Motor Function in the Stomach and Small Intestine in the Neonate
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Motor Function in the Stomach and Small Intestine in the Neonate

Carol Lynn Berseth, MD*

Objectives
After completing this article, readers should be able to:

1. List the muscle and neural structures of the small intestine.
2. Describe the various components of regulation of motor function in the small intestine.
3. Recognize the two basic patterns of motor function in the small intestine.
4. Provide examples of interactions of feeding techniques on motor function in the small intestine.
5. Provide examples of drugs that stimulate or inhibit motor function in the small intestine.

Introduction
The fetus begins to swallow by the end of the first trimester and ingests 500 mL of amniotic fluid daily by term. Ingested fluid traverses the small and large intestines by the end of the second trimester, and stressed infants can pass meconium as early as 22 to 24 weeks’ gestation. Many aspects of motor function are immature in the preterm infant, particularly in the small intestine. If immaturity of motor function precludes delivery of sufficient nutrients to the infant, orogastric tube and transpyloric tubes can be used to bypass the pharynx, upper and lower esophagus, and stomach to deliver nutrients directly into the stomach or small intestine. However, there are no mechanical methods to bypass the small intestine, the site of active nutrient absorption. For this reason, immaturity of small intestine motor activity often limits the delivery of enteral nutrients to the preterm infant. Various studies have shown that mucosal function of preterm infants is adequately mature to digest and absorb nutrients. Feeding intolerance is largely due to immaturity of motor function rather than mucosal function.

As shown schematically in Figure 1, the mucosa is circumferentially surrounded by three muscle layers. The innermost layer, called the muscularis mucosae, underlies the mucosa and is the thinnest of the three muscle layers. The fibers of the middle layer, or circular muscle, are arranged circumferentially around the intestine. The nerves of the submucosal plexus are located between the muscularis mucosae and the circular muscle. The outermost layer, the longitudinal muscle, is arranged 90 degrees in opposition to the circular muscle, or along the length of the intestine. The nerves of the myenteric plexus lie between the circular and longitudinal muscle.

These muscle layers and their accompanying nerves perform a variety of functions throughout the length of the gut. They may relax to accommodate food in the stomach, contract tonically to prevent the forward movement of food in the pyloric sphincter, or contract intermittently to churn or expel food in the small and large intestines. This article describes the embryogenesis of these structures as well as the integration of the regulation of motor activity as it relates to stomach and small intestine.

Embryology and Physiology of Motor Function Regulation
The establishment of structures of the motor units for the small intestine is initiated early in fetal life when neural crest cells migrate from the primitive neural tube. These cells track along the major arterial vessels into the primitive gut. On arrival in the gut, they release a series of cellular messages to the surrounding mesenchyme to trigger differentiation of
surrounding cells into muscle cells. These cells, in turn, evolve to form the circular muscle layer of the intestine and release messengers to the primitive neural cells to trigger the formation of mature neural cells, resulting in the formation of the myenteric plexus. In leap-frog fashion, these cells subsequently trigger the formation and maturation of the longitudinal muscle layer and its accompanying plexus and the muscularis mucosae (Fig. 2). Specialized muscle cells, the interstitial cells of Cajal, are the final structure to emerge. Although the basic components of motor function are present by 22 to 24 weeks’ gestation, a recent study has shown that local neural transmission and integration mature throughout fetal life. Full maturation of these functions emerges throughout the first postnatal year.

Motor function of the small intestine results from the integration of intrinsic autonomic muscle function (ie, pacemaking) and neural regulation, as detailed in the Table. Similar to cardiac muscle, intestinal muscle has an intrinsic rate of contraction due to the electrical properties of the cell membrane. Thus, stomach muscle contracts 3 to 5 times/min, duodenum contracts 9 to 11 times/min, and mid-gut contracts 6 to 8 times/min. These local contractions are coordinated throughout the length of the intestine by neural regulation. Neural regulation is largely supplied by the enteric nervous system (ENS), which is comprised of nerves whose cell bodies are located within the intestine, and functions independently of the central nervous system (CNS). Although the ENS is the major source of neural regulation of motor function, the autonomic nervous system and CNS can modulate gut function. An example of this modulation is the gross inhibition of motor function that occurs as the “fight or flight” response during stress. The interstitial cells of Cajal are specialized muscle cells located primarily in the duodenum and upper small intestine. They also play a role in triggering coordinated contractions in the intestine. Finally, motor function can be modulated by gastrointestinal hormones and
peptides, which may exert endocrine, paracrine, or neurocrine activity, resulting in inhibitory (eg, peptide YY) or excitatory (eg, vasoactive intestinal peptide) modulation. All of the muscle and neural structures are present by 32 weeks’ gestation, although full neural and neuroendocrine integration is not achieved until late in infancy.

Motor Function in the Stomach

The stomach consists of two functional regions. The proximal region, the fundus, accommodates ingested nutrients by receptive relaxation. In the adult, receptive relaxation is mediated largely by the CNS via the vagal nerve. However, little is known about receptive relaxation in the newborn. Gastric wall compliance in newborns is less than that seen in adults, but it improves rapidly over the first three postnatal days, as feeding volumes increase.

In contrast to the fundus, the distal region of the stomach, the antrum, has tonic activity. It is responsible for the churning of nutrients with secretions to initiate early digestion and empty stomach contents into the upper small intestine. Gastric emptying in newborns is similar to that seen in adults when ingesting liquids. Contractile activity in the antrum is coordinated with that in the duodenum to promote emptying of contents into the upper small intestine. Hence, physical characteristics of nutrients trigger feedback to the antrum to hasten or slow emptying. As in the adult, diluted formula or milk empties more slowly from the newborn stomach than does full-strength formula or milk. Gastric emptying is not altered by feeding temperature or non-nutritive sucking. However, it is delayed during extreme stress, such as the presence of systemic illness.

Motor Function in the Small Intestine

The intrinsic contractile rhythm of the stomach, duodenum, and small intestine are present as early as 24 weeks’ gestation. Whether it is present earlier has not yet been determined. Because full neural integration is not yet present, gastric contents are emptied more slowly in the preterm infant than the term infant, and overall intestinal transit is slower. Overall gut transit can be assessed by instilling a nonabsorbable dye into the stomach or upper small intestine and observing how many hours elapse until the dye is excreted in the stool. When using this assessment, the appearance of dye is delayed up to 7 days during the first postnatal week. This type of assessment does not specify which region(s) of the gut is (are) responsible for this delay. The delay could be due to poor small intestine motility or it could reflect poor motility in the large intestine or the rectal/anal area. A recent trial has shown that motor function in the rectal/anal area is adequate in the preterm infant as young as 24 weeks’ gestation. However, current technical and ethical concerns limit the ability to assess the motor function of the large intestine and its contribution to overall transit in the preterm infant.

Basic Motor Patterns in the Small Intestine

The small intestine exhibits two basic patterns of motor activity: those present during fasting and those present during active feeding. During feeding, all the muscle layers of the gut contract in a chaotic, disorganized fashion, as shown on the right side of Figure 3. This results in the active, continuous mixing and churning of nutrients with secretions and gastrointestinal peptides and hormones and the presentation of partially digested nutrients to the mucosal surface for absorption.

When the gut is not actively “feeding,” the interdigestive pattern appears, as shown on the left side of Figure 3. The contractures of the gut cease or become quiescent. This pattern is called phase I. Over time, single or clustered contractures occur at various levels of the gut. The occurrence of these contractions gradually increases in number and intensity, but they are not coordinated distally along the gut. This pattern is termed phase II. Finally, the contractures are sustained for 2 to 10 minutes and migrate sequentially distally down the length of the gut. This pattern is called phase III or the migrating motor complex (MMC). It is responsible for about 50% of the forward movement of nutrients and is considered the “intestinal housekeeper.” This pattern is replaced by randomly occurring contractures that terminate in the reappearance of quiescence (phase IV). The entire sequence of phase I through IV is called the interdigestive migrating motor complex (IMMC). In adults, the entire IMMC recurs periodically throughout the day unless interrupted by active feeding, which triggers the appearance of the fed pattern. The IMMC recurs at the completion of the active fed pattern, the duration of which depends on the nature of the nutrient that is being digested and processed.

The appearance of the MMC also is controlled by the interstitial cell of Cajal, which can be triggered by the hormone motilin. Plasma concentrations of motilin cycle sinusoidally in the adult, with the peak associated with the occurrence of the MMC. Preterm infants exhibit fasting levels of motilin that are similar to those seen in adults, but motilin fails to cycle in the preterm infant. The initial amino acid configuration of the antibiotic erythromycin mimics that of the hormone motilin, and
low doses of erythromycin trigger initiation of the MMC in the adult as well as preterm infants whose gestational ages exceed 32 weeks. Administration of erythromycin fails to trigger MMCs in infants younger than 32 weeks, suggesting that the motilin receptor is absent before 32 weeks' gestation. Thus, the absence of the MMC in the very preterm infant appears to be the result of overall immaturity of the integration of motor pattern, absence of the motilin receptor, and absence of sinusoidal cycling of motilin.

**Motor Patterns in the Stomach**

Contractions in the antrum occur as single isolated events or in clusters (Fig. 4). With feeding and distention of this region, contractions cease. However, it is not known if this is due to actual cessation of contractions or to the artifact caused by antral disten-

tion. The MMC during fasting includes the antrum, with clusters of contractions occurring in the antrum temporally coordinated with those in the proximal duodenum.

**Motor Patterns in Preterm and Term Infants**

Motor patterns during both fasting and feeding are immature in the preterm infant compared with those seen in the term infant, which, in turn, are more immature than those seen in the adult.

During fasting, preterm infants rarely exhibit the complete IMMC before 34 to 36 weeks' gestation. Rather, they exhibit a pattern of clustered phasic contractions (Fig. 4). The phasic contractions progressively increase in duration and intensity from 28 to 34 to 36 weeks' gestation, when the complete IMMC appears. Interestingly, infants who have feeding intolerance are more likely to have more immature patterns than those who are tolerant of feedings. However, giving small enteral feedings during the first 10 postnatal days causes more mature motor patterns to appear precociously, which is associated with better feeding tolerance.

![Figure 3. A representative recording of small intestinal motor activity in a term infant.](image)

![Figure 4. A representative recording of motor activity in the antrum and upper small intestine in a preterm infant.](image)
During feeding, only about 50% of preterm infants display an active “fed response” (Fig. 5). Similar to what has been described for motor patterns during fasting, the mature “fed response” also matures precociously with feeding experience.

Feedings Affect Motor Function
Giving preterm infants small feedings (20 to 24 mL/kg per day) induces maturation of fasting motor patterns. Because of the complexity and redundancy of neural and hormonal regulation of motor function, feedings possibly could induce maturation of motor patterns by triggering maturation of either of these singularly or together. Although infants given small feedings have higher plasma concentrations of gastrin, gastric inhibitory polypeptide, and motilin, they have lower concentrations of peptide YY and similar concentrations of neurotensin compared with unfed infants. Characteristics of motor patterns fail to change as a function of plasma concentrations of any of these peptides. These findings are consistent with the conclusion that feedings induce maturation of neural regulation rather than hormonal regulation, but this has yet to be tested in preterm infants. Maturation of motor function is reflected by faster gastric emptying and intestinal transit.

Interestingly, there is no dose-response relationship for feeding volume and maturation of motor patterns; that is, infants fed 150 to 160 mL/kg per day exhibit similar motor patterns to those exhibited by infants fed 20 to 24 mL/kg per day. This observation has two elements of practical application for the clinician. First, if there are concerns that large feeding volumes precipitate necrotizing enterocolitis, small feedings can be employed as effectively as larger volumes to induce maturation of motor patterns. Second, when feeding volumes must be limited because of concerns for feeding intolerance or for other nongastrointestinal-related issues such as surgery or sepsis, such smaller feeding volumes are providing the same benefit with respect to maturation of motor patterns.

As noted previously, approximately 50% of preterm infants fail to exhibit a mature fed response when fed by bolus over 1 to 2 minutes. When these same infants are provided the same feeding volume more slowly over 1 to 2 hours, they exhibit a mature fed response. It appears that this phenomenon is due, in part, to immaturity of vagal regulation of motor activity, which may be related to immaturity of gastric accommodation/relaxation.

We have shown that infants resume their prefeeding motor pattern approximately 1 to 2 hours after being fed by slow infusion over 1 to 2 hours. However, resumption of the prefeeding pattern may be delayed up to 3 to 4 hours in some infants, who may benefit from longer intervals between feedings.

Drugs Affect Motor Function
Because motor function is regulated by the ENS, administration of drugs that increase or decrease the release of neurotransmitters may stimulate or inhibit motor function. The neonatologist needs to be aware that some commonly used drugs have adverse effects on gastrointestinal motility. For example, the gut is rich in morphine receptors, and motor function and gut transit are significantly diminished when opioids are administered. The parasympathetic effects of mydriatics given for routine ophthalmologic screening for retinopathy of prematurity often result in a loss of the fed response and an increase in overall quiescence during fasting, causing significantly more feeding intolerance.

Concluding Thoughts
Although small intestinal manometry remains a research tool that is not widely available in neonatal intensive care units, understanding motor patterns and their interactions with feeding and drugs may permit the neonatologist to adopt a more well-informed approach to feeding. For example, if feeding intolerance limits the ability to provide full feeding volumes to an infant, smaller feeding volumes...
volumes may be just as capable of inducing maturation. Similarly, an infant who is intolerant to bolus feedings may tolerate feedings that are given over 1 hour every 3 hours. An infant who has large gastric residuals may tolerate feedings better when longer intervals between feedings are provided. The neonatologist also may want to exercise caution when administering certain drugs to the preterm infant.

Suggested Reading

NeoReviews Quiz

7. During fetal development, neural crest cells migrate from the primitive neural tube along major arterial vessels into the primitive gut. Upon arrival in the gut, they trigger the differentiation of mesenchymal cells into muscle cells, which, in turn, trigger the maturation of neural cells, resulting in the formation of the myenteric plexus. Of the following, the precise location of the myenteric plexus within the cross-section of the intestine is:
   A. Between the circular muscle and the longitudinal muscle.
   B. Between the muscularis mucosa and the circular muscle.
   C. Within the mucosa.
   D. Within the muscularis mucosa.
   E. Within the submucosa.

8. Interstitial cells of Cajal are specialized cells located in the wall of the gastrointestinal tract that trigger coordinated contractions within the gut. Of the following, the primary location of the interstitial cells of Cajal is in the:
   A. Colon.
   B. Duodenum.
   C. Esophagus.
   D. Rectum.
   E. Stomach.

9. You are describing to medical students the consequences of incomplete structural and functional development of the gastrointestinal tract in preterm infants and the resultant signs and symptoms of feeding intolerance. Of the following, the most accurate statement regarding gastrointestinal development and enteral feeding in preterm infants is that:
   A. Diluted milk empties more slowly from the stomach than does undiluted milk.
   B. Feeding intolerance is largely due to immaturity of mucosal function rather than motor function.
   C. Gastric emptying is influenced by the temperature of the milk.
   D. Large feeding volumes induce maturation of motor patterns of the gut more effectively than small feeding volumes.
   E. Motor function develops earlier in the stomach/small intestine than in the rectum/anal canal.
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