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# Effects of Omeprazole on Mechanisms of Gastroesophageal Reflux in Childhood

S. CUCCHIARA, MD PhD, R. MINELLA, MD, A. CAMPANOZZI, MD PhD, G. SALVIA, MD, O. BORRELLI, MD, E. CICCIMARRA, MD, and M. EMILIANO, MD

Prolonged recordings of esophageal motility have shown that dynamic changes of lower esophageal sphincter (LES) pressure such as transient LES relaxation and LES pressure drifts are the most common mechanisms underlying gastroesophageal reflux (GER). The coexistence of a delayed gastric emptying has also been reported in a high proportion of patients with reflux disease. However, not much information is available on the effects of antireflux therapy on the pathogenetic mechanisms of GER. The purpose of this study was to determine in a group of children with severe reflux disease the effect of omeprazole therapy on motor changes of LES underlying GER as well as on gastric emptying time. Twenty-two children (median age: 6.6 years) with GER disease, refractory to combined ranitidine and cisapride administration, entered into an eight-week omeprazole course. Ten subjects with moderate GER disease served as controls (median age: 6.0 years). Before and after omeprazole administration, the following variables were assessed: esophagitis grading, fasting and fed simultaneous prolonged recording of distal esophageal sphincter pressure (with a sleeve catheter) and intraesophageal pH, LES and esophageal peristalsis amplitude, and gastric emptying time of a mixed solid–liquid meal (measured with gastric ultrasound). As compared to controls, patients showed a higher rate of transient LES relaxation and LES pressure drift ($P < 0.01$), a reduced amplitude of basal sphincter pressure ($P < 0.01$) and peristalsis ($P < 0.05$), and a more prolonged gastric emptying time ($P < 0.05$). After ending omeprazole, there was no significant change in any of the motor abnormalities of the esophagus and in gastric emptying time despite a marked improvement of symptoms and esophagitis in all patients. Sixteen patients were symptomatic when reevaluated on a clinical basis two months after ending therapy. We conclude that in children with severe GER disease, an abnormally high rate of both transient LES relaxation and LES pressure drift and slow gastric emptying are not affected by omperazole treatment, even though esophageal mucosal damage is markedly improved or cured. These abnormalities represent a primary motor disorder and can be implicated in the refractoriness of reflux disease.

**KEY WORDS:** gastroesophageal reflux; esophagitis; lower esophageal sphincter; transient relaxation.

It is commonly agreed that several factors are involved in the pathogenesis of gastroesophageal reflux (GER) (1). Symptoms and clinical sequelae of the disorder are mainly due to the reflux of gastric acid content into the esophagus; however, the rate and the duration of reflux episodes are determined by gut motor abnormalities such as defective lower esophageal sphincter (LES) pressure (LESP), impaired esophageal peristalsis (3, 4), and delayed gastric emptying (5, 6). In the last years, prolonged recordings of the motor profile at the gastroesophageal junction

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From the Gastrointestinal Endoscopy and Motility Unit, Department of Pediatrics, University of Naples "Federico II," Naples, Italy.

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Address for reprint requests: Dr. Salvatore Cucchiara, Gastrointestinal Motility & Endoscopy Unit, University of Naples "Federico II," Via S. Pansini 5, 80131 Napoli, Italia.



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have shown that transient LES relaxation (TLESR) is the major mechanism underlying reflux both in normal subjects and in patients with GER disease (7); it has also been reported that in patients with severe grades of GER disease, GER episodes can also occur as a result of gradual loss of basal LES tone (LESP drift) (8–10).

Even though motor abnormalities play a crucial role in the occurrence of GER events, acid suppressive drugs remain the cornerstone in the medical treatment of GER disease (11). Recently, the use of proton pump inhibitors, such as omeprazole, has markedly increased the rate of healing of esophagitis and symptom improvement, mainly in patients with severe GER disease (12–14). However, no much information is available on the effects of omeprazole on the motor function of the esophagus as measured by manometry (15, 16); furthermore, the effect of healing esophagitis on the most common mechanisms underlying GER, ie, TLESR and LESP drift, as well as on gastric emptying delay, has received little attention. The present study was designed to evaluate in a group of children with severe reflux esophagitis the effect of omeprazole administration on both dynamic changes of LESP and gastric emptying time.

## MATERIALS AND METHODS

Twenty-two children (10 females) (median age: 6.6 years; range: 19 months–12 years) with reflux esophagitis refractory to a previous eight-week therapeutic course of ranitidine (8 mg/kg/day) and cisapride (0.6 mg/kg/day) formed the basis of this study. Systemic diseases as well as underlying disorders promoting severe GER disease were excluded in all patients. The latter were selected for a new therapeutic course consisting of omeprazole given for two months, in a single administration in the morning, at a daily dose of 1 mg/kg (roughly corresponding to 40 mg/1.73 $m^2$ SA). According to the manufacturer's instructions, most of the patients were given the granular content of the capsule in a few milliliters of an acidic vehicle such as grapefruit or orange juice. The patients had symptoms interfering with daily activity and health: recurrent emesis was present in 17 patients, epigastric pain in 14, chronic cough and/or wheezing in 12, hematemesis in 5, abnormal posture of the neck in 2, rumination in 1. Before omeprazole, the patients were evaluated endoscopically (with biopsies of the distal esophageal mucosa) and with manometry. Endoscopy was performed with a pediatric videoendoscope (Olympus, Torino, Italy) having a 2.8-mm-diam. biopsy channel, after sedation with intravenous meperidine (1–2 mg/kg) and diazepam (0.3 mg/kg). At least two biopsy specimens were taken from distal esophageal mucosa in each patient, avoiding biopsies from the most distal 20% of the esophagus. Biopsy specimens were examined for basal zone thickness, elongation of papillae, presence of intraepithelial neutrophils and/or eosinophils, and for mucosal slough or ulcerations. Histologic evidence of esophagitis was required when only nonspecific endoscopic findings such as hyperemia, friability, and/or granularity were present. Severity and extent of esophagitis were assessed according to an endoscopic classification reported in a recent study in children (14): grade 0, absence of mucosal abnormalities; grade 1, no macroscopic erosions, but erythema, friability, or granularity of the mucosa; grade 2, superficial erosions involving $<10\%$ of the mucosal surface of the last 3–5 cm of the esophageal squamous mucosa; grade 3, superficial erosions or ulcerations involving 10–50% of the mucosal surface of the last 3–5 cm of the esophageal squamous mucosa; and grade 4, deep ulcerations localized anywhere in the esophagus or confluent erosions of $>50\%$ of the mucosal surface of the last 3–5 cm of the esophageal squamous mucosa.

Esophageal manometry was performed after an overnight fast using a probe incorporating a pediatric Dentsleeve and introduced through the nose. The probe was an assembly of six catheters (ID 0.8 mm) with distal side holes. A 4-cm-long sleeve sensor (with a 4-mm diam.) was located at the distal end of the probe. The side holes were located 1 cm beyond the distal sleeve margin, and 2.5, 5, 7.5, and 10 cm proximal to the sleeve. Basal LESP was measured with a station pull-through technique: the probe was located with all orifices in the stomach, and then moved at 0.5-cm intervals through the esophagus. The mid-respiratory level of the sphincter pressure was measured at the level of the three most distal side holes along the esophageal body (2.5, 5, and 7.5 cm proximal to the sleeve) with mean intragastric pressure as zero reference. The pull-through was done three times, giving nine readings and a final mean value was calculated. The manometric probe was then positioned so that the sleeve sensor straddled the LES; the side hole located at the distal margin of the sleeve recorded fundic pressure, whereas esophageal body pressure was recorded through the orifices located proximally to the sleeve. Catheter position was maintained by taping the catheter to the nose. A small flexible glass pH electrode (Ingold, Switzerland, 1.5 mm diam.) was then introduced through the nose and located with its tip at 87% of the distance nares–LES, previously measured by manometry. The electrode was calibrated at the start and end of each recording session with buffer solutions of pH 7.0 and 4.0 and connected to a Beckman pH meter (No. 39042). The manometric probe was continuously perfused with a low-compliance pneumohydraulic pump (Arndorfer Medical Specialties, Greendale, Wisconsin) at a flow rate of 0.3 ml/min. Pressure signals were transmitted to external transducers (Beckman 4-327-C), whose output was recorded on the polygraph. Swallowing events were detected by two cutaneous electrodes placed in the submental mylohyoid region, one on each side of the midline; a ground electrode was attached to the arm. The skin electrodes were connected to a Beckman coupler (9852A) that was set to record signals from DC to 30-Hz frequency. The manometric, electromyographic, and pH signals were recorded on the same polygraph (Beckman R611) at a paper speed of 2.5 or 1 mm/sec.

Simultaneous pH and manometric recordings were performed for 1 hr fasting and for 1 hr after giving apple juice (15 ml/kg, pH 5.0). Children underwent pH manometric recording supine and were generally quiet, without seda-

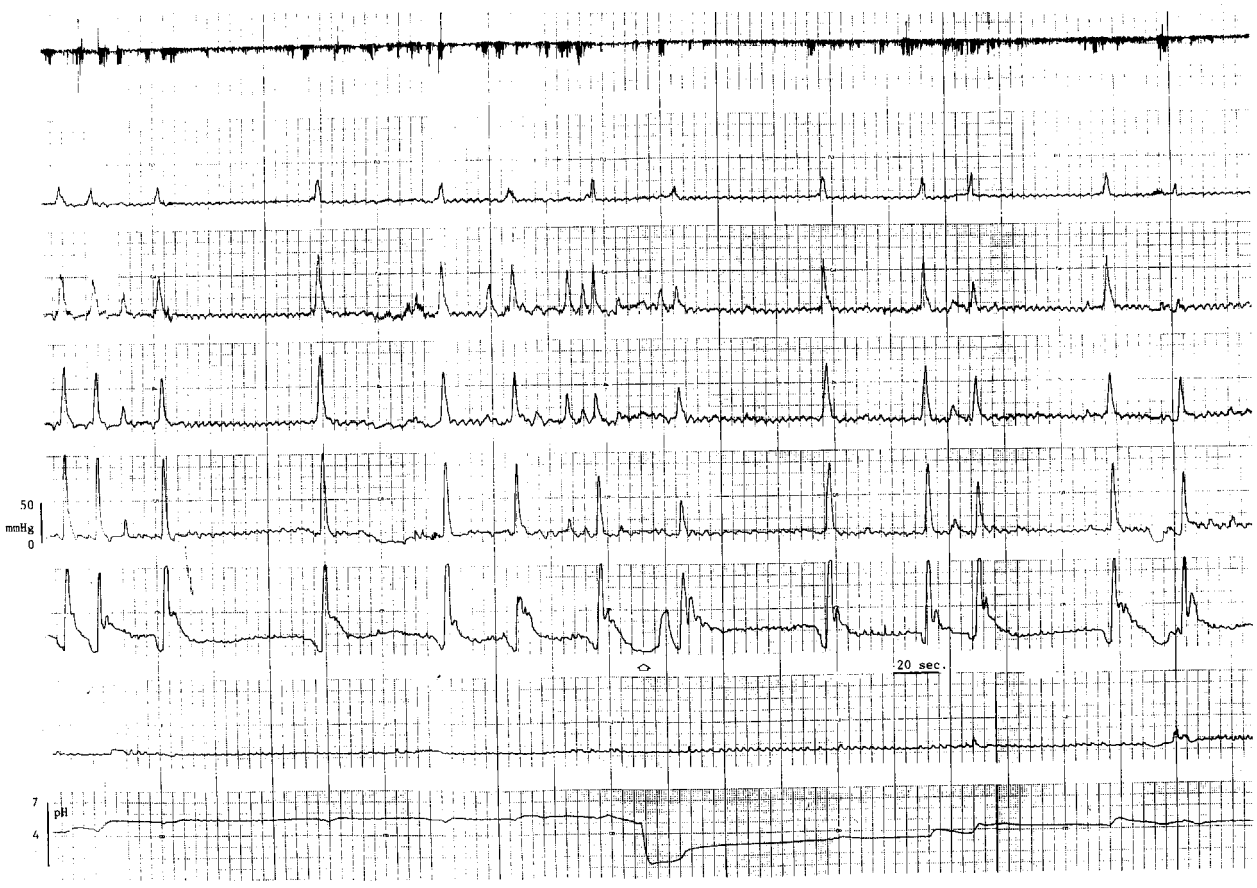


**Fig 1.** Episode of transient lower esophageal sphincter (LES) relaxation (arrow), intermingled with episodes of relaxations following swallowing. From top to bottom recording of swallowing, esophageal body activity (channels 1–4), LES, gastric fundus, esophageal pH. A reflux episode occurs during transient LES relaxation.

tion; periods with artifacts because of fussiness were eliminated from analysis. The LES motor profile was analyzed during periods immediately before and after each episode of GER as well as during periods without GER events. Acid reflux was defined as a drop in the intraesophageal pH below 4.0 for at least 20 sec.

Two main patterns of LES events at the occurrence of GER were identified: (1) the transient lower esophageal sphincter relaxation (TLESR), that is a fall in LESP of at least 10 mm Hg lasting for more than 5 sec and beginning at least 3 seconds before a submental burst of electromyographic activity indicating swallowing (Figure 1); and (2) LESP drift, that is a progressive slow downward drift of LES tone to very low levels, usually $\leq$4.0 mm Hg, lasting for at least 30 sec (Figure 2) (9).

At the end of each recording session, amplitude of esophageal peristalsis was measured at the level of the three most distal recording holes along the esophageal body. Swallowing events, 30 sec apart, were elicited by giving 5% dextrose (2–5 ml). Only peristaltic sequences preceded by at least 20 sec of quiescent motor activity in the esophageal body were measured. Amplitude of esophageal peristalsis was calculated as the peak pressure minus the mid-respiratory esophageal body pressure. Contractions in the esophageal body were defined as the increase in the esophageal pressure of at least 15 mm Hg. A mean value of 10 peristaltic sequences for the three recording sites was given for each patient.

Manometric tracings were compared with those recorded in 10 control children with a median age of 6.0 years (range: 22 months–10 years). Symptoms in this group consisted of recurrent emesis, in the absence of underlying diseases predisposing to severe GER disease, and never interfered with daily activity or health. In all control subjects abnormal intraesophageal acid exposure had been documented by prolonged intraluminal pH test and endoscopy did not show erosive esophagitis. All controls had successfully been treated with positional therapy, dietary advice, and prokinetics; depending on symptoms, $H_2$-receptor antagonists had been added in some patients. The pH manometric tracings were analyzed by one of the authors (R.M.) without knowledge of clinical data and esophagitis grading. Both patients and controls underwent gastric emptying time measurement by real-time ultrasound of the gastric antrum, according to a procedure previously described in children with functional gastrointestinal disorders (17). During the therapeutic course, all patients were evaluated on a clinical basis and instructed not to use any other antireflux drug. Esophageal manometry, endoscopy, and gastric ultrasound

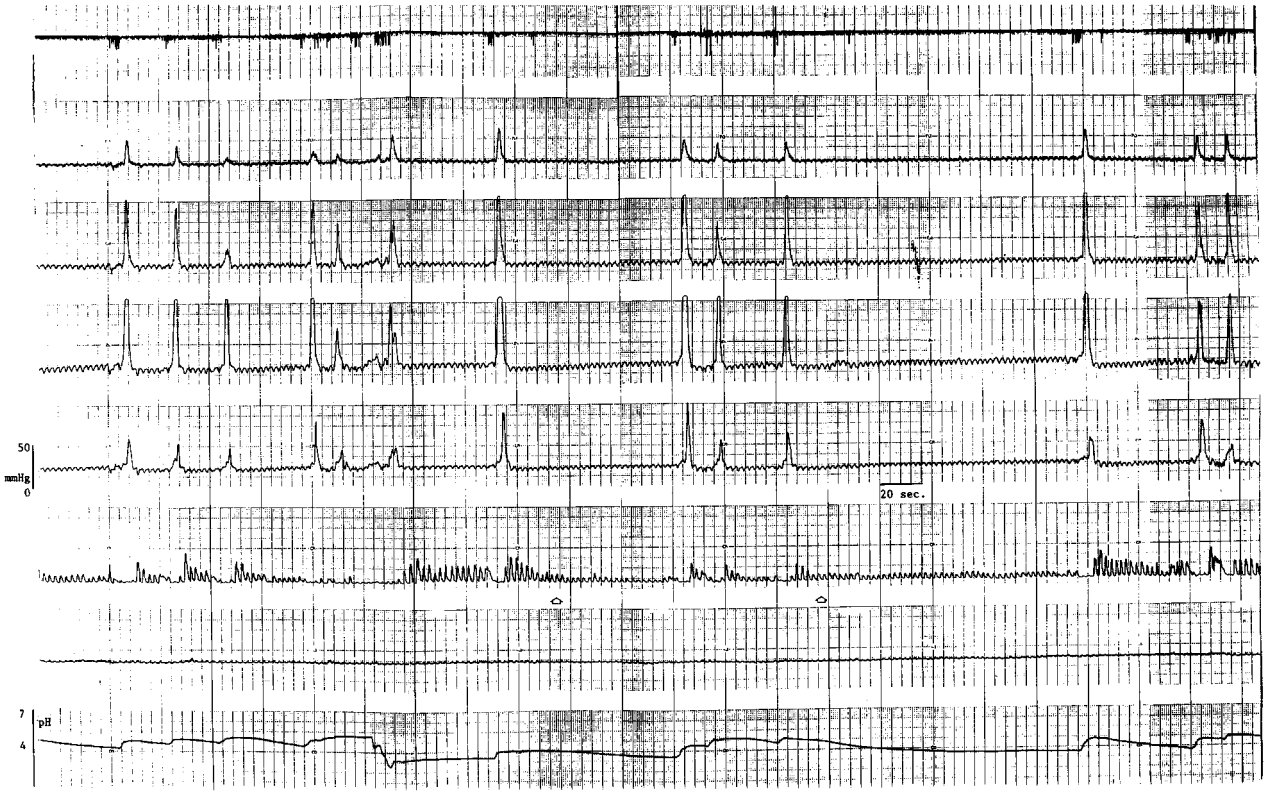


**Fig 2.** Episodes of prolonged decrease of LES pressure to a very low level (LES pressure drift) (arrows), coincident with reflux events. From top to bottom recording as in Figure 1.

were repeated during the first week after stopping drug administration. Data were given as mean ± SD and analyzed with parametric *t* test and the nonparametric signed-rank tests, with $P < 0.05$ considered significant. The study was approved by the ethical committee of our department and parents gave informed written consent.

## RESULTS

As compared to controls, in the 22 patients undergoing omeprazole treatment, baseline esophageal manometry revealed a significantly higher rate (number of episodes per hour) of TLESR and LESP drift episodes both in the fasting and fed periods (Table 1); the rate of TLESR and LESP drift episodes at the occurrence of GER events was also significantly higher in the patients than in controls (Table 1). Basal LESP, as measured during stationary pull-through, was significantly lower in the 22 patients (7.6 ± 2.4 mm Hg) than in controls (18.2 ± 4.6 mm Hg; $p < 0.01$). The amplitude of esophageal peristalsis was also significantly lower in the patients than in controls at the all recording levels ($P_1$: proximal, $P_2$: middle, $P_3$: distal) (patients, $P_1$: 69.1 ± 12.4 mm Hg; $P_2$: 62.6 ± 10.8 mm Hg; $P_3$: 53.4 ± 10.2 mm Hg) (controls, $P_1$: 90.8 ± 11.5 mm Hg, $P < 0.05$; $P_2$: 78.7 ± 10.2 mm Hg, $P < 0.05$; $P_3$: 74.5 ± 8.5 mm Hg, $P < 0.05$). Finally, patients exhibited a more prolonged gastric emptying time (minutes) (median and ranges) (197 ± 31; 165–270) than controls (150 ± 21.3; 120–180; $P < 0.05$). Esophagitis was endoscopically scored

TABLE 1. RATE (NUMBER OF EPISODES/HOUR) OF TLESR AND LESP DRIFT EVENTS IN FASTING AND FED PERIODS IN PATIENTS (BEFORE OMEPRAZOLE ADMINISTRATION) AND CONTROLS*

| | *Patients* | *Controls* |
|---|---|---|
| TLESR fasting | | |
| Total episodes† | 5.18 ± 1.3 | 2.6 ± 0.8 |
| GER + episodes† | 3.6 ± 1.09 | 1.4 ± 0.6 |
| TLESR fed | | |
| Total episodes† | 8.5 ± 2.0 | 3.6 ± 0.9 |
| GER + episodes† | 6.9 ± 1.7 | 2.4 ± 0.5 |
| LESP drift fasting | | |
| Total episodes† | 3.5 ± 1.2 | 1.6 ± 0.6 |
| GER + episodes† | 2.0 ± 0.8 | 0.7 ± 0.6 |
| LESP drift fed | | |
| Total episodes† | 5.2 ± 1.5 | 2.8 ± 0.7 |
| GER + episodes† | 3.5 ± 1.3 | 1.6 ± 0.5 |

* The rate of TLESR and LESP drift events at the occurrence of GER episodes (GER +) is also reported (mean ± SD).
† $P < 0.01$.

TABLE 1. RATE (NUMBER OF EPISODES/HOUR) OF TLESR AND LESP DRIFT EVENTS IN FASTING AND FED PERIODS IN PATIENTS BEFORE AND AFTER OMEPRAZOLE ADMINISTRATION *

| | *Pretrial* | *Posttrial* |
|---|---|---|
| TLESR fasting | | |
| Total episodes† | 5.18 ± 1.3 | 4.8 ± 1.73 |
| GER + episodes† | 3.6 ± 1.09 | 3.0 ± 1.6 |
| TLESR fed | | |
| Total episodes† | 8.5 ± 2.0 | 8.0 ± 2.8 |
| GER + episodes† | 6.9 ± 1.7 | 5.9 ± 2.5 |
| LESP drift fasting | | |
| Total episodes† | 3.5 ± 1.2 | 3.3 ± 1.3 |
| GER + episodes† | 2.0 ± 0.8 | 1.9 ± 1.0 |
| LESP drift fed | | |
| Total episodes† | 5.2 ± 1.5 | 4.2 ± 1.7 |
| GER + episodes† | 3.5 ± 1.3 | 2.8 ± 1.6 |

* The rate of TLESR and LESP drift events at the occurrence of GER episodes (GER/+) is also reported (mean ± SD).
† NS.

as grade 4 in four patients, grade 3 in six, grade 2 in seven, and grade 1 in five; the latter had histologic evidence of esophagitis.

At the end of the therapeutic course, symptoms dramatically improved or disappeared in all patients. Four patients improved from grade 4 esophagitis to grade 2 (two cases) or grade 1 (two cases); of six patients with grade 3 esophagitis, two improved to grade 2 and four to grade 1; seven patients improved from grade 2 to grade 0 or 1; the five patients with grade 1 improved to grade 0. As shown in Table 2, the rate of TLESR and LESP drift episodes did not differ from values detected prior to administration of omeprazole, both during fasting and fed periods. Basal LESP, measured during the manometric stationary pull-through phase, did not statistically differ from baseline values (8.5 ± 3.1). Likewise, there was no significant change in the amplitude of peristalsis at the all recording levels ($P_1$: 71.0 ± 11.1 mm Hg; $P_2$: 65.0 ± 10.4 mm Hg; $P_3$: 56.0 ± 10.1 mm Hg). Gastric emptying time (190 ± 27.6 min; 120–240 min) was also statistically not different from the values detected before omeprazole treatment.

Sixteen patients were markedly symptomatic when reevaluated on a clinical basis two months after ending therapy. They were considered for a new investigative program and treatment consisting of prolonged administration of omeprazole.

## DISCUSSION

Esophageal motor abnormalities such as low basal LESP and failure of peristalsis have often been detected in patients with GER disease; their prevalence and severity usually increase with the severity of esophagitis (3, 4, 12, 18). Reports on the effects of antisecretory drugs on esophageal motility in GER disease have yielded controversial results: either improved or persisting esophageal dysmotility with healing of esophagitis have been documented (3, 14, 18–26). However, these studies were performed during short-term manometric recording sessions and examined traditional esophageal manometric parameters such as basal LESP and the characteristics of peristalsis. Recent pathophysiologic investigations, through prolonged recording of LESP with manometric catheters incorporating a sleeve, have indicated that phasic changes of LES tone are the main pathogenetic mechanisms underlying GER (8–10). Other studies have shown that delayed gastric emptying can be included among variables playing a role in the pathogenesis of GER (5, 6, 17). Since the effects of antireflux therapy on the mechanisms of GER are poorly understood (27–29), it was of interest to determine whether the occurrence rate of phasic changes of LESP profile and gastric emptying time could be favorably influenced by antisecretory therapy aimed at healing esophagitis. This study shows that healing of esophagitis with a powerful antisecretory agent in a pediatric population with severe reflux disease does not improve the esophageal motor variables playing a role in the pathogenesis of GER disease, ie, an abnormally high rate of TLESR and LESP drift episodes, as well as slow emptying of the stomach.

The nature and the control mechanisms of phasic changes of LESP, either transient or prolonged, have not been defined. Gastric distension, through stimulation of tension receptors in the gastric wall, has been shown to play a role on the afferent side of the transient LES response, the efferent pathway being represented by the noncholinergic, nonadrenergic intramural nerves (30, 31). The pharyngeal region and an inflamed esophageal mucosa have also been indicated as sites involved in triggering TLESR events (8). Whatever the afferent stimulus, considerable evidence has accumulated that TLESR events occur on a neurologic basis, after integration in the brain stem of sensory signals from peripheral regions (7). The fact that both TLESR and LESP drift episodes are usually intermingled with periods of normal LES tone suggests that these events can be due to a defective neurological control of LESP, likely because of a poorly sustained vagal stimulatory activity (32).

This study suggests that abnormal rates of both TLESR and LESP drift episodes in children with severe reflux esophagitis can be a primary esophageal

motor abnormality. It also seems to exclude the injured esophageal mucosa as an afferent source of phasic changes of the LES, as the rate of both TLESR and LESP drift events was unchanged with healing of esophagitis. Interestingly, healing of esophagitis was not accompanied by improvement in gastric emptying time. Our data indicate that severe reflux esophagitis in children is characterized by a primary motor disorder involving both the esophagus and the regions of the gut beyond the LES. Given the experimental evidence that TLESR episodes are consistently elicited by gastric distension (33, 34), it is conceivable that persistence of delayed gastric emptying in our patients might have triggered an unchanged high rate of TLESR and LESP drift events, despite healing of esophagitis. Indeed, a recent study in children indicates that an exaggerated gastric distension due to food of high volume and osmolality produces high rates of transient changes of LESP profile (35). It was also of interest that abnormalities of other motility variables, such as low basal LESP and low peristalsis amplitude, did not improve at the end of the therapeutic course. In contrast, a previous report from our unit in children with reflux disease had shown an improvement in esophageal motility following healing of esophagitis (3). Those subjects, however, had a significantly lower age and less severe changes of the esophageal mucosa than patients in this study, furthermore, their GER disease responded to antacids and prokinetics, whereas patients in this study had GER disease refractory to prokinetics and $H_2$-receptor blockers. It is tempting to suggest that GER disease of short duration is characterized by mild to moderate esophageal dysmotility that can be reversed with antireflux therapy; moreover, we cannot exclude that in infants with GER disease a process of maturation of esophageal motility can promote a functional recovery of the esophagus during antireflux treatment (36). Persistence of esophageal and gastric motor abnormalities, as described in this study, can determine a high likelihood of relapse of GER disease when active treatment is withdrawn. It is worth mentioning that almost two thirds of our patients were significantly symptomatic when reevaluated clinically two months after ending therapy. These subjects underwent a new investigative program and were candidates for long-term treatment with omeprazole or surgery. We cannot exclude, however, that the patients investigated in this study might have benefited from a longer therapeutic course with omeprazole. Indeed, a recent study in a group of children with severe GER disease, refractory to traditional antireflux drug therapy, has shown that long-term use of omeprazole can result in sustained symptomatic and endoscopic improvement (14). The same study also indicates the usefulness of titrating the dose of omeprazole upward against repeated intragastric pH studies in order to reach an effective intragastric acid suppression.

Our study emphasizes the observation that GER disease is primarily a motor disorder of the gastroesophageal junction and of the stomach, even though antisecretory therapy is successful in improving symptoms and healing esophagitis. The crucial role of gastroesophageal dysmotility in GER disease is also highlighted by a recent report showing that detecting a high rate of LESP failure events and delayed gastric emptying, at the initial investigative approach, can be of value in predicting a refractory course of the disease (35). Future studies should be focused on investigating whether long-term courses of powerful suppressive therapy of gastric acidity might affect pathogenetic mechanisms of GER and the clinical outcome of GER disease. Up to now no pharmacologic agents have been shown to affect the rate of episodes of transient or prolonged LESP failure underlying GER.

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