Feeding and Maturation of Gut Motility

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Motor function is exerted by the three muscle layers that comprise the outer layers of the intestine. These muscle layers must contract in a coordinated fashion:

1. to mix and churn intraluminal nutrients during the process of digestion and
2. to move the unused materials aborally for expulsion.

Motor activity is responsible for the movement of nutrients from the posterior pharynx to the stomach through the esophagus, the emptying of gastric contents into the proximal duodenum, the movement of nutrients distally through the small and large intestines, the storage of fecal material, and the expulsion of waste. This muscle activity is under neural regulation. The most direct neural regulation is exerted by the enteric nervous system (ENS), which is considered to be part of the autonomic nervous system. Although the central nervous system, sympathetic nervous system, and parasympathetic nervous system can modulate motor function, neural regulation of intestinal motor function by the ENS occurs when input from any of these three other systems is interrupted. Thus the ENS can function independently of the other systems. In addition, the ENS has a unique, intimate relationship with the mucosal surfaces of the gastrointestinal tract. First, primary afferent nerves provide input concerning events related to the intraluminal nutrients, such as distention of the luminal wall. Second, local neural reflexes may be triggered by physical or chemical properties of the intraluminal nutrient, such as osmotic load or the presence of fat. Finally, the presence of intraluminal nutrients triggers the release of gastrointestinal hormones and peptides, which may exert endocrine, paracrine, or neurocrine regulation of motor function. In summary, the regulation of motor activity in the small intestine is very complex, and the quantity and the quality of the nutrients present in the lumen of the gut exert significant influence on motor function.

Despite the complexity of neural and hormonal regulation of motor activity in the small intestine, two basic patterns of activity are described in the adult (1). During fasting, motor activity cycles through three types of patterns every 60 to 90 minutes. First, there is motor quiescence, or an absence of motor contractions. This pattern in turn is gradually replaced by one of irregular contractions. These irregular contractions in turn are replaced by a series of intense, phasic contractions that are initiated.
in the distal antrum and sweep distally through the duodenum, jejunum, and ileum in a coordinated, sequential fashion. This latter event is called the migrating motor complex, or MMC, and the complete cycle of all three patterns is called the interdigestive cycle (Fig. 1). It is the MMC that is responsible for propelling intraluminal nutrients forward, and as such is called the intestinal housekeeper (2). When a meal is ingested, this cyclical pattern is disrupted by the presence of persistent uncoordinated contractions occurring at all levels of the intestine. This pattern is called the fed response (Fig. 2). The duration of the fed response is dependent upon the volume and the characteristics of the meal ingested.

In adults there is a reciprocal relation between motor function and the type of foods or nutrients ingested. When loss of neural regulation of motor function occurs, as the result of diabetic neuropathy for example, the process of emptying foods from the stomach or the overall time required to move the food from the mouth to the rectum may be significantly delayed. Conversely, the presence of specific nutrients may slow gastric emptying or hasten intestinal transit. Thus it has been shown that when fats are not completely digested or absorbed, their presence in the distal intestine may stimulate the release of peptide YY, which in turn may slow gastric emptying (3). Although many aspects of gastrointestinal function are immature in the preterm and term neonate, there are many that are partially or fully present. Thus certain aspects of the intimate relation between feeding and motor function may be exploited in designing enteral feeding strategies for these high risk infants.

It has been well recognized that motor function in the preterm infant differs from that seen in the adult as well as in the term infant. The ability to suck does not appear
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FED PATTERN IN A TERM INFANT

Proximal duodenum

Mid duodenum

Distal duodenum

Proximal jejunum

25 mm Hg

1 min

FIG. 2. The magnification and configuration of this tracing are similar to those in Fig. 1. Continuously recurring contractions are seen at all four levels of the intestine. (Reproduced with permission from ref. 9.)

until 32 weeks of gestation (4). Lower esophageal tone and function is immature in the preterm infant compared with that seen in older infants (5). Gastric emptying is more delayed in the preterm infant than in the term infant (6), and overall intestinal transit is slower in the preterm infant (7). Although enteral feeds can be given by oro-gastric or transpyloric tubes, immaturity of gastric emptying and intestinal transit often precludes the use of enteral feeding. Thus the major focus of this discussion will be on motor function of the stomach and small intestine.

Motor patterns during fasting and feeding have been described in preterm and term infants. While characteristics of antral motor patterns are similar, the patterns seen in the duodenum differ in preterm and term infants (8,9). Though adults display full interdigestive cycles during fasting, few infants with gestational ages of less than 34 to 35 weeks do so. Instead, preterm infants display short episodes of motor quiescence that alternate with irregular contractions. In addition, infants display a pattern that is not commonly seen in adults, called the cluster (Fig. 3). Clusters consist of regular, phasic contractions that do not migrate. They are arbitrarily defined as short if they have a duration of less than 2 minutes and long if their duration exceeds 2 minutes. This pattern occupies 40% of the manometric recordings of preterm infants. Although term infants show complete interdigestive cycles, they also display a prominence of clusters. Characteristics of clusters change with increasing gestational age, in that the duration of individual episodes increases and the overall occurrence decreases. These maturational changes can be used to assess the level of functional maturation of the neonate’s intestine in order to assess feeding strategies.

Motor responses to feeding are also immature in the preterm infant. Neonates most commonly ingest feeds over 15 to 20 minutes whether they are being breast-fed or
ingesting an artificial formula. The term infant who is fed over 15 minutes displays a brisk fed response, in that the overall occurrence of contractions increases and interrupts the presence of the interdigestive cycle. When the preterm infant is fed over 15 minutes, only 40% will display an increase in contractions to interrupt the fasting pattern. The others will display a decrease in motor activity (10).
EFFECTS OF FEEDING ON MOTOR ACTIVITY

Exposure of the gut to intraluminal nutrients hastens maturation of motor function. A series of clinical trials has demonstrated that characteristics of duodenal motor activity in the preterm infant evolve quickly when infants are given routine feeds, in that the complete interdigestive cycle emerges and the duration of individual episodes of clusters increases, while the overall occurrence decreases (11). When infants are given parenteral nutrition supplemented with small feeds of 24 ml/kg-d of regular formula or an equal volume of sterile water, motor activity matures faster in those given the formula feeds. In addition, plasma concentrations of gastrointestinal peptides that modulate motor function—such as gastrin, motilin, and gastric inhibitory peptide—increase in infants who receive these small feeds. This enhancement of maturation of gut function is in turn reflected clinically, as these infants make a faster transition to full enteral feeding and have fewer days of feed intolerance compared to the unfed babies. This effect of feeding appears to be related to the presence of nutrient and not volume, as babies who receive “feeds” containing sterile water do not show the maturation of motor function and plasma hormone release that occurs in babies fed nutrients (12).

Studies in animals have provided some additional insight into the volume of nutrient that is necessary to trigger maturation of motor activity. When newborn dogs are given chronic parenteral nutrition and their energy intake is supplemented with varying levels of enteral feeding, only feed volumes that provide in excess of 30% of daily estimated energy intake cause an increase in gut growth, as assessed by bowel weight and DNA and protein content (13). On the other hand, enteral feed volumes that provide as little as 10% of daily estimated energy intake cause an increase in the maturation of the appearance of migrating motor activity. We speculate from these findings that feeding strategies that provide enteral feed volumes of 10% or more of daily estimated energy intake are sufficient to trigger the maturation of gut motility if there are clinical indications to limit the volume of enteral feeding given to the preterm infant.

Just as in the adult, the composition, volume, and rate of feeding can all affect the type of motor responses seen in preterm infants when they are given feeds. As noted earlier, when preterm infants are fed by bolus over 15 minutes, about half will show a decrease in duodenal motor activity (11). This decrease in motor activity is associated with a decrease in the rate at which gastric contents are emptied from the stomach into the upper intestine. When these same infants are fed the same volume over 120 minutes, they show an increase in motor activity similar to that seen in term infants, and they empty their gastric contents more quickly. Thus this subgroup of infants may tolerate enteral feeds better if they are given as a slow, intermittent infusion.

The presence of a small volume of feed (e.g., 4 ml/kg) is as capable as a larger feed volume (e.g., 10 ml/kg) of eliciting a motor response to feeding (14). Therefore when one is using minimal feed volumes to enhance gut maturation, small volumes appear to be able to achieve the same level of stimulation of motor function as larger ones. This effect can be elicited when using enteral feed volumes that provide as little as 10% of the infant’s daily estimated energy intake.
Feeding diluted formula to preterm infants results in a diminished motor response (14,15). However, the intestine responds similarly to feeds given intragastrically or transpylorically. As in the adult, warming or chilling formula does not result in any alteration in motor activity or gastric emptying.

EFFECT OF MOTOR FUNCTION ON FEEDING

Because motor function is regulated by neural and hormonal input, the administration of drugs or nutrients that alter the release of neurotransmitters or hormones can in turn alter motor function. The administration of antenatal steroids has been shown to induce maturation of the central nervous system as well as intestinal mucosal enzyme release. Therefore one could postulate that preterm infants exposed to antenatal steroids might show more mature motor function. Morriss demonstrated that duodenal motor contraction rate was higher in preterm infants who had been exposed to antenatal steroids than in those who had not (16). Similarly, we have recently shown in a large retrospective study that infants exposed to one or more doses of steroids antenatally show more motor quiescence and less cluster activity than infants who had not received antenatal steroids (17). These infants also experienced better feeding tolerance. Others have reported that infants exposed to antenatal steroids have a lower incidence of necrotizing enterocolitis, but this finding has not been confirmed.

Opioids are commonly used to sedate preterm infants who require ventilator support. The gastrointestinal tract is richly populated with opioid receptors. In another study we have shown that recordings of motor activity in babies who are fed within 24 hours of their most recent dose of morphine show significantly more motor quiescence than babies fed 48 to 72 hours after the most recent dose of morphine. As a result, the former infants have a more rapid rate of gastro-anal transit, suggesting that they have not had as good an opportunity to absorb nutrients.

Mydriatics instilled for routine screening for retinopathy of prematurity alter parasympathetic and sympathetic input. When preterm infants receive eyedrops before their first eye examination, they show a profound decrease in gut motor activity, and this results in a delay in gastric emptying (18).

The antrum and upper duodenum possess receptors for the hormone motilin. When motilin binds to these receptors, an episode of migrating activity is initiated. The antibiotic erythromycin binds competitively to the motilin receptor. Intragastric administration of erythromycin can trigger the initiation of migrating activity in preterm infants whose gestational ages exceed 32 weeks, and it can be used to increase gastric emptying in these infants (19).

THE INTERRELATION OF NUTRIENTS AND MOTOR FUNCTION IN DEVELOPMENT OF FEEDING STRATEGIES

An improved understanding of the interrelation between motor function and the presence of intraluminal nutrients may enable a more pragmatic approach to decisions about feeding preterm infants. For example, providing small enteral feeds to ex-
tremely premature infants may permit the bowel to mature faster, smoothing the transition to larger feed volumes later on. It appears that a volume as small as 10% of daily estimated energy intake, or approximately 15 to 20 ml/kg-d, can achieve this goal. If there are clinical reasons to limit the volume fed to the baby—such as concerns about the association between higher feeding volumes and necrotizing enterocolitis, or the need to reduce fluid intake in a baby who has chronic lung disease—current studies suggest that the benefits of enteral feeding on motor function can still be achieved using small volumes. In infants who have immature responses to bolus feeds, one may wish to consider the use of intermittent slow infusions to improve gastriic emptying and feed tolerance.

Many different drugs are given to preterm infants as part of their routine care, including opioids, methylxanthines, prostaglandin inhibitors, mydriatics, and antibiotics. All these drugs may have unintended effects on gastrointestinal motor function. Thus the neonatologist may wish to withhold or alter feeding strategies while infants are receiving these drugs. Alternatively, as more information on the control of developing motor function has become available, the intentional use of agonists or antagonists of neural input to the intestine may be useful in enhancing the ability to provide nutrients enterally. Feeding selective nutrients enterally may also trigger the endogenous mechanisms for neural or hormonal regulation of motor function.

REFERENCES

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DISCUSSION

Dr. Da Silva: In relation to pharmacological manipulations, do you have any information about the use of cisapride, in animal models, for example?

Dr. Berseth: There has been very little work done on cisapride in neonates. My concern with many drugs is that we don't know what receptors are present, or what neural mechanisms. We know from work on erythromycin that there is a gestational evolution of response to that drug, and there is a very precise dose/response effect in neonates that is significantly different from what one sees in the older child. Based on those data, I would certainly speculate that we would see differences in the way cisapride is handled. However, a group in Europe demonstrated increased gastric emptying with cisapride [1], though I don't know the gestational ages of the babies. We need a lot more information. One should keep in mind that the intestinal tract may be telling us that it is not ready. When we force it by using such agents, we may be doing more harm than good.

Dr. Costalos: We have just completed a study on preterm babies where we measured gastric emptying ultrasonically. We found much faster gastric emptying with cisapride.

Dr. Walker: As you know, there is an intimate relation between the enteric immune system, the enteric nervous system, and by implication the muscles within the intestine. What do you know about inflammatory cytokines and their role on motility in the immature intestine? I'm referring particularly to studies that Scott reported a number of years ago, though not on premature infants, suggesting that inflammatory cytokines released under conditions of mast cell stimulation can enhance peristaltic movement in the intestine [2]. I wonder if there is anything known about this in the context of the very small infant?

Dr. Berseth: I don't think this has been looked at specifically in the human infant. It's an important issue that needs study, particularly in view of the pathophysiology of necrotizing enterocolitis, which is usually heralded by abdominal distention.

Dr. Rashwan: Could you summarize the advantages of continuous versus intermittent feeding? And did you study position? Previous studies mentioned that positioning the infant at 45°, for example, enhances gastric emptying.

Dr. Berseth: I want to make clear that when we did our studies, we were not looking at continuous infusions. We looked at an intermittent infusion given slowly versus an intermittent infusion given rapidly. We found that emptying was incomplete with the slow, intermittent infusion regimen, suggesting that when continuous infusions are used we may not be allowing the intestine to clear material completely. But I don't want to give the impression that we were assessing continuous infusions; we weren't. When I'm feeding babies, I prefer some sort of cycling where there is a period of feeding and a period of fasting. Both cyclical fasting activity and the feeding response may be important for normal physiological gut activity.

With reference to position, we often don't have the ability to choose this, because the position is dictated by the needs of pulmonary care. When we do our gastric emptying studies as a
research tool, we are careful about making sure that the babies are positioned the same way, to minimize posture as an additional variable, but we haven’t specifically investigated that aspect.

Dr. Rashwan: But does position enhance emptying or not?

Dr. Berseth: Yes, Victor has shown that the position does influence emptying [3]. If one were just concerned with emptying, one would place the baby right side down.

Prof. Cooke: One of the reasons usually given for delaying feeding sick newborn infants is that their gastric motility is likely to be abnormal when they’re hypotensive or acidotic or hypoxic. Do you have any evidence from your studies that any of these abnormal physiological conditions alter gastric motility in preterm infants, or can we actually ignore the fact that the infant is sick and carry on feeding?

Dr. Berseth: We know that the central nervous system and the parasympathetic and sympathetic systems can have a tremendous effect on gut motor function. We don’t choose to study babies when they are in a stressed condition, but there are some who develop difficulties while we are doing the studies, and in those instances we can see their activity tapering off. I don’t think we have any way of being able to assess the effect directly in any given clinical situation, but in general one would anticipate that any stress is going to have an inhibitory effect on motor function.

Dr. Sedaghatian: Have you done any studies on breast milk versus formula? Most of your babies seem to have been on Similac.

Dr. Berseth: Studies were done comparing breast milk with formula some years ago in a very small number of babies [4]. There was some evidence of a faster return to the prefeeding pattern when babies were fed breast milk. We have not repeated those studies, but that would be of interest.

Prof. Lucas: From our own studies, human milk and formula have a profoundly different effect on gastrointestinal hormones, so I think that would be a fruitful area to pursue. Do you think that motilin has any promise as a therapeutic agent for stimulating gut maturation or gut motility in clinical situations where there is a functional ileus or where immaturity seems too great for enteral feeding? I am aware of one case report, but you may know of more data on this.

Dr. Berseth: To remind those who may be rusty on the subject, motilin is a hormone that is released cyclically into the blood. It binds to motilin receptors in the distal stomach and upper intestine and triggers the migrating motor complexes. Our original reason for looking at erythromycin was specifically that its amino acid structure makes it a competitor for the motilin receptor. We found that there is no cyclical release of motilin in preterm babies; however, beyond about 32 weeks of gestation they will respond to erythromycin, so it does appear that the receptor is present. In the older infant therefore there may be opportunities to use motilin or an analog as a prokinetic agent, and there are some reports of its use in postoperative babies with feeding difficulties. A nonantibiotic analog of erythromycin has been developed and is undergoing clinical trials in adults. If this were to become available for pediatric use, it would be a very interesting drug to evaluate.

Dr. Costalos: We measured gut hormone levels in babies fed intragastrically or naso-jejunally, and we found almost identical hormone patterns.

Dr. Berseth: The only difference we found in our studies was the release of gastrin. When we use transpyloric feeding, we are not able to show gastrin release.

Dr. Horpaopan: In your study of mydriatics for eye examination, how long does the effect last?

Dr. Berseth: We did not continue to record throughout the day after the eye examination,
so I don’t know. However, it seems that even with the low doses now in use, we are getting systemic absorption and we are seeing gastrointestinal effects as a result. Neonatologists need to be aware of this in terms of possibly altering the feeding regimen on the day of the examination.

**Dr. Devane:** Do you have information on day-to-day variability in a given baby in gut motor patterns?

**Dr. Berseth:** We don’t record from day to day. Most of our babies had records on three separate occasions. Despite the fact that there is a maturational change going on, every baby has a very characteristic pattern, so I think there is consistency over time in a given baby. But obviously there are things that change every day in the nursery—babies develop infections, they may have apnea, bradycardia, and so on, so there are many other factors that may cause day-to-day variation.

**Prof. Moro:** There seem to be two different ways of feeding VLBW infants, practically speaking. One is to use continuous feeding 24 hours a day, and the other is to use small bolus feeds every 1 or 2 hours. According to what you have told us, there could be a third option—to feed continuously for periods of several hours, interspersed with some hours of rest. Could you comment on this?

**Dr. Berseth:** Schanler has just finished a very large trial looking specifically at the use of continuous feeding versus bolus feeding. I have been using the third alternative you describe—that is, 1- or 2-hour infusions followed by 2 hours of fasting. The reason I used 2 hours of fasting was that from earlier studies it appeared that a small number of babies took about 90 minutes to return to the fasting pattern; thus I chose 2 hours to ensure that they all returned to a prefeeding pattern. Now that we have some of our gastric emptying data available, we have some concern about the use of continuous infusions, even though the overall outcome in terms of weight gain and the establishment of feeding were not different between the two feeding strategies.

**Prof. Ziegler:** Bile aspirates are obtained every now and then and they usually cause alarm. Am I correct in saying that retrograde paradoxical duodenal motility may explain these bile stained aspirates?

**Dr. Berseth:** Some babies certainly have retrograde migration, though others may have episodes of ileus that account for the finding.

**REFERENCES**


