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Gastro-oesophageal reflux and the migrating motor complex

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SUMMARY Distal oesophageal pH and gastroduodenal motor activity were recorded simultaneously throughout nocturnal (23 30–08 30 h) and diurnal (08 30–17 30 h) periods of fasting in seven healthy subjects. At night, episodes of gastro-oesophageal reflux (GOR) accounted for 1·2±0·7% of recording time. Periods of gastric motor activity, representing the gastric component of the migrating motor complex (MMC), recurred every 78±31 min during the night and were interspersed with periods of gastric motor quiescence. Nocturnal episodes of GOR during periods of gastric motor activity were of longer duration ($p<0·001$) and more frequent ($p<0·005$) than during periods of gastric motor quiescence. At night, periodic gastric motor activity was thus correlated ($p<0·001$) with an increase in the duration and number of GOR episodes and associated with a 100-fold increase in oesophageal acid exposure. During the day, the gastric component of the MMC, recurring every 131±64 min, was correlated ($p<0·02$) with an increase in the duration and number of GOR episodes, and a three fold increase in oesophageal acid exposure. Further, 89% of nocturnal, and 83% of diurnal gastric MMCs were temporally associated with episodes of GOR. We conclude that fasting episodes of GOR occur coincidentally with the gastric component of the MMC.

In health and disease most gastro-oesophageal reflux (GOR) occurs postprandially.[1–4] Recent studies suggest, however, that nocturnal episodes of GOR, which also occur in healthy subjects,[2 5 6] are an important factor in the pathogenesis of gastro-oesophageal reflux disease.[1 7 8] Such nocturnal episodes of GOR are associated with a temporary decrease in the depth of sleep[2 5 6] and a transient inappropriate relaxation of the lower oesophageal sphincter (LOS).[2] Such periods of arousal from deep sleep recur cyclically and are marked by a characteristic EEG pattern.[9–11] As with distal oesophageal acidification,[12] it is likely that nocturnal episodes of GOR result in arousal from sleep.

Several other nocturnal periodic phenomena, such as body movement,[9 10 13] swallowing[5] and gastric motor activity,[11 13–15] are also associated with arousal from sleep. The cyclic recurrence of gastric motor activity is of particular interest in view of the possibility that forceful gastric contractions might give rise to GOR.[8] These periods of gastric motor activity represent the gastric component of the migrating motor complex (MMC). The MMC is a characteristic feature of fasting gastrointestinal motor activity which occurs most frequently at night.[16] On this evidence, it might be anticipated that nocturnal episodes of GOR will occur in temporal association with the gastric component of the MMC; this does not appear to have been investigated.

In the present study, 24-hour monitoring of distal oesophageal pH and gastroduodenal motor activity was undertaken in healthy subjects to ascertain whether episodes of GOR occur in association with the gastric component of the MMC. The gastric component of the MMC was recognised as that period of fasting during which large amplitude gastric contractions were present, including both phase 2 and phase 3 activity, and which preceded the duodenal activity front. During the nocturnal recording period we made no EEG assessment of the stage of sleep.

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Methods

SUBJECTS

Seven healthy volunteers (five men, two women) with a mean age of 24±5 years participated in this study after informed consent was obtained. None had symptoms or a history of gastrointestinal disease, nor was any participant taking medication. Subjects refrained from smoking or alcohol ingestion for 24 hours before the study. The experimental protocol for this study was approved by the Ethics Committee of the Tower Hamlets Area Health Authority.

OESOPHAGEAL pH

A glass pH microelectrode (Russel pH, Auchtermuchty, Scotland) was passed transnasally into the distal oesophagus and positioned 5 cm above the proximal margin of the manometrically defined LOS. A silver-silver chloride reference electrode (Medicotest, Olstykke, Denmark) was attached suprasternally. A microprocessor controlled data logger (pH 100, Gaeltec Research, Dingwall, Scotland) was used to sample oesophageal pH at 10 sec intervals throughout the 24-hours period, data being stored in a 32K random access memory.[17] Oesophageal pH was also recorded directly by a pH meter (Type PH25, Radiometer, Copenhagen, Denmark), the output of which was recorded on a polygraph (Graphtec Linearcorder WR 3101, Graphtec Corp, Japan).

MANOMETRY

A catheter assembly consisting of four fused polyethylene tubes (ID 0·6 mm, OD 1·1 mm) was used to record intraluminal pressures from the lower oesophageal sphincter, gastric antrum and two sites in the duodenum. Each catheter had a lateral opening equal to the internal diameter of the tube and was closed distal to this opening with a metal marker which enabled fluoroscopic localisation of the recording orifices, positioned 1, 11, 26, and 41 cm from the distal end. The catheter was introduced transnasally and positioned so that the most orad recording orifice lay within the lower oesophageal sphincter. Each recording orifice was constantly perfused with water at a rate of 0·1 ml/min using a pneumohydraulic pump (Arndorfer Medical Specialties, Greendale, W1, USA). Pressures were transmitted to external pressure transducers (Gaeltec S8b, Gaeltec Ltd, Skye, Scotland), the output of which was recorded on the polygraph.

EXPERIMENTAL PROTOCOL

Subjects were intubated 12 hours before the study period. After an overnight fast, simultaneous manometric and pH recordings were made for the subsequent 24 hour period starting at 08 30 h. Subjects were seated and awake during the day, remaining fasted until a 540 kcal meal (consisting of 125 g roast chicken, 14 g mashed potato, 85 g peas, 28 g cheddar cheese and a dessert of 30 g ice cream) was eaten at 17 30 h. Recordings continued throughout the night in the presence of an observer who reported that all subjects were supine and asleep by 23 30 h. Studies were concluded at 08 30 h when the subjects were awoken.

DATA ANALYSIS

The study was considered as comprising a nine hours diurnal fasting period (08 30–17 30 h), a nine hours nocturnal fasting period (23 30–08 30 h) and a three hour postprandial period (17 30–20 30 h). Data from each of these periods were analysed separately.

OESOPHAGEAL pH

Recordings obtained during the 24-hours study were transferred from the logger to a computer (Apricot PC, ACT Computers Ltd, Halesowen, England), stored on magnetic disk and plotted using a dot matrix printer (Mannesman Tally, Japan). These, together with the direct recordings of distal oesophageal pH, were analysed visually by two observers. An episode of GOR was defined as a decrease in pH to <4 for at least 10 seconds.[18] The number, duration and frequency of GOR episodes, and the percentage of recording time for which they accounted, were determined for each study period.

MANOMETRY

Recordings were analysed visually by two observers. During fasting, the gastric component of the MMC was recognised as a period of at least five minutes duration during which large amplitude (>20 mm Hg) contractions occurred at a frequency of 1–3/min. This preceded the duodenal activity front, recognised as being of at least three minutes duration during which contractions occurred at a frequency of 11–13/min.[19] The MMC cycle length in both the stomach and in the duodenum was determined. The duration of the gastric component of the MMC, and the amplitude of gastric contractions, was measured.

RELATIONSHIP BETWEEN FASTING OESOPHAGEAL pH AND MANOMETRY

The percentage of nocturnal and diurnal recording time occupied by gastric motor activity associated with the MMC was determined. Nocturnal and diurnal episodes of GOR concomitant with either gastric motor activity or gastric motor quiescence were analysed separately. The number and duration of these GOR episodes and the percentage of recording time for which they accounted were determined. The incidence of GOR episodes was then

correlated with the occurrence of gastric motor activity. Finally, the periods of gastric motor activity both with and without concomitant episodes of GOR were noted.

STATISTICAL ANALYSIS

Data presented throughout this study have been expressed as mean±SD; statistical significance was assessed using Student's *t* test for paired data. Correlation was assessed by computing a contingency coefficient (C) and determining its significance using the χ^2 test.[20]

Results

OESOPHAGEAL pH

During both nocturnal and diurnal periods of fasting, episodes of GOR were observed in each subject (Fig. 1). A total of 185 reflux events were noted during fasting. These were of longer duration at night than during the day (46±30 *v* 25±13 sec; $p<0.005$), but occurred less frequently (0·9±0·4 *v* 1·6±0·4 h^{-1}; $p<0.01$). Thus, the percentage of time accounted for by GOR episodes did not vary between nocturnal and diurnal fasting periods (1·2±0·7 *v* 1·1±0·5%; $p>0.4$). A total of 66 reflux episodes were noted during the postprandial period (representing 40% of the number of GOR episodes). Postprandial episodes of GOR had a duration of 43±25 sec and occurred with a frequency of 3·2±0·8 h^{-1}. These GOR episodes accounted for 3·7±1·6% of recording time, a greater percentage ($p<0.001$) than during fasting.

MANOMETRY

During fasting, each subject exhibited cyclic gastroduodenal motor activity. A total of 88 MMCs were observed in the duodenum, a gastric component being present in 92% of diurnal, and 85% of nocturnal, MMCs. Migrating motor complex cycle length was shorter at night than during the day, both in the stomach (78±31 *v* 131±64 min; $p<0.001$) and duodenum (66±27 *v* 122±58 min; $p<0.001$). The duration of the gastric component of the MMC was also shorter at night, however, than during the day (33±18 *v* 43±27 min; $p<0.01$). Thus the gastric component of the MMC occupied 43±12% of nocturnal, and 38±13% of diurnal, recording time; these values were not different ($p>0.4$). The amplitude of gastric contractions associated with the MMC did not vary between nocturnal and diurnal periods (27±9 *v* 31±8 mm Hg; $p>0.4$).

RELATIONSHIP BETWEEN FASTING OESOPHAGEAL pH AND MANOMETRY

During periods of gastric motor activity, episodes of nocturnal (Fig. 2) and diurnal (Fig. 3) GOR were of longer duration ($p<0.001$), and were more frequent ($p<0.005$), than during the intervening periods of gastric motor quiescence. Thus, GOR episodes accounted for a greater proportion ($p<0.005$) of nocturnal and diurnal recording time during periods of gastric motor activity than during gastric motor quiescence (Table). Episodes of GOR during nocturnal gastric motor activity were longer ($p<0.005$), but no more frequent ($p>0.25$), than those observed during diurnal gastric motor activity.

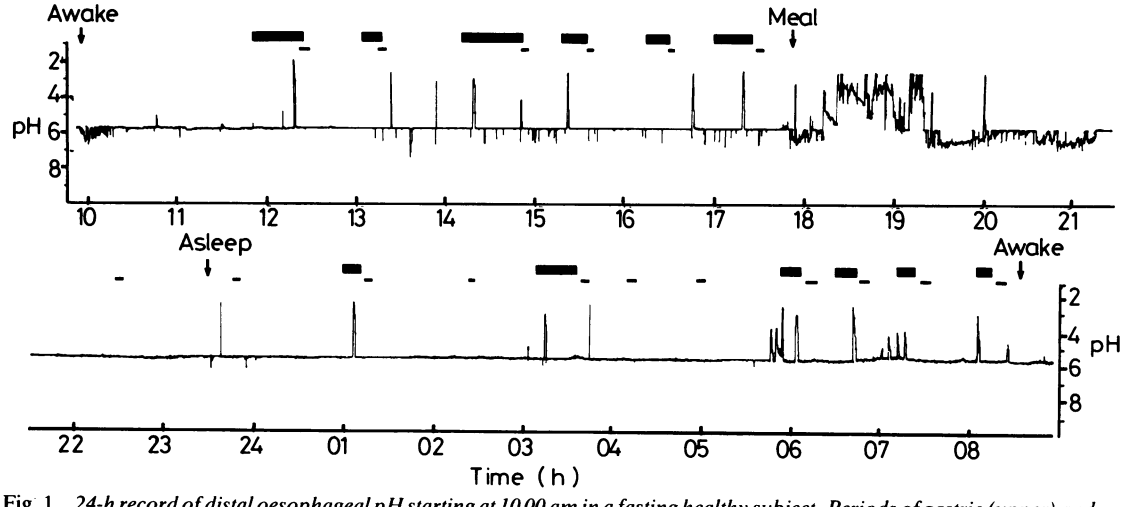

Fig. 1 *24-h record of distal oesophageal pH starting at 10 00 am in a fasting healthy subject. Periods of gastric (upper) and duodenal (lower) motor activity associated with the migrating motor complex (MMC) are indicated above the pH trace. Note coincidence of gastro-oesophageal reflux episodes and gastric components of the MMC throughout both diurnal and nocturnal fasts.*

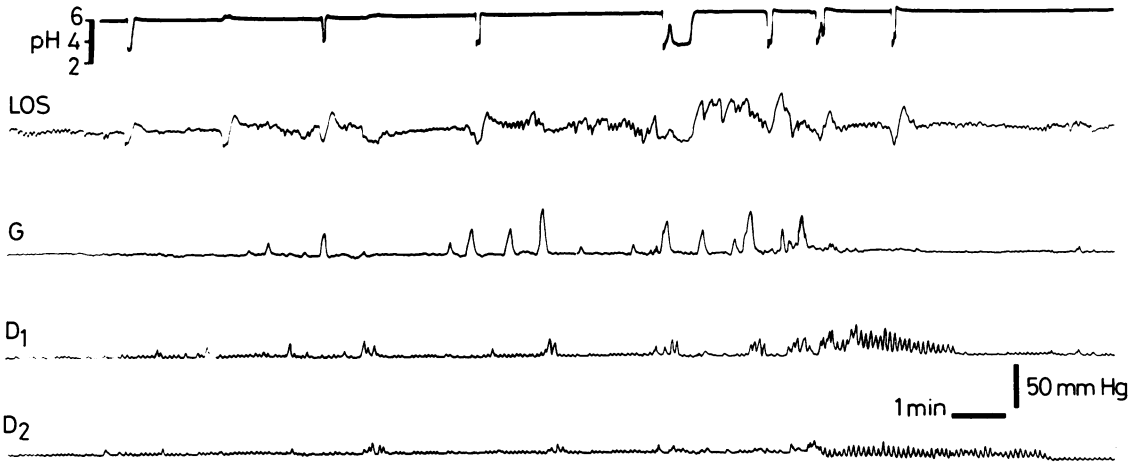

Fig. 2 *Nocturnal recording of distal oesophageal pH in a healthy subject during a migrating motor complex (MMC). Manometric recordings were obtained from the lower oesophageal sphincter (LOS), gastric antrum (G) and two sites in the duodenum (D). Two episodes of gastro-oesophageal reflux (pH <4 for >10 sec) were observed during the gastric component of the MMC. Relaxation of the LOS occurred concurrent with the first of these episodes.*

Thus, GOR episodes accounted for a greater proportion ($p<0.05$) of nocturnal than of diurnal periods of gastric motor activity (Table). During gastric motor quiescence, the duration of GOR episodes did not differ ($p>0.25$) between nocturnal and diurnal periods, although they occurred less frequently ($p<0.001$) at night. Thus, during periods of gastric motor quiescence, GOR episodes accounted for a lesser proportion ($p<0.001$) of nocturnal than of diurnal recording time (Table).

Nocturnally, periodic gastric motor activity was correlated with an increase in the duration ($C=0.52$; $p<0.001$), and number ($C=0.46$; $p<0.001$), of GOR episodes. Further, diurnal periodic gastric motor activity was also correlated with an increase in the duration ($C=0.31$; $p<0.001$), and number ($C=0.21$; $p<0.02$), of GOR episodes. Episodes of GOR were not correlated with MMCs which lacked a gastric component (Fig. 4). Indeed, 57% ($^{57}/_{100}$) of diurnal fasting, and 95% ($^{81}/_{85}$) of nocturnal, GOR episodes were associated with periods of gastric motor activity. Finally, 83% ($^{24}/_{29}$) of diurnal, and 89% ($^{43}/_{48}$) of nocturnal, periods of gastric motor activity were temporally associated with episodes of GOR.

Discussion

The major finding of the present study was the coincidence of fasting episodes of GOR and the gastric component of the MMC. This relationship

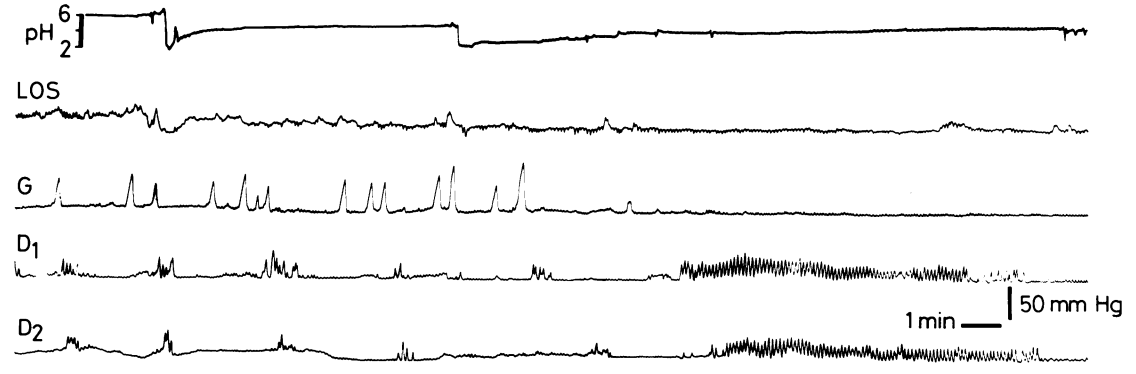

Fig. 3 *Diurnal recording of distal oesophageal pH in a healthy fasting subject during a migrating motor complex (MMC). Manometric recording sites were designated as in Figure 2. One episode of gastro-oesophageal reflux (pH <4 for >10 sec) occurred during the gastric component of the MMC.*

Table *Characteristics of nocturnal and diurnal gastro-oesophageal reflux episodes during fasting periods of gastric motor activity and motor quiescence*

	Gastric motor activity		*Gastric motor quiescence*	
	Nocturnal	*Diurnal*	*Nocturnal*	*Diurnal*
Duration (sec)	50±29	30±14	10±5	18±9
Frequency/hour	3·0±1·8	2·4±0·7	0·12±0·11	1·1±0·6
Time pH <4 (%)	3·9±1·7	2·0±0·8	0·03±0·03	0·6±0·4

was most marked nocturnally, when MMC related episodes of GOR were of longest duration, and GOR during gastric motor quiescence was least frequent. Our findings in respect to the incidence and duration of GOR episodes, and the percentage of time for which they accounted, are consistent with previous reports of GOR in healthy subjects, both during nocturnal[1 2 5 6] and diurnal[4 21] fasting, and also post-prandially.[1 4 18 22]

We defined the gastric component of the MMC as a period of large amplitude gastric contractions preceding the duodenal activity front.[19] This was considered appropriate as contractions during the gastric activity front are sporadic,[23] preventing precise identification of phase 2 and phase 3 components. In confirmation of previous reports,[15 19] we observed that a gastric component preceded 87% of duodenal MMCs. Episodes of GOR were unlikely to be the consequence of a manometric assembly being positioned across the LOS, as this has been shown to have no effect on the frequency or duration of reflux episodes.[3 21]

There would appear to be two mechanisms by which episodic GOR might be related to fasting

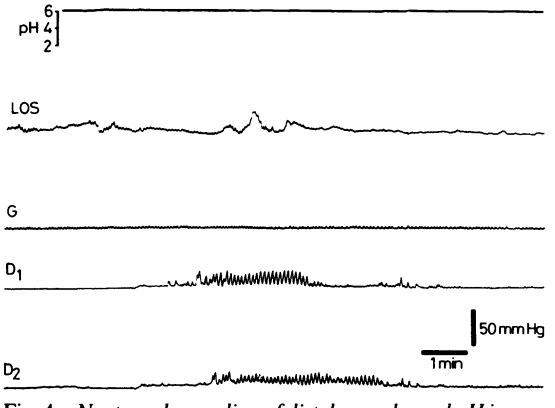

Fig. 4 *Nocturnal recording of distal oesophageal pH in a healthy subject during a migrating motor complex (MMC) lacking a gastric component. Manometric recording sites were designated as in Figure 2. Note the absence of gastro-oesophageal reflux.*

periodic gastric motor activity. First, it is possible that forceful gastric contraction might increase intragastric pressure and result in retropulsion of gastric content through the LOS, as has been observed in dogs.[24] Operation of this mechanism during the gastric component of the MMC would appear to be at variance with the concept that phasic contractions of the LOS occur concurrently with those of the proximal stomach during fasting.[25–28] Recent evidence suggests, however, that marked increases in intragastric pressure may result in reflux irrespective of LOS relaxation.[4]

It is perhaps more likely that fasting gastric contractions provoke transient inappropriate relaxations of the LOS and hence increase the likelihood of GOR. This would account for the significant proportion of those LOS relaxations which occur independently of coexistent motor activity in the body of the oesophagus.[2 4] In this context, it has been shown that the afferent discharge of gastric mechanoreceptors may be modulated by contraction of either the proximal or distal stomach.[29 30] Stimulation of these receptors by forceful gastric contraction associated with the MMC might, by activation of vago-vagal reflexes, modify efferent vagal activity[31 32] and thus lead to inappropriate relaxation of the LOS.[33] In this regard, gastric distension has recently been reported to increase the incidence of such transient inappropriate relaxations of the LOS, a finding attributed to activation of vago-vagal reflex pathways.[34 35]

The occurrence of forceful gastric contractions,[11 13–15] transient inappropriate relaxations of the LOS,[2] and swallowing activity[5] have all been associated with interruption of deep sleep. These associations would be expected if fasting gastric contractions, either with or without concurrent relaxation of the LOS, were to result in GOR, consequent arousal from sleep, and subsequent initiation of swallowing activity. Indeed, distal oesophageal acidification results in arousal from sleep[5 6 12] and initiation of swallowing activity.[5 12] In pathological GOR, it has been suggested that failure of this acid arousal mechanism results in prolonged exposure of the oesophageal mucosa to refluxate.[12] Gastro-oesophageal reflux occurring during the gastric MMC would be most likely to result in mucosal damage as acid[36 37] and pepsin[36] secretion is increased at this time.

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