Small Bowel Motility: Ready for Prime Time?

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The primary function of the small bowel is the absorption of nutrients, and the motor patterns of the healthy bowel are intended to promote that function. The motor patterns of the small bowel are the result of close interaction between the enteric nervous system, extrinsic nerves, regulatory peptides, and the intestinal smooth muscle. The basic electrical rhythm governing intestinal contractions is determined by specialized pacemaker cells called the interstitial cells of Cajal. Diseases affecting any of these components may result in intestinal dysmotility and its associated symptoms. Although transit studies and intestinal manometry are helpful in the diagnosis of dysmotility, our understanding of pathophysiology is hampered by the difficulties involved in obtaining and analyzing intestinal tissue. Treatment of intestinal dysmotility relies on dietary manipulations and nutritional support (enteral or parenteral) because there is no drug therapy that can effectively enhance the propulsive function of the small bowel. Small bowel transplantation remains a life-saving intervention for patients who fail to respond to other therapies.

Introduction

Small bowel motility in health is programmed to maintain an optimal balance between the need for absorption of nutrients and the assurance of timely propulsion of intestinal contents in order to avoid the consequences of stasis, or conversely, rapid transit. This is accomplished by the patterns of motility, which are common to many species and are peculiar to the antrum and small bowel. Motility patterns have been determined by recording of electrical activity or contractions from the intestines of laboratory animals (mostly dogs) and humans. The motility activity of the antrum and small bowel in these, and many other species, is characterized by periodic motor activity observed during fasting—the migrating motor complex (MMC)—which is replaced by the fed pattern of contractions after ingestion of a meal [1].

The Migrating Motor Complex

The MMC has three distinct phases. In phase III (activity front), a short burst of rhythmic contractions starts in the antrum or proximal small bowel and migrates aborally over various lengths of the small bowel. It is followed usually by phase I, a period of motor quiescence, which in turn is followed by phase II, a period of intermittent contractions (Fig. 1). The MMC depends on an intact enteric nervous system; even a variety of insults to the external nerve supply to the bowel do not abolish this basic pattern [2]. As such, the MMC is a measure of the integrity of the enteric nervous system. However, the MMC is modulated by extrinsic nerves and gastrointestinal regulatory peptides [3]. Recent investigations suggest that a highly specialized group of cells known as the interstitial cells of Cajal are of critical importance in the control of small bowel motor function [4••]. These cells are electrically coupled to intestinal smooth muscle cells via gap junctions and possess special ionic conductance which generates electrical slow waves, allowing them to function as pacemaker cells (Fig. 2).

The importance of the MMC is highlighted by the fact that bacterial overgrowth, and in particular colonization of the upper small bowel with gram-negative bacilli, are observed when the MMC is absent or impaired [5,6]. Phase III is considered the most effective propulsive pattern [7,8], referred to as “the gatekeeper of the intestine.” However, normal contractile activity during phase II of the MMC is also important for propulsion, because, during treatment with somatostatin [9], or in the postoperative period [10]—conditions that are associated with markedly reduced or abolished phase II activity— small bowel transit is delayed, whereas the frequency of phase III is increased.

Fed pattern

Following the ingestion of food, the MMC cycle is interrupted by a period of irregular contractions usually lasting 6 to 7 hours, depending on the caloric value of the meal [11], until the MMC resumes again (Fig. 3). Extrinsic innervation is essential in the modulation of the fed pattern, as suggested by the effects of vagal manipulations and sleep [12–14]. Contraction waves following a meal propagate over a short distance [8], whereas transit is slowed when end products of digestion (fatty acids) trigger inhibitory feedback mechanisms known as the ileal brake [15,16] and the jejunal brake [17]. The result is better mixing of chyme

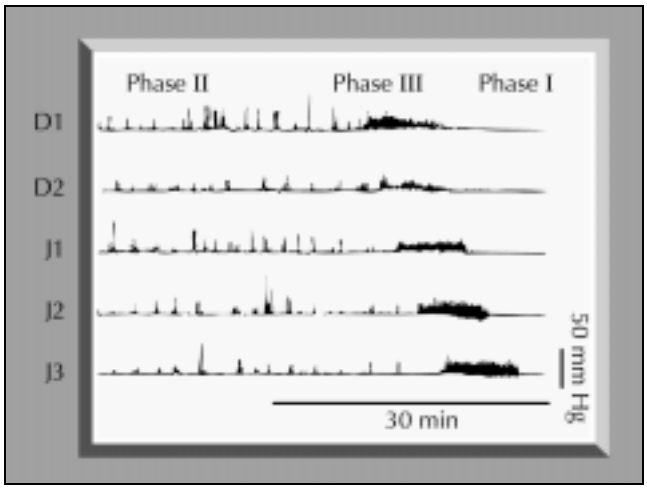

Figure 1. The normal migrating motor complex is depicted. Phase III is the most distinct and consists of a short burst of contractions that migrate aborally. It is usually followed by a period of quiescence, phase I, which in turn is followed by a period of intermittent contractions, phase II. D—duodenum; J—jejunum. *From* Soffer [51]; with permission.

and adequate contact time between nutrients and small bowel, thus promoting absorption [8].

Intestinal Dysmotility in Disease States

Although intestinal dysmotility may accompany a variety of clinical conditions, its precise pathophysiology remains elusive in most cases. The cause and basic pathophysiology of certain conditions are well known. Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi*, can cause small bowel dysfunction and an achalasia-like picture in the esophagus [18]. As with achalasia, there is a loss of nitrinergic neurons in the myenteric plexus [19]. Conversely, in advanced scleroderma, the predominant feature is myopathy, with replacement of the muscle, particularly in the circular muscle layer, by fibrous tissue [20]. In other situations, the pathologic basis may not be well defined. In diabetes mellitus, involvement of the autonomic nervous system and the enteric nerves, complicated by metabolic effects of hyperglycemia, can affect gut motility [21,22]. In Parkinson's disease, pathologic abnormalities are observed in the central, autonomic, and enteric nervous systems [23], as well as deficiency of neurotransmitters in the enteric nerves [24]. A large body of evidence suggests that inflammation in the gut can alter enteric nerves and smooth muscle function and may contribute to the motor dysfunction observed in a number of inflammatory or infectious conditions [25], although the predominance of selective mechanisms in the pathophysiology of dysmotility may be difficult to determine. Another category of patients is comprised of those who present with symptoms suggestive of upper gut dysmotility, such as nausea, vomiting, abdominal pain, distention, or evidence of bacterial overgrowth, and abnormal manometric findings, but in whom neither the cause nor the pathology of dysmotility are known [26].

There may be a number of reasons for this. First, symptoms of small bowel dysmotility are not specific, and thus do not distinguish between various disease processes. However, the most difficult problem is that of obtaining and interpreting intestinal tissue. Evaluation of enteric nerves and intestinal muscle requires examination of a full-thickness sample from the gut wall. Although laparoscopy, rather than open laparotomy, has simplified the process [27], it remains an invasive intervention and hence is rarely performed exclusively for this purpose. Furthermore, for a meaningful evaluation of the enteric nerves, special cuts and staining of the tissue, including immunohistochemical studies [28], need to be performed, and these can be provided by only a handful of laboratories.

Intestinal Dysmotility and Functional Gut Syndromes

Many studies have reported the results of small bowel manometry, using perfused or solid state systems, in patients with functional syndromes, mostly in irritable bowel syndrome (IBS). Although quantitative differences (*eg*, MMC frequency, duration of various phases, and motility index of the postprandial period) were observed in some of these patients, and between subgroups of IBS, overall, patterns of small bowel motility are well preserved in this group of patients [29].

Diagnostic Measures

Intestinal dysmotility is suspected in any patient who presents with the symptoms discussed previously. Mechanical intestinal obstruction, particularly in patients with previous abdominal operations or those who present with a radiologic picture suspicious for mechanical obstruction, has to be excluded first using barium meal with small bowel follow-through, enteroclysis, or abdominal CT scan. In the latter case, intestinal pseudoobstruction is diagnosed, even if the cause cannot be determined. In symptomatic patients without abnormal radiologic features, or when a known cause for intestinal dysmotility is not apparent, special tests such as intestinal manometry or transit are helpful.

Intestinal transit

Small bowel transit is tested by scintigraphy, and the time between gastric emptying and colonic filling can be determined by various measurements [30•]. Delayed small bowel transit provides no clues to the underlying pathology and is observed in patients with dysmotility associated with myopathic or neuropathic processes [31]. Furthermore, a wide variability in transit time exists between and within subjects [30•]. Consequently, the test may be especially useful as an extension of the gastric

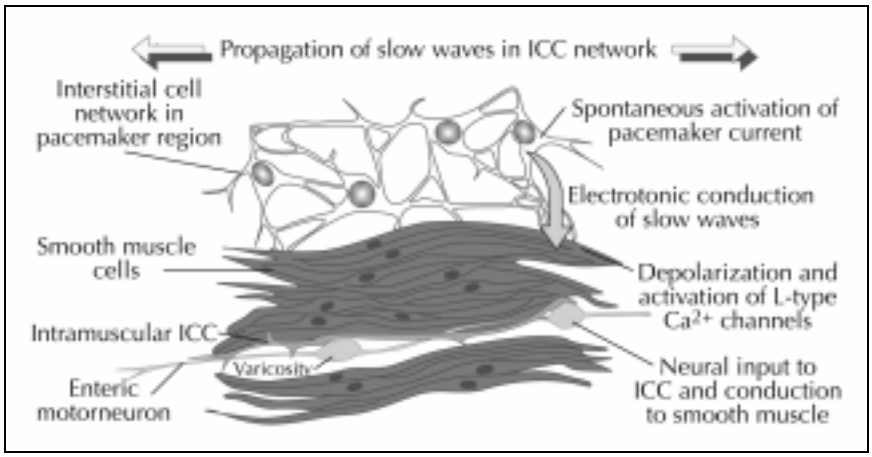

Figure 2. A model for generation and modulation of electrical activity in gastrointestinal muscles. Interstitial cell networks in pacemaker regions express the ionic mechanism to generate slow waves. These events can actively propagate through the interstitial cells of Cajal (ICC) network via gap junctions connecting the ICC. Slow waves electronically conduct into the smooth muscle cells, which are also electrically coupled to the ICC but appear to lack the mechanism for regenerating slow waves. Neural input can modulate smooth muscle response to slow waves and intramuscular ICC function. *Modified from* Horowitz *et al*. [4••]; with permission.

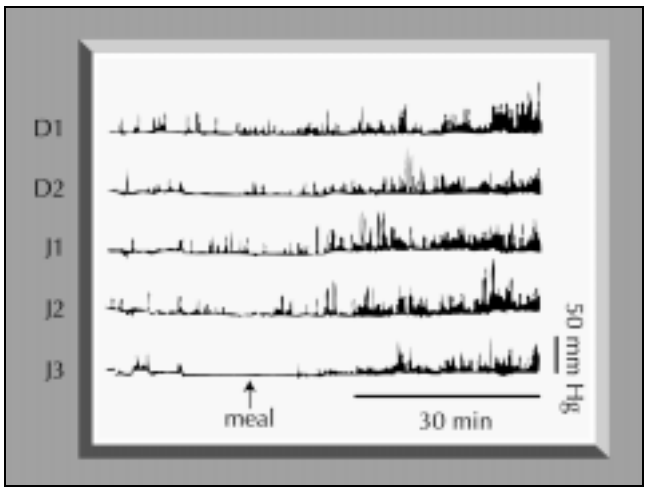

Figure 3. Increased contractile activity follows the ingestion of food—the normal fed pattern. D—duodenum; J—jejunum. *From* Soffer [51]; with permission.

emptying study, particularly because intestinal dysmotility and gastroparesis may present with similar symptoms.

Intestinal manometry

Intraluminal pressure recordings from the gut are obtained by water-perfused catheters or catheters that incorporate solid state pressure transducers, and conducted over short (6 to 8 hours) or long (24 hours) sessions. The technical aspects have been recently reviewed [30•,32]. Whereas both techniques provide, for the most part, comparable data, assessment of the MMC requires long recording during fasting in the awake state or during sleep.

Manometry provides information concerning the presence and migration pattern of the MMC, the motor response to food, and the presence of abnormal contractile patterns [30•]. The information obtained from manometry is helpful in a number of clinical situations, as shown in studies performed mostly in the pediatric population. The presence of spontaneously occurring MMC predicts clinical response to prokinetic therapy and success of enteral feeding in children with chronic intestinal pseudoobstruction [33,34]. Poor response to enteral feeding can also be predicted when a myopathic process is suggested by a low motility index [35], and small bowel manometry can be used to predict readiness for enteral feeding in preterm infants [36]. Finally, normal gastroduodenal manometry in children suspected clinically of having chronic intestinal pseudoobstruction has helped to redirect the diagnostic effort, resulting in various different final diagnoses such as Munchausen's syndrome-by-proxy and congenital abnormalities [37]. Less information is available on the usefulness of manometry in the adult population. Motility changes induced by acute administration of drugs can predict response to chronic therapy with such agents in adults [38]. In a retrospective study, manometry influenced treatment in approximately 50% of patients presenting with symptoms consistent with dysmotility who were found to have abnormal manometric findings [39]. Prospective outcome studies in adults are needed in order to determine the clinical usefulness of this test. Currently, manometry is most helpful in excluding intestinal dysmotility as the cause for unexplained "dysmotility" symptoms.

Treatment

Medical or surgical measures used in the treatment of patients with intestinal dysmotility serve a number of purposes: 1) identification and treatment of reversible causes, primarily mechanical small bowel obstruction, but also metabolic, biomedical, and drug-related factors; 2) reduction of symptoms and improvement of nutrition; and 3) improvement of the propulsive function of the gut.

Dietary manipulations are particularly helpful when gastroparesis is present. They include small frequent feeding, liquid formula supplementation, and reduction or elimination of nondigestible fiber-containing foods. Antibiotic therapy for bacterial overgrowth is commonly tried. A low-fat diet is recommended because fat can delay gastric emptying as well as small bowel transit, by way of the intestinal brake mechanism [17]. This mechanism is also useful in disease states associated with rapid transit, such as short bowel syndrome, diabetes mellitus, and post-

gastrectomy states. The ingestion of oleic acid prior to a meal was shown to prolong intestinal transit time and improved symptoms and nutritional status in such patients (Lin HC, Personal communication).

Direct delivery of liquid food to the intestine can also be used and is particularly helpful when gastroparesis is predominant. Data from the pediatric population [38] indicate that, in selected children with intestinal dysmotility, jejunal feeding can be an alternative to total parenteral nutrition (TPN). Whether adult patients with intestinal dysmotility would respond in a similar fashion is not clear, but because the morbidity, mortality, and cost associated with TPN so outweigh those associated with enteral feeding, such a trial may be warranted prior to embarking on TPN. A trial of nasojejunal feeding, by drip, for a few days to determine tolerance to infusion can precede the surgical placement of a feeding tube. Percutaneous gastrostomy can also be used to advance feeding tubes into the small bowel [40]. Polymeric formulas can be used, as elemental ones have no proven advantage.

Total parenteral nutrition

When dietary modifications and enteral feeding are not sufficient to maintain nutritional status, home TPN is used. In patients with intestinal failure resulting from benign disease, the long-term prognosis is good [40,41]. Some enteral feeding should be attempted, even in patients who depend on TPN, to prevent cholestatic liver disease [42] and as an attempt to maintain the mucosal integrity of the bowel [43].

Prokinetic Agents

Our understanding of the basic mechanisms responsible for dysmotility syndromes lags well behind the knowledge of the clinical, epidemiologic, and manometric aspects of such diseases. Consequently, pharmacologic therapy is mostly nonspecific, aimed at enhancing the propulsive function of the bowel. This is done either by enhancing intestinal contractile activity, usually by promoting the release of acetylcholine from enteric neurons, or by enhancing propulsive patterns of contractions in the upper gut. The few available prokinetic agents are far more effective in improving gastroparesis than intestinal dysmotility, and they have been periodically reviewed [44]. A new agent, tegaserod, acting as a partial 5-hydroxytryptamine ($5HT_4$) agonist, was recently shown to accelerate small bowel transit in patients with constipation-predominant IBS [45•], and this agent may prove to be useful in patients with intestinal dysmotility.

Surgical Therapy

Surgical treatment is aimed at resecting or bypassing poorly functioning and dilated segments of the bowel (such as megaduodenum), decompressing the bowel by way of jejunostomy tubes, or replacing the diseased bowel by intestinal transplantation. Ablative surgery is not appropriate when long segments of the bowel are involved; it should be used very sparingly and in highly selected patients. Venting jejunostomy [46], which can be done via laparoscopy, may be very helpful, particularly in patients with intermittent obstructive symptoms. The most radical treatment is small bowel transplantation. Experience and long-term follow-up with this intervention, performed mostly in children and usually for short bowel syndrome, continue to accumulate [47,48]. The 1-year graft/patient survival rate for transplants performed after February 1995 was 55%/69% for intestinal grafts, with comparable results for small bowel and liver grafts and multivisceral grafts [48•]. Better results were observed in more experienced centers, and approximately 75% of current survivors could discontinue TPN and resume enteral feeding. Graft rejection, sepsis, and post-transplant lymphoproliferative disorders are the major complications [48•]. For these reasons, intestinal transplantation is currently a life-saving option for those patients with intestinal failure who cannot be maintained on TPN.

Intestinal Pacing

Recently, the use of gastric pacing has been shown to improve symptoms and gastric emptying of a solid meal in patients with gastroparesis [49•]. Pacing may be less effective in the small bowel than in the stomach, because of technical and physiologic differences between these two segments of the gut, but encouraging data suggest that the technique is feasible in an animal model and potentially applicable and helpful in humans [50•].

Conclusions

Our understanding of the motor function of the small bowel has advanced in the last decade. The various patterns of small bowel motility are better defined, and the importance of the enteric and autonomic nervous systems and regulatory peptides in the control of such patterns is better clarified. At the cellular level, the interstitial cells of Cajal are recognized as pacemaker cells and as the source of electrical rhythmicity in the gut. More and more causes for intestinal dysmotility are appreciated, from radiation enteropathy to central nervous system disorders. Special staining of enteric nerves and immunohistochemical techniques provide better understanding of the anatomy and function of the enteric nervous system. Scintigraphy or, more commonly, manometry can be used to diagnose motor dysfunction. Studies of healthy subjects have allowed for better definition of normal versus abnormal contractile patterns. In the pediatric population, manometry can guide the choice of drug therapy and the need for alternative methods of nutrition. Data in adults are far more limited, and consequently manometry in adults is

particularly helpful in excluding intestinal dysmotility as the cause for unexplained symptoms.

Dietary manipulations and antibiotic therapy for bacterial overgrowth remain an important part of the therapy. The search for an effective prokinetic agent for the small bowel continues; however, no such drug is available yet. Alternative feeding methods, both enteral and parenteral, can sustain patients with advanced disease. Intestinal transplantation can be a life-saving procedure for patients in whom such measures have to be discontinued. With increased experience, survival following transplantation is improving, and results are now comparable with those seen in patients undergoing lung transplantation.

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