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# Gestational Maturation of Electrical Activity of the Stomach

SALVATORE CUCCHIARA, MD, PhD, GENNARO SALVIA, MD, ALDA SCARCELLA, MD, STEFANIA RAPAGIOLO, MD, OSVALDO BORRELLI, MD, GABRIELLA BOCCIA, MD, GIUSEPPE RIEZZO, MD, and FILIPPO CICCIMARRA, MD

Gestational maturation of gastrointestinal motility is a key factor in readiness of the preterm neonates for enteral nutrition. Since gastric motility mainly depends on the electrical activity of the smooth muscle cells, it was of interest to investigate the developmental aspects of electrical activity of the stomach. The latter was recorded weekly through cutaneous electrogastrography in 27 preterm infants (aged 29–34 weeks of gestation). Recordings were done for 1 hr before and 1 hr after meal. The electrogastrographic variables measured were: percentage of normal gastric rhythm, ie, 2–4 cpm; percentage of tachygastria (>4 cpm); the fed-to-fasting ratio of the dominant electrogastrographic power; and the instability coefficient of the dominant frequency. Data were compared with those measured in 10 full-term infants. Peaks of normal electrical activity (2–4 cpm) were present in most of the recordings at all the gestational ages; however, percentages of both normal electrical rhythm and tachygastria in preterm infants were similar to those measured in full-term infants (mean ± SD) (normal rhythm; fasting: 70.2 ± 3.8, fed: 72.2 ± 5.0; tachygastria: fasting: 24.6 ± 4.0, fed: 19.1 ± 3.5) by 35 weeks of gestation (normal rhythm; fasting: 67.5 ± 2.0, fed: 69.6 ± 4.4; tachygastria: fasting: 27.1 ± 4.0, fed: 25.6 ± 4.1). The coefficient of instability of the dominant frequency in preterm infants was also similar to the value measured in full-term infants by 35 weeks of gestation, whereas the EGG power showed a significant increase in the postprandial state at all the gestational ages. We conclude that a maturation pattern of the electrical activity of the stomach can be detected by means of a noninvasive tool such as cutaneous electrogastrography: a normal electrical rhythm can be detected at very early gestational ages; however, this activity becomes dominant at around the 35 weeks of gestational age. In preterm infants developmental changes of gastric electrical activity are a function of advancing postnatal age.

**KEY WORDS:** electrogastrography; gastric electrical activity; gastric emptying; premature infants.

Many preterm infants are nowadays surviving because of advances in management of pulmonary disease (1); their continued survival is related to the development of specific intestinal functions such as digestion, absorption, and contractile activity (2, 3). Adaptation of the preterm infants to enteral nutrients requires maturation and integration of intestinal absorption and motility (3). The latter is responsible for processes such as grinding of food and intraluminal transit and its immaturity may preclude feeding readiness in preterm infants (4).

Food is processed by contractions of gastric wall and gradually emptied from the stomach at a rate compatible with duodenojejunal absorption (5). Gastric emptying is a complex event that depends on gastric contractions and gastroduodenal motor coordination (6). Previous studies in preterm infants have

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From Gastrointestinal Endoscopy and Motility Unit; Neonatal Intensive Unit Care, Department of Pediatrics, University of Naples "Federico II," Naples; and from Scientific Institute of Gastroenterology, Catellana Grotte, Italy.

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

investigated the pattern of gastric emptying and the effect on it of different variables, ie, caloric density and composition of the formula (7–10); gastric motility has also been measured (11). However, these studies are rare and have required invasive procedures.

Because gastric motility is primarily determined by the cyclic electrical activity at the level of the membranes of smooth muscle cells (12), we have investigated the developmental aspects of gastric electrical activity in preterm infants through a noninvasive and recently developed technique known as electrogastrography (EGG) (13). Knowledge of the maturation of gastric electrical and other motility variables of the gut may provide physiologically and clinically important information.

## MATERIALS AND METHODS

**Subjects.** Longitudinal EGG studies were carried out weekly during two years in 27 preterm infants (aged 29–34 weeks of gestation, weight 1080–2850 g). Gastric electrical activity was recorded in each subject at regular intervals of one week from birth to the gestational age of 42 weeks. The study was approved by the Ethical Committee of the Department, and parents gave informed written consent before children were entered into the study.

**Protocol.** Preterm infants were selected if the following criteria were satisfied: absence of or complete recovery from respiratory illness; no evidence of gastrointestinal disease; no drug treatment (only antibiotics given intravenously were permitted); breast milk or infant formula given by nasogastric tube. The interval between the beginning of enteral nutrition and that of the EGG recording session was 1.5 ± 0.5 days. In each patient exclusive enteral nutrition was reached in about 10 days; therefore, by the second to third week of the recording sessions, all patients were receiving enteral nutrition exclusively. The caloric intake was determined taking into account weight and days of life, and fluid requirement was calculated as follows: 60 ml/kg during the first day of life + 10 ml/day until 150 ml/kg were reached. Daily feed volume was given at 2- or 3-hr intervals; feedings were administered over a mean period of 6 min (range: 4–11). Formula consisted of nonfortified expressed breast milk or appropriate infant formula (Similac Special Care Formula, Ross Laboratories, Columbus, Ohio). Gestational age at birth was calculated from maternal history based on last menses and physical examination of the infant at birth according to Dubowitz's score (14). The EGG data were compared with those detected in 10 full-term infants with a range weight of 3050–4200 g, studied within the first week of birth.

**Measurement.** The EGG was performed by placing two Ag–AgCl bipolar surface electrodes (Commed Andover Medtronic, Haverill, Massachusetts) on the epigastric skin. One electrode was positioned approximately on the midline of the abdomen, between the umbilicus and the xiphoid process, after sonographic localization of the antrum; the second electrode was placed on the subject's left side, above the level of the first electrode; a reference electrode was placed below the right costal margin at the level of the mid-clavicular line. The EGG was performed for 1 hr before and 1 hr after milk ingestion. The electrodes were connected to a 96-kilobyte portable battery operated recorder (Synectics Medical, Milan, Italy). All recordings were done at a sampling frequency of 4 Hz; the high and low cutoff frequencies were set at 0.01 and 0.5 Hz, respectively. The EGG data were digitized and processed by means of Redtech GiPC software. To analyze EGG data accurately, the EGG segments with motion artifacts were identified by visual analysis. The exact time corresponding to the beginning and the end of the EGG waves preceding the motion artifacts was calculated and converted in their relative sample number. After obtaining the data related to the waves, the artifact period was cut off from the original EGG signal by using the "cut-and-paste" option of the GiPC software (15). This procedure avoids to add "false frequencies" in the EGG signal. Prolonged recording sessions were obtained in order to analyze clean periods of 1 hr both for preprandial and postprandial data after artifact removal. The data were obtained by running spectral analysis. In this technique spectra were obtained as follows: every 64 sec a power spectrum was computed from the preceding 256 sec of the EGG time signal to which a Hamming window had been applied to reduce leakage; this procedure generates a series of overlapping spectra graphed as running spectra and makes both frequency and time analysis possible. A rhythmic activity of 2.0–4.0 cpm is defined as normal frequency range. The following parameters were measured: (1) percentage of normal gastric electrical rhythm and percentage of tachygastria (if the dominant peaks is in the 4.0- to 9.0-cpm range), ie, the percentages of time during which normal electrical frequency and tachygastria, respectively, are observed in the EGG—a dysrhythmic episode had to be recorded for at least 2 min with simultaneous absence of the normal rhythm; (2) the instability of the electrical frequency measured by the dominant frequency instability coefficient (percentage) and calculated during all the recording period—this variable is a measure of the dominant frequency change over the EGG recording period; and (3) fasting to fed ratio of the dominant EGG power (μV), that is the power at the dominant frequency in the power spectrum of the EGG (power ratio).

**Data Analysis.** Data (mean ± SD) were evaluated using analysis of variance for repeated measures (ANOVA), the Wilcoxon signed rank test, and Friedman's nonparametric test for repeated measures. $P < 0.05$ was considered to be significant.

## RESULTS

In full-term infants the percentage of normal slow wave frequency was 70.2 ± 3.8 and 72.2 ± 5.0, in the fasting and fed states, respectively; fasting and fed percentages of tachygastria were 24.6 ± 4.0 and 19.1 ± 3.5, respectively. Figure 1 shows a running spectral analysis from a full-term infant. In full-term infants, the power ratio and coefficient of instability of

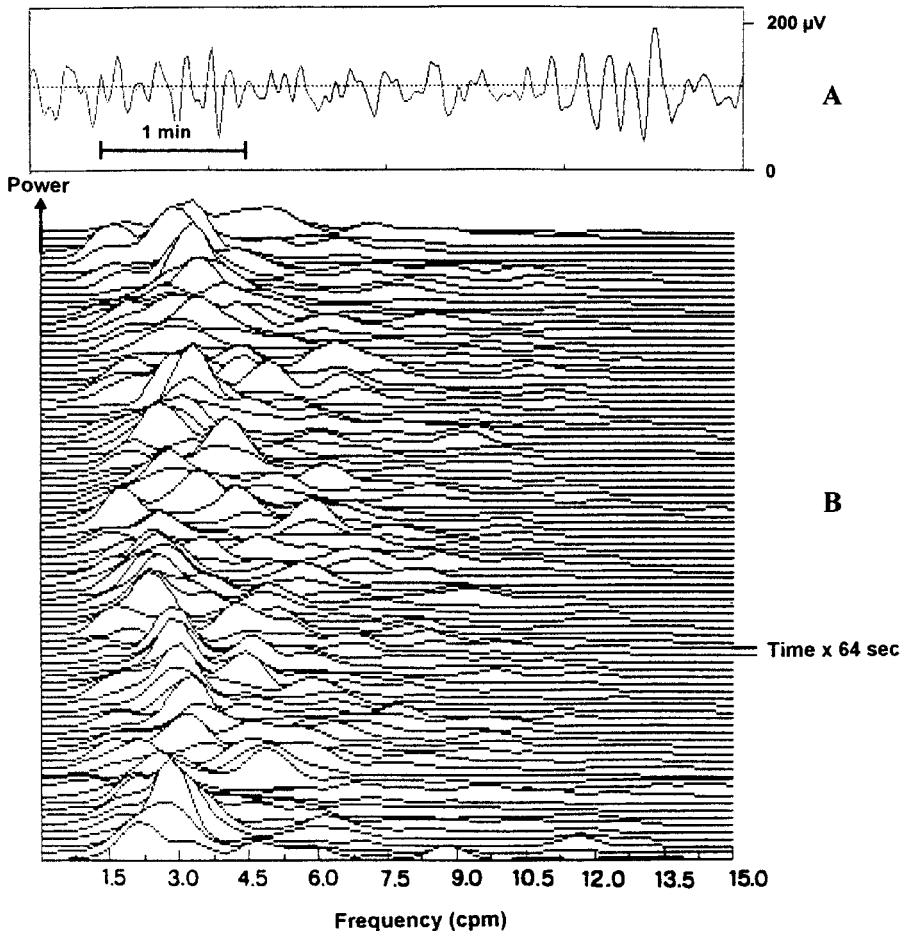


**Fig 1.** Example of a running spectral analysis from a full-term infant. Regular 3 cpm activity is observed for most of the recording time. The *x* axis indicates the frequency of the signal cpm; the *y* axis indicates time where the running spectral analysis represents consecutive segments of the EGG. A short extract of the cutaneous tracing is reported.

dominant frequency (percentage) were 1.7 ± 0.3 and 28.2 ± 6.6, respectively.

Table 1 shows changes of the EGG variables measured in preterm infants at various gestational ages. Percentages of both normal slow wave frequency and tachygastria were similar to those measured in full-term infants by the 35 weeks of gestation, whereas power ratio in preterm infants did not differ from full-term infants for all gestational ages. The coefficient of instability of dominant frequency was also similar to the value detected in full term infants by the 35 weeks of gestation.

## DISCUSSION

Intestinal smooth muscle cells exhibit a spontaneous cyclic electrical activity due to fluctuations in the resting membrane potential. This cyclic activity is known as slow waves or electrical control activity (16). Gastric slow waves originate from a pacemaker region along the greater curvature, near to the orad one third of the corpus, and propagate aborally towards the pylorus (6). Normal frequency of slow waves in the human stomach is about 3 cpm (0.05 Hz). If membrane potential depolarizes beyond a threshold level, slow waves are accompanied by a second type of electrical activity, known as spikes or electrical response activity. The latter determines the occurrence of mechanical contractions, whereas slow waves are responsible for spatial and temporal organization of the mechanical activity (16). Therefore, study of the profile of the electrical activity of the stomach as well as of other areas of the gut can be an indirect and meaningful way to assess mechanical activity.

Studies on ontogeny of gastric electrical activity are

TABLE 1. CHANGES IN ELECTROGASTROGRAPHIC VARIABLES MEASURED AT DIFFERENT GESTATIONAL AGES (MEAN ± SD)

| *Gestational age (weeks)* | *29* | *32* | *35* | *42* |
|---|---|---|---|---|
| Normal slow waves (%) | | | | |
| Fasting | 57.6 ± 2.3* | 60.7 ± 2.8* | 67.5 ± 2.0† | 71.0 ± 4.0 |
| Fed | 59.1 ± 3.0* | 61.6 ± 2.4* | 69.6 ± 4.4† | 73.8 ± 5.1 |
| Tachygastria (%) | | | | |
| Fasting | 39.7 ± 5.0* | 35.5 ± 5.1* | 27.1 ± 4.0† | 24.6 ± 3.1 |
| Fed | 38.4 ± 3.2* | 34.1 ± 4.8* | 25.6 ± 4.1† | 20.1 ± 4.2 |
| Fed/fasting power ratio | 1.5 ± 0.2† | 1.3 ± 0.3† | 1.5 ± 0.25† | 1.6 ± 0.1 |
| Coefficient of instability of the dominant frequency (%) | 41.0 ± 6.0* | 37.4 ± 5.5* | 32.0 ± 6.1† | 30.0 ± 7.5 |

* Significant difference from values detected in full-term infants (unpaired *t* test) and from values detected at 42 weeks of gestation in the same subjects (paired t-test) (29 weeks of gestation: $P < 0.01$; 32 weeks of gestation: $P < 0.05$).

† No statistical difference from values measured in full term infants and in the same subjects at 42 weeks of gestation.

rare and have involved small numbers of infants (17–19); furthermore, a wide and systematic investigation on the developmental aspects of gastric electrical activity has never been performed. In these studies it was shown that a 3-cpm activity could be detected by the postconceptional age of 32 weeks. However, a recent report on patterns of gastric electrical activity in human subjects of different ages indicates that a significant presence of normal electrical rhythm was established only by the age of 2 months (20); nevertheless, in this study peaks of normal electrical rhythm were recorded in preterm as well as in full-term infants. Very recently, Liang et al have shown that the gastric electrical activity is immature at birth and the percentage of normal slow waves increases from birth to 6 months of age (21). They have also shown that the percentage of normal slow waves at this age is lower than that detected in healthy adults. These results are at variance with those reported in our study. It is possible that more preterm infants with smaller gestational ages were recruited in our study; therefore the subjects we have investigated might have received a more prolonged exposure to enteral feedings as compared to those in the study of Liang. This is an important aspect since feeding is thought to stimulate the development of gastric slow waves in infants (13). It is also possible that the high values of the percentage of normal slow waves detected in our study might be due to the effect of antenatal betamethasone, which is routinely administered in our department to the mothers of preterm infants before delivery. Antenatal betamethasone has been shown to have a maturational effect on intestinal motility, which seems to be more pronounced in infants whose gestational age at birth is 26–29 weeks (22).

Preterm infants enrolled into the study had no systemic disorders. This is important, since previous observations from our unit suggest that gastric electrical activity can be deranged during pulmonary disease and sepsis (23). Analysis of EGG data showed that the normal slow wave frequency was detected for more than 70% of the recording time in full term infants and that significant changes of gastric electrical activity occurred at different gestational ages. A predominance in the normal gastric slow wave frequency and a decrease in the band of tachygastria were observed by 35 weeks of gestation. The coefficient of instability of the dominant rhythm gradually decreased with the increase of gestational age and was not different from the value measured in full-term infants by 35 weeks of gestational age. While the percentage of normal gastric slow waves is a quantitative assessment of the regularity of slow waves, the instability coefficient of the dominant frequency reflects subtle changes within a certain frequency range (24).

There is experimental evidence that a network of fibroblast-like cells, the interstitial cells of Cajal (ICCs), located between the circular and longitudinal muscle layers in the stomach, is the pacemaker region responsible for the generation of electrical slow waves (25, 26). Studies in the developing opossum and murine intestine have shown that ICCs are detected from very early days of development, although they lack gap junctions with smooth muscle cells, the low resistance connections allowing rapid spreading of depolarizing current (27–30). Although the normal pattern of intestinal smooth muscle organization can be observed by 22 weeks of gestation (28), our data suggest that complete maturation of ICCs and effective cou-

pling with adjacent smooth muscle cells occur at around 35 weeks of gestation.

Interestingly, intestinal manometry in preterm infants has shown a gradual maturation of intestinal motility with the increase of gestational age (31) and occurrence of interdigestive migrating motor complexes at around 34–36 weeks of gestation (32). This has been attributed to maturation of the enteric nervous system and its secreted neuropeptides (4). Thus, we would suggest that development of the intrinsic neural system is also involved in the maturation of electrical activity of the smooth muscle cells. Indeed, it has been shown that ICCS are intimately associated with intramural nerves and can mediate impulses from enteric nerves (33); there is also evidence that both the developing enteric nervous system and enteric smooth muscle can modulate differentiation and maturation phases of each other (28).

An increase of the fed-to-fasting ratio of the dominant EGG power was found in the preterm infants at all the gestational ages and in full-term infants. The significance of the postprandial increase of the dominant power is still unsettled. Despite the fact that physical distension of the stomach has been thought to determine the postprandial increase of the EGG power, there is a wide agreement that this increase is associated with antral contractions (13, 34, 35). We were attempting to interpret the increase of postfeeding EGG power in our subjects as the electrical counterpart of mechanical contractions. This explanation is at variance with the decrease in the antral mechanical activity reported in preterm infants after feedings (36, 37), whereas an increase in the number and amplitude of antral contractions is usually seen in adults and older children after feeding. These observed differences should be interpreted cautiously, due to the many variables that can affect the recording of antral motor activity, such as the amount of calories given, mode of delivery, relative intragastric placement (and displacement) of the recording sites, and number of antral recording ports. It is also possible that the increased EGG dominant power after feeding in our subjects can be due to the effect of postprandial delivery of neuropeptides, most of which are known to modulate motor activity of the gut (38, 39).

In conclusion, we have shown a clear maturation pattern of the electrical activity of the stomach by means of a noninvasive tool—the surface EGG. A normal slow wave frequency can be detected at very early gestational ages; however, this activity becomes dominant at around the 35 weeks of gestational age. Since gastric electrical activity determines spatial and temporal arrangement of mechanical contractions of the stomach, future studies should be focused on the relationship between gastric electrical activity and other functional variables of the stomach such as emptying and motility.

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