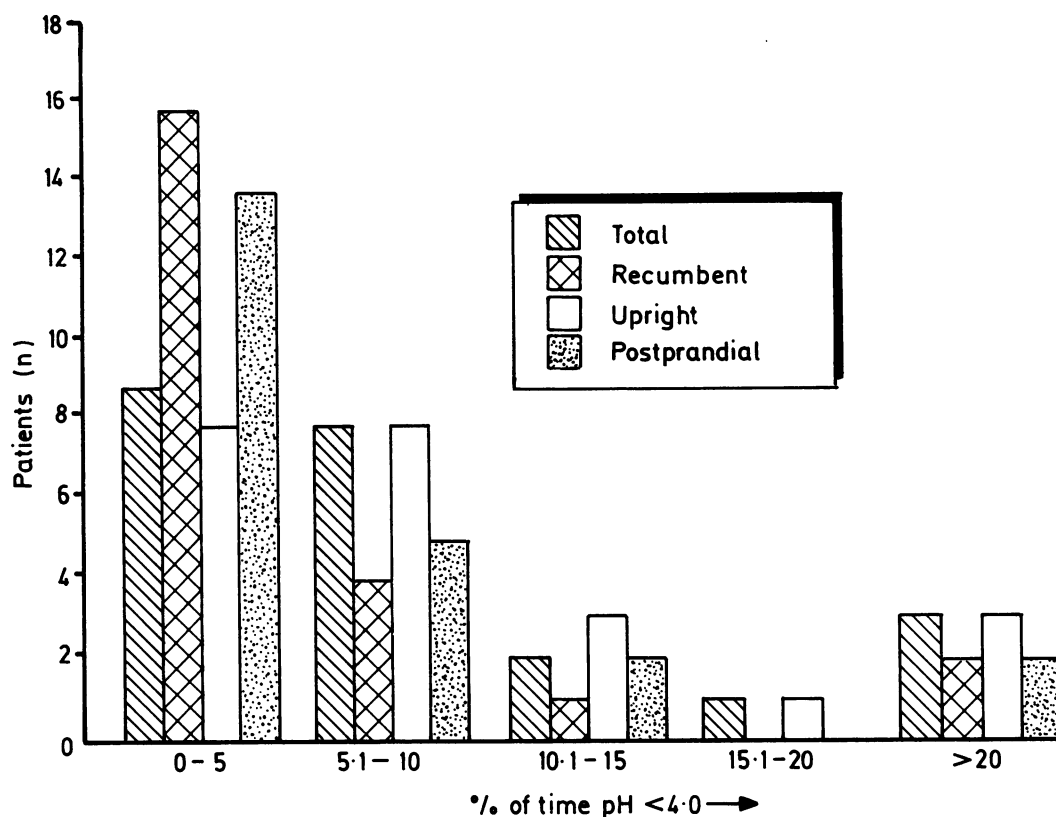
Fig. 3   *Numbers of patients without oesophagitis in relation to magnitude of acid exposure.*

correlations were also found in respect of the 29 patients who had oesophagitis (Table 2, right hand column). In the 23 patients without oesophagitis, low values for recumbent and postprandial acid exposure were frequently encountered (Fig. 3). In contrast, only three patients with oesophagitis had less than

Table 2   *Correlation of oesophageal acid exposure and oesophagitis*

|  | Spearman rank correlation coefficient (R) | |
|  | v oesophagitis grades O–III | v oesophagitis grades I–III |
| --- | --- | --- |
| Acid exposure in: | | |
| Total (23 h) period | 0·57 | 0·54 (p<0·001) |
| Recumbent period | 0·49 | 0·43 (p<0·05) |
| Upright period | 0·56 p<0·001 | 0·52 (p<0·01) |
| Postprandial period | 0·70 | 0·50 (p<0·01) |

Spearman rank correlation coefficients (R) were derived by comparing acid exposure in the total, recumbent, upright or postprandial period with increasing degree of ocsophagitis in all patients (left hand column), and in the 29 patients with ocsophagitis (right hand column).

5% acid exposure postprandially, but 10 had low (<5%) values during recumbency (Fig. 4). Seventeen patients with oesophagitis had greater than 20% acid exposure in the postprandial period compared with eight during the recumbent period. Thus in the patients with oesophagitis, low values for recumbent exposure were relatively common whereas higher acid exposure was more often encountered in the postprandial period.

Additionally, we noted that of the 10 patients with less than 5% recumbent acid exposure, eight had grade I oesophagitis and the remaining two patients had grade II and III oesophagitis. These patients all had larger magnitudes of daytime acid exposure. The three patients with oesophagitis who had less than 5% acid exposure in the upright or postprandial period were all classed as grade I.

To summarise these results, low values of acid exposure were associated with the absence of oesophagitis and, in addition, increasing acid exposure was associated with increasing severity of oesophagitis. The best correlation was found comparing oesophagitis with postprandial acid
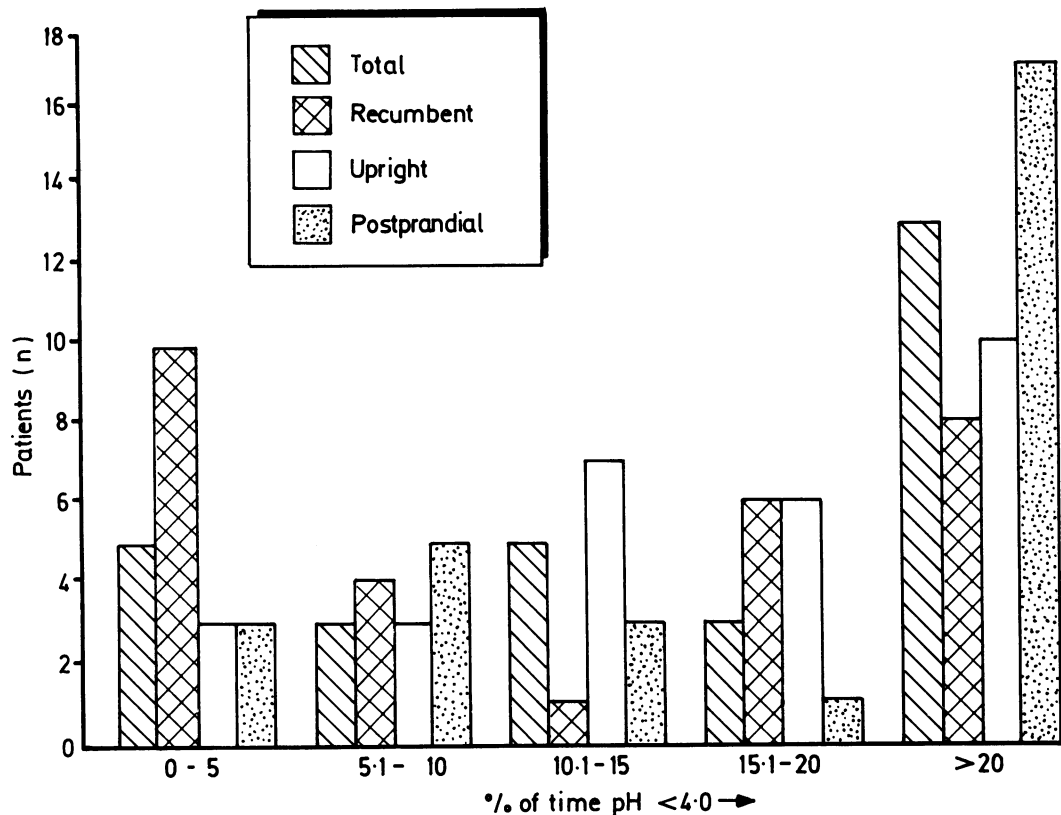
Fig. 4   *Numbers of patients with oesophagitis (regardless of grade) in relation to magnitude of acid exposure.*

exposure whereas recumbent reflux provided the poorest correlation.

Table 3 shows that the number of reflux episodes correlated with the grade of oesophagitis, despite the lower median number of reflux episodes for most periods in patients with grade III oesophagitis than in those with grade II.

Figure 5 displays the acid clearance times for each of the periods of study. Prolongation of acid clearance time was seen as the grade of oesophagitis increased during the total, recumbent and postprandial periods. This increase was also apparent during the 60–180 minute postprandial period but upright acid clearance showed little change. A wide scatter of overlapping values of acid clearance was obtained for each grade of oesophagitis, and was especially obvious in the recumbent period.

In Table 4, acid clearance is compared with increasing degree of oesophagitis. Significant correlations were found whether clearance was represented as the acid clearance time, the number of reflux episodes lasting longer than five minutes or the longest reflux episode observed, with the best

correlations for the postprandial period. Thus in patients with oesophagitis, delay in oesophageal clearance occurs after meals, but is less obvious in the 'upright' period taken as a whole.

### Discussion

In consequence of the work of Demeester and colleagues, 'upright', 'supine', and 'combined' patterns of abnormal gastro-oesophageal reflux have been described,[5] with the implication that upright and supine reflux may be distinct and independent entities. Our results provide no evidence to justify such a distinction. Oesophageal acid exposures during the upright (sitting or ambulant) period correlated most closely with total 23 h acid exposure and acid exposure during recumbency was related to acid exposure when upright. The latter relationship was noted previously by Atkinson and van Gelder.[4]

When the relationship between recumbent and upright acid exposure is examined (Fig. 2b), it is apparent that the regression line cuts the x-axis at about 9%, showing that some upright reflux occurs in

Table 3   *Reflux episodes (median and range) (n)*

| Oesophagitis grade | Total* | Recumbent† | Upright‡ | Post-prandial‡ |
|---|---|---|---|---|
| O (n=23) | 55 (0–298) | 7 (0–28) | 51 (0–282) | 10 (0–85) |
| I (n=14) | 79 (3–181) | 6 (0–49) | 71 (3–132) | 19 (1–49) |
| II (n=9) | 156 (110–212) | 30 (14–87) | 109 (93–144) | 25 (16–45) |
| III (n=6) | 91 (49–149) | 20 (0–39) | 65 (49–110) | 25 (5–28) |

Number of reflux episodes during each study period observed in patients grouped according to grade of oesophagitis. Using Kruskal-Wallis one way analysis of variance by ranks, the number of reflux episodes increased significantly with increasing grade of oesophagitis, although it will be noted that grade III patients had less reflux episodes than grade II.
*p<0·0005; †p<0·001; ‡p<0·005.

the absence of recumbent reflux. In contrast, the regression of upright and total acid exposure intersects at zero (Fig. 1b) implying that recumbent reflux does not occur in the absence of upright reflux. This also is in agreement with the findings of Atkinson and van Gelder[4] and with more recent studies.[15] Thus we have found no evidence to support the contention that increased reflux may occur only in the recumbent position as reported by others in 23–37% of their patients.[5 16 17] It may be calculated from Figure 2b, however, that the slope of the regression line relating recumbent to upright acid exposure is 4·8, indicating

Table 4   *Correlation of acid clearance and oesophagitis*

| Period | (a) Mean acid clearance | (b) Reflux episodes >5 mins (n) | (c) Duration of longest reflux episode |
|---|---|---|---|
| Total | 0·42 ⎫ p<0·01 | 0·47 ⎫ p<0·001 | 0·53 ⎫ |
| Recumbent | 0·38 ⎭ | 0·47 ⎭ | 0·51 ⎪ |
| Upright | 0·33  p<0·02 | 0·36  p<0·02 | 0·40 ⎬ p<0·001 |
| Postprandial (3 hours) | 0·65  p<0·001 | 0·55  p<0·001 | 0·56 ⎭ |
| Postprandial (2 hours) | 0·47  p<0·01 | — | — |

Spearman rank correlation coefficients (R) were derived by comparing mean acid clearance (column (a)), the number of reflux episodes lasting >5 min. (column (b)) and the duration of the longest reflux episode (column (c)) during each of the study periods with increasing grade of oesophagitis. The postprandial (2 hours) period excludes the first prandial hour during which food ingestion occurred.

that as exposures increase, exposure in the recumbent position contributes a progressively greater proportion of total exposure.

Three factors may contribute to this difference from previous reports. First, there is poor agreement about normal values of oesophageal acid exposure, especially during recumbency. Taking the mean
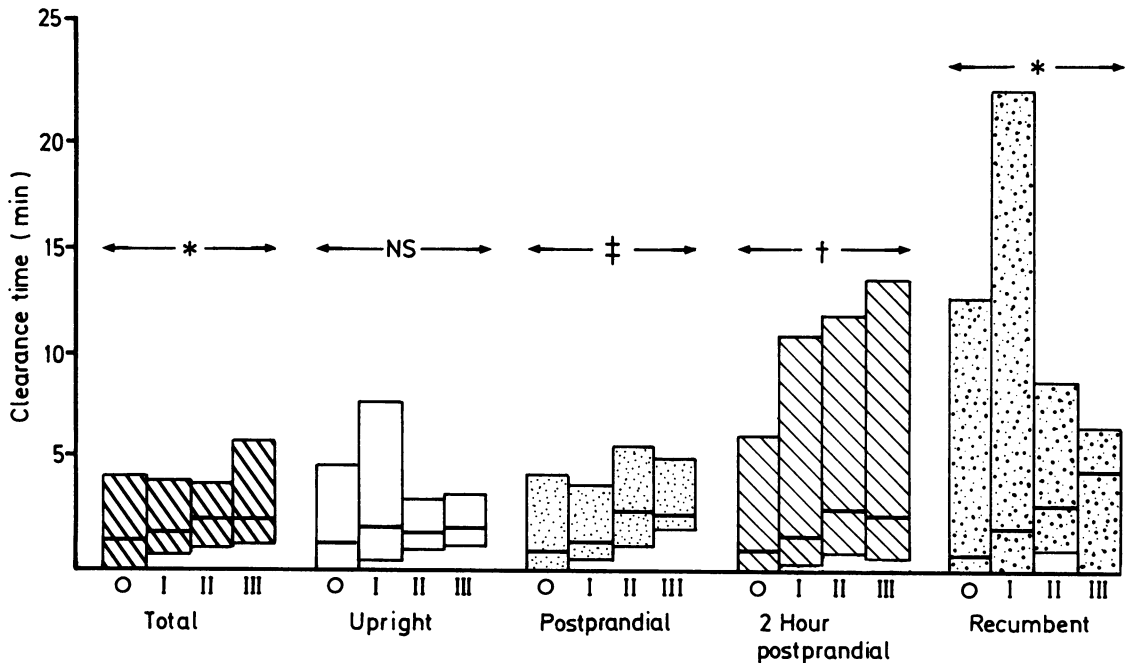


Fig. 5   *Oesophageal acid clearance (median and range) during each of the study periods calculated for patients according to oesophagitis grading. Using Kruskal-Wallis one way analysis of variance, by ranks, acid clearance time increased significantly with grade of oesophagitis for the total, postprandial, 2 hour postprandial (excluding the first prandial hour) and recumbent periods, but not the upright period. *p<0·05  †p<0·01  ‡p<0·005.*

+2 SD to indicate the upper limit of 'supine' exposure time (pH<4) in control subjects, values of 1·22,[16] 5·7,[17] and 10·1%[18] have been reported by different investigators. With such variation in the definition of normality, differing conclusions about patterns of abnormality seem likely. Our findings do not depend on reference to a normal range as our purpose was simply to explore the relationship of reflux to oesophagitis. Secondly, studies using radio-telemetry to monitor 24 h intraoesophageal pH in ambulant patients have shown that acid exposure is greater with the patient in his usual home or work environment than in hospital.[19] The difference relates particularly to the day time period. The mobility of patients in Demeester's studies was restricted by the apparatus used[5 16] and it is possible that the magnitude of day time reflux was thereby reduced. Thirdly, we have found that while most patients tolerate the pH probe well, and are able to eat and drink normally, a few remain apprehensive and feel unable to eat or drink much during the period of study. As food and drink often promote the occurrence of reflux,[20 21] it is possible that in some patients a poor intake during the period of study diminishes their day time reflux. This consideration may explain our findings in one patient (identifiable on Figure 2b), in whom predominant recumbent reflux with minimal upright reflux was observed. This individual did not have oesophagitis nor had he been treated with antireflux therapy.

Although animal studies have shown a relationship between acid mucosal contact time and the development of oesophagitis,[22-25] studies in man have suggested that total acid contact time does not necessarily predict the occurrence of oesophagitis. It has been suggested that a given amount of acid exposure resulting from multiple rapidly cleared reflux episodes may be less noxious than a similar amount of acid exposure resulting from a few poorly cleared episodes of acid reflux.[7 11] In this connection, it is thought relevant that clearance of refluxed material from the oesophagus is particularly delayed during the night, being fostered by a recumbent posture,[26] by sleep,[27 28] and by diminished salivation in response to an oesophageal acid load.[29] In our view, however, there are difficulties with the concepts of delayed clearance and the preeminance of night time reflux in the generation of oesophagitis. Although clearance of an exogenous acid load is delayed in patients with oesophagitis,[30] delayed clearance is also found in many symptomatic patients without oesophagitis.[11] Failure of arousal during sleep apparently delays oesophageal acid clearance in patients with oesophagitis, but this also occurs in asymptomatic volunteers.[2 27] Abnormal acid clearance in patients with oesophagitis can be minimised

by medical treatment for the oesophagitis, raising the possibility that impaired clearance is a consequence, not a cause of oesophagitis.[31] It is also clear that an appreciable number of patients with oesophagitis, including some with severe inflammation and ulceration, do not reflux during the night.[15]

Although delayed acid clearance has been related to histological markers of oesophageal mucosal response to refluxate[7] and an association has been observed between delayed clearance and oesophagitis regardless of grade,[11 31] we are not aware of previous studies that have examined the relationship between clearance and severity of endoscopic oesophagitis. Our results show that acid clearance time does correlate with increasing grade of oesophagitis, and that the relationship is not restricted to the night time. Indeed, delayed postprandial clearance bore the closest relationship with oesophagitis. Why clearance should be delayed after a meal in patients with oesophagitis is not clear. It is possible that the apparent delay in clearance is an artefact resulting from the superimposition of multiple reflux episodes; alternatively, food, like alcohol and smoking,[26] may alter oesophageal function. Whatever the mechanism, the result is the same, namely increased exposure of the oesophageal mucosa to acid during the postprandial period.

Several studies have shown a high degree of correlation between recumbent reflux and the presence of oesophagitis[4-6] or oesophageal epithelial reactive changes[7] and although some have also noted a similar association of oesophagitis with upright and postprandial reflux,[4 9] a recent review has encapsulated the most widely held opinion in the words '. . . night seems (to be) the critical time for the most detrimental reflux to occur'.[8] Our results show that oesophagitis correlates with total acid exposure and since daytime and night time exposures are themselves correlated, we find no reason to believe that night time reflux is inherently more injurious to the oesophagus than reflux during the day.

There may be practical implications in the observation that the best correlation between severity of oesophagitis and acid exposure was obtained from the three hour postprandial period. At present, long periods of ambulatory intraoesophageal pH monitoring, which include the overnight period, are recommended to identify abnormal gastro-oesophageal reflux,[16] but if comparable results could be obtained from a short period of day time monitoring, it would obviously be attractive. Our results and the findings of others[32 33] suggest that a three hour period of postprandial ambulatory monitoring provides the best prediction of oesophagitis and in the context of clinical diagnosis, may be sufficient for identification of abnormal gastro-oesophageal reflux.

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