PATHOPHYSIOLOGY OF CHRONIC CONSTIPATION AND IBS*

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The pathophysiology of chronic constipation (CC) and irritable bowel syndrome (IBS) involves consideration of disturbances in colonic sensorimotor activity, often resulting from disordered extrinsic and/or intrinsic innervations. The mechanisms by which normal colonic activity is altered to cause constipation or IBS are complex, as are the enteric neuropathologic changes that are present in some patients with slow-transit constipation and the serotoninergic disturbances in patients with IBS. Using normal colonic motor patterns and functions as a starting point, this article explores these processes in some detail. It also addresses the assessment of colonic sensorimotor function, the causes of slow-transit constipation, the role of high-amplitude propagated contractions and loss of interstitial cells of Cajal in constipation, the role of serotonin in the gut, and the serotoninergic disturbances in IBS. (Adv Stud Med. 2006;6(2A):S58-S66)

NORMAL COLONIC MOTOR PATTERNS AND FUNCTIONS

The functions of the colon are to extract water and electrolytes from the lumen, digest dietary fiber and other nutrients that are not digested by enzymes, propel contents from the ileum to the rectum, and evacuate feces from the rectum in a controlled manner.

Although the colon is generally regarded as a single organ, there are several distinct differences in anatomy, blood and nerve supply, and functions among the right colon, the left colon, and the rectosigmoid colon. The right colon functions primarily as a reservoir where water and electrolytes are absorbed and intestinal contents are mixed, while the left colon, under normal circumstances, functions primarily as a conduit. The rectosigmoid is involved in defecation. The average normal colonic transit time is 36 hours: 12 hours in the right colon, 12 hours in the left colon, and 12 hours in the rectosigmoid.

The nerves supplying the colon are crucial to its normal functions. The intrinsic or enteric nerves primarily regulate colonic sensorimotor functions and the extrinsic nerves modulate colonic motility. With

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regard to the latter, sympathetic nerves inhibit motility, whereas parasympathetic nerves stimulate it.

The sympathetic nerves supplying the right colon are derived primarily from the cecum and the superior mesenteric ganglia, whereas those supplying the left colon are derived from the inferior hypogastric plexus. The vagus nerve provides the parasympathetic supply to the right colon. The parasympathetic nerves supplying the rest of the colon originate in the sacral parasympathetic segments (S2-S4), which travel through the inferior hypogastric plexus to the left colon and thereafter ascend within the colonic wall to supply part of the transverse colon. Therefore, it is conceivable that a segmental colonic resection will affect neural regulation in the proximal colon above the resected segment.

The colon also communicates with other parts of the gastrointestinal (GI) tract and the brain, as exemplified by the ileal brake, whereby the presence of fats in the distal small intestine leads to the release of hormones, such as peptide YY, neuropeptide, and enteroglucagon. These hormones, in turn, retard motility in the stomach and proximal small intestine, thereby limiting the transfer of nutrients into the ileum.

Other neurally mediated reflexes permit communication between the colon and other parts of the GI tract. In addition, rectal or colonic distention can inhibit motor activity in the stomach (ie, the cologastric reflex), small intestine, or colon. These inhibitory reflexes are mediated by extrinsic reflex pathways with synapses in the prevertebral ganglia, independent of the central nervous system. The rectocolonic inhibitory reflex, which is characterized by inhibition of colonic motor activity in response to rectal distention, may explain why colonic transit is often delayed in patients with obstructed defecation.

Unlike motor activity in the stomach or small intestine, colonic motor activity is markedly irregular, and ambulatory colonic motility studies clearly demonstrate diurnal variation. Essentially, the colon is asleep at night and awake during the day, with periods of increased activity upon awakening and after meals. The colon responds not only to nerves and hormones but also to intraluminal stimuli, such as fat, short-chain fatty acids, and osmotic laxatives, all of which induce colonic contraction.

**Assessment of Colonic Sensorimotor Function**

A simple, inexpensive way to identify major disturbances of colonic motor function is to measure colonic transit by radiopaque markers or scintigraphy. Colonic sensorimotor function can also be assessed by the barostat-manometric assembly. This apparatus can record colonic motor activity, compliance, and sensation. It consists of a highly compliant polyethylene balloon connected by a tube to a barostat, which is essentially a rigid piston within a cylinder. The balloon is inflated to a low constant pressure, thus it is in contact with the lining of the colon. When the colon contracts, air is displaced from the balloon to the cylinder. However, when the colon relaxes, the machine inflates the balloon to ensure that it is in constant contact with the lining of the colon. A manometric recording of the gastrocolonic response (ie, the colonic contractile response to a meal) is shown in Figure 1.

Although they occur relatively infrequently, colonic high-amplitude propagated contractions (HAPCs) are important because they are responsible for the mass movement of colonic contents from one segment of the colon to another, and they often precede defecation. HAPCs may occur spontaneously or after a meal and can also be induced by the cholinesterase inhibitor neostigmine, which increases the availability of acetylcholine at neurons in the myenteric plexus and at the neuromuscular junction and markedly accelerates colonic transit in healthy subjects.

**Figure 1. Manometric Recording of the Gastrocolonic Response**

Tonic and phasic components

- Manometry
  - Descending
- Sigmoid
- Colonic Barostat Pressure
- Volume

- Meal
- Cramps
- Defecation

HAPC = high-amplitude propagated contraction.
Studies by Cook et al that simultaneously assessed motor activity by manometric sensors and colonic transit have shown that propagated pressure waves are associated with the migration of colonic contents. In contrast, nonpropagated pressure waves, the predominant component of colonic motor activity, are associated with the to-and-fro motion of colonic contents that probably enables the colon to mix the contents and absorb water and electrolytes.

However, the relationship between motor activity and propulsion is not entirely clear because isotope movements through the colon were sometimes associated with nonpropagated wave activity. Conversely, propagated sequences, which occurred infrequently after meals, may or may not be associated with propulsion of colonic content.

UNDERLYING MECHANISMS OF CHRONIC CONSTIPATION

Management of the patient with CC begins with a careful history to assess for upper GI symptoms, alarm symptoms (eg, blood in the stool), and symptoms suggestive of pelvic floor dysfunction; to rule out secondary causes, such as an organic lesion in the colon or drug-induced constipation; and to ascertain the efficacy of conservative measures, such as dietary fiber and laxatives that patients have tried. The next step is to assess colonic transit and pelvic floor functions to characterize whether patients have normal transit and pelvic floor function, isolated slow-transit constipation, or pelvic floor dysfunction with or without slow-transit constipation. It is important to assess colonic transit and pelvic floor function because most patients with pelvic floor dysfunction also have delayed colonic transit.

It has been suggested that slow-transit constipation may be caused by increased resistance to colonic propagation (eg, excessive phasic pressure activity in the sigmoid colon) or increased periodic rectal motor activity may serve as a “brake” to retard the flow of colonic contents), and/or by ineffective colonic propulsion resulting from fewer colonic HAPCs and/or impaired colonic contractile responses to physiologic stimuli, such as a meal. Patients with idiopathic constipation or constipation secondary to antidepressants have fewer HAPCs. Healthy subjects have an average of 5 HAPCs a day, with a range of 1 to 15 HAPCs every day. Because the normal range is so wide, it is difficult, except in patients with no HAPCs, to ascribe CC to fewer HAPCs in the individual patient. The tonic colonic contractile response to a meal is also impaired in patients with slow-transit constipation, but preserved in those with normal-transit constipation. The tonic response to a meal was also impaired in patients with obstructive defecation, underscoring the prevalence of colonic motor dysfunction in these patients.

To examine whether slow-transit constipation is a generalized or localized colonic disorder, Stivland et al measured segmental colonic transit in 8 patients with CC. In 5 of 7 patients with slow colonic transit, the transit delay affected the whole colon (pancolonic inertia), suggesting a generalized dysfunction. In 2 patients, transit in the ascending and transverse colon was normal, but solids moved through the left colon slowly, suggesting a localized disorder of colonic motor function.

The evidence that emerges is that motor disturbances in CC are heterogeneous, as exemplified in a 3-day manometric colonic motility study of 40 patients with severe slow-transit constipation but no pelvic floor dysfunction who underwent colon cleansing and followed a low-residue diet for several days. Key findings for each of 4 subgroups based on the predominant motor disturbance are summarized in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tr>
<td>n</td>
<td>10 females</td>
<td>3 females; 2 males</td>
<td>7 females; 1 male</td>
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<td>Delayed colonic transit</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Phasic motility</td>
<td>↓</td>
<td>↑ sigmoid + descending colon</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Postprandial phasic response</td>
<td>Absent</td>
<td>Yes</td>
<td>↔</td>
<td>↔</td>
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<tr>
<td>Spontaneous HAPCs</td>
<td>Absent</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
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<tr>
<td>Bisacodyl-induced HAPCs (on day 3)</td>
<td>6</td>
<td>↔</td>
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↑ = increased; ↓ = decreased; ↔ = unchanged; HAPC = high-amplitude propagated contraction.

Colonic transit is routinely assessed in evaluating CC. Intraluminal motor activity, measured by stationary or ambulatory manometry or by a barostat-manometric assembly, is increasingly used to identify motor dysfunction in CC. To determine whether colonic manometry influences the management of CC, Rao et al conducted a 24-hour ambulatory manometric study in 21 patients with slow-transit constipation and 20 controls. They found that 53% of the patients had a neuropathy, as identified by the absence of 2 of 3 motor responses (ie, waking, eating, and HAPCs), 26% had a myopathy (responses were present, but attenuated), and 21% were normal. Three months later, none of the 10 patients with a neuropathy had improved, but there was some improvement (50%–80%) in those with normal motility or a myopathy. At 1 year, 6 of 7 patients with neuropathy did well after a colectomy. The remaining 3 patients with a neuropathy, in addition to all 5 patients with a myopathy, remained on laxatives and reported a mean improvement of 50% in their bowel symptoms on a visual analogue scale.

These findings underscore the need for prospective studies to assess the utility of colonic motility testing in patients with CC.

ENTERIC NEUROPATHOLOGY

In resected colonic specimens from patients with slow-transit constipation, histopathology assessed by routine (H and E) stains is generally normal. However, recent studies using special stains demonstrated marked loss of colonic nerves and interstitial cells of Cajal (ICC) in CC. The loss of ICCs is particularly significant because they are the pacemaker cells of the gut and are also responsible for conveying signals from nerves to smooth muscle.

There is a marked reduction in the number of ICCs in longitudinal and circular muscle (Figure 2), in addition to in the myenteric plexus. The ICCs that remain are deformed, with irregular surface markings and loss of fine processes. Loss of ICCs and these morphologic changes are also seen in megacolon.

Along with evidence of colonic myenteric neuropathy in CC, these findings raise questions about the extent to which loss of ICCs, loss of nerves, or both is responsible for the disturbances in colon function, and the extent to which the disturbances are primary or secondary to laxative use or other factors. Clearly, these questions warrant further investigation.

SEROTONIN AND THE GUT

The overwhelming majority of serotonin (5-HT) in the body (95%) is in the gut, mostly in the enterochromaffin (EC) cells. Receptors for 5-HT are present in gut neurons, smooth muscle cells, and EC cells. Of the 7 receptor types and more than 20 subtypes, the 5-HT1, 5-HT2, and 5-HT4 receptors are most important for GI sensorimotor functions. When the gut is stimulated by distention or a chemical stimulus, 5-HT is released by the EC cells. By activating 5-HT4 receptors on neurons, 5-HT increases the release of acetylcholine from cholinergic neurons and thereby increases gut contractility proximal to the point of stimulation. At the same time, activation of 5-HT4 receptors also stimulates the release of inhibitory neurotransmitters (eg, nitric oxide) from other neurons, thereby facilitating relaxation distal to the point of relaxation. Together, this coordinated process of contraction and relaxation promotes peristalsis.

The 5-HT3 receptors are also located on extrinsic afferent nerves that travel to the spinal cord, and also on the vagus nerve to convey sensory input to the
brain. This explains why 5-HT₃ receptor antagonists are very effective in reducing nausea and vomiting and providing analgesic effects. The 5-HT₃ receptors are also situated on intrinsic primary afferent neurons, and on interneurons, which may explain why 5-HT₃ antagonists also delay GI transit.

A recent study demonstrated enteric mucosal serotoninergic disturbances in rectal biopsies taken in 15 patients with diarrhea-predominant IBS and 16 patients with constipation-predominant IBS and compared to 34 healthy controls (Table 2).²⁰,²¹ Similar disturbances were observed in both IBS subtypes. In IBS, the number of EC cells was preserved, but tryptophan hydroxylase mRNA was decreased, which probably explains why mucosal 5-HT levels were lower. However, despite lower 5-HT levels, 5-HT release in response to stimulation was adequate, possibly because the activity of serotonin transporter, which is responsible for inactivating serotonin, was reduced. With the exception of the reduced number of EC cells in ulcerative colitis, the disturbances of enteric serotoninergic metabolism were similar in IBS and ulcerative colitis.

In contrast to these findings, other studies suggest that the number of EC cells is increased in postinfectious IBS and also in an experimental model of trinitrobenzene sulfonic acid (TNBS)-induced colitis (Table 2).²²

These findings demonstrate that changes in serotoninergic signaling can occur in IBS. The presence of similar changes in the postinfectious IBS and TNBS colitis models suggests that changes in serotoninergic signaling can occur in response to inflammation.

However, it is unclear if these changes are restricted to the enteric mucosa or also affect the enteric neurons, whether the changes noted are primary or secondary to inflammation, and whether the effects of inflammation on 5-HT metabolism are influenced by genetic factors. Furthermore, these observations do not explain why symptoms differ between patients with predominant constipation and diarrhea. It has been suggested that although excess 5-HT causes diarrhea, downregulation of 5-HT receptors may explain the transition from diarrhea to constipation.

### CONCLUSIONS

Normal colonic motor activity is characterized by regional differences in colonic functions, communication between the colon and other parts of the GI tract, tonic and phasic components, diurnal variation, a contractile response to eating, and HAPCs. However, the relationship between motor activity and transit is not completely understood.

There is evidence that slow-transit constipation may be caused by increased resistance to colonic propagation and/or ineffective propulsion resulting from fewer colonic HAPCs and/or impaired colonic contractile responses to physiologic and/or pharmacologic stimuli.

Some patients with slow-transit constipation also have enteric neuromuscular pathology, such as loss of myenteric neurons and ICCs. The ICCs are the pace-maker cells of the gut that are also responsible for conveying signals from nerves to smooth muscle.

Most of the serotonin in the body is in the gut, primarily in EC cells. Serotonin receptors, which promote peristalsis, are situated at multiple sites in the gut. Enteric mucosal serotoninergic disturbances in IBS are similar to those seen in patients with ulcerative colitis.

### Table 2. Enteric Mucosal Serotoninergic Disturbances in Irritable Bowel Syndrome

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>IBS-D</th>
<th>IBS-C</th>
<th>PI-IBS</th>
<th>TNBS Colitis*</th>
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<tbody>
<tr>
<td>EC cells</td>
<td></td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Tryptophan</td>
<td></td>
<td>↓</td>
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<tr>
<td>hydroxylase</td>
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<td>↓</td>
<td>↓</td>
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<tr>
<td>mRNA</td>
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<td></td>
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<tr>
<td>Mucosal 5-HT</td>
<td></td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>5-HT release</td>
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<td>↑</td>
</tr>
<tr>
<td>5-HT transporter</td>
<td></td>
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<td>↓</td>
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<tr>
<td>immunoreactivity</td>
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<td></td>
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<tr>
<td>mRNA</td>
<td></td>
<td></td>
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*Experimental data.

↑ = increased; ↓ = decreased; ↔ = unchanged; EC = enterochromaffin cells; IBS-C = irritable bowel syndrome-constipation predominant; IBS-D = irritable bowel syndrome-diarrhea predominant; PI-IBS = postinfectious irritable bowel syndrome; TNBS = trinitrobenzene sulfonic acid; UC = ulcerative colitis. Data from Coates et al²⁰; Dunlop et al²¹; Linden et al²².
**DISCUSSION**

**Dr Chang:** I’m curious about the rectocolonic reflex—that colonic motility slows if you have some type of functional obstruction in the pelvic floor area. I always thought that patients had underlying chronic constipation, and that all the straining would lead to rectal prolapse or rectocele. But, is it really the other way around—that they initially have some defect such as functional obstruction?

**Dr Bharucha:** There is more evidence to suggest that colonic motor dysfunction is secondary to pelvic floor dysfunction than vice versa. It is conceivable that retained stool in the rectosigmoid colon secondary to pelvic floor dysfunction inhibits colonic motor activity via rectal distention. A small study by Mollen et al assessed colonic motor responses to a meal before and after pelvic floor retraining by biofeedback therapy. In this study, colonic motor responses to a meal improved after biofeedback therapy, but pre-versus postdifferences were not statistically significant, probably because the study was relatively small. Lastly, a recently published study demonstrated that colonic transit improved after biofeedback therapy in patients with pelvic floor dysfunction.

As you suggest, some patients with chronic constipation due to colonic motor dysfunction strain excessively and develop secondary pelvic floor dysfunction.

**Dr Rao:** When we initially tried to subdivide patients into separate groups, such as slow transit and dyssynergia, we looked at X-ray patterns. If all the stool markers were in the pelvic floor region, we said, “This is dyssynergia,” and if stool markers were scattered throughout the colon, we said, “This is slow transit.” However, that paradigm does not hold because you can see scattered distribution of markers and accumulation of all the markers in the rectosigmoid region in patients with dyssynergia because stool accumulation in the rectosigmoid region will induce the rectocolonic reflex, which in turn inhibits the flow of stool.

Now, the body is smart. It responds to the presence of excessive stool by slowing down stomach function and colon function. The result is sluggish transport. Once you’ve corrected dyssynergia, colonic transit improves. Therefore, there are no clear-cut “slow-transit” or “dyssynergia” compartments based on X-rays, but an overlap.

Prolapse patients are slightly different. Although they may have had some slow transit initially, many of them also have a sensory dysfunction in which they have this constant urge to defecate. To get rid of this urge, not necessarily stool, they force and strain, and ultimately, they prolapse the rectum.

**Dr Chang:** Then, if it is truly a sensory disorder, they will still have it even if you correct the prolapse. That’s probably why there’s recurrence.

**Dr Rao:** Very true, and that’s what you see in patients with solitary rectal ulcer syndrome.

**Dr Lee:** You said that it’s difficult to know what the relationship is between HAPCs and actual motility. Have patients who have developed acute constipation (eg, in Ogilvie’s syndrome) been studied? What do we know about their physiology?

**Dr Bharucha:** It’s thought that Ogilvie’s syndrome represents an imbalance between the sympathetic and the parasympathetic supply to the colon. The sympathetic nervous system inhibits colonic motility, primarily via α2-adrenergic receptors, whereas the parasympathetic system increases colonic motility. In Ogilvie’s syndrome, the stress of an underlying medical condition or surgery (eg, hip fracture) presumably increases sympathetic tone, which in turn inhibits colonic motility, causing marked colonic distention.

There is now evidence that neostigmine effectively restores motility and reduces colonic distension in patients with Ogilvie’s syndrome. However, I’m not aware of any studies that have directly evaluated colonic motility during an episode of Ogilvie’s syndrome because of the risk of perforation with endoscopy.

**Dr Rao:** I don’t think anyone has studied motility in Ogilvie’s syndrome because you’ll never get it through an IRB (Institutional Review Board), but studies have been done in models of disordered colonic function, such as postspinal cord injury. A group from Chicago showed that patients with chronic constipation in a spinal cord injury unit have significant impairment of colonic motor function and absent or diminished HAPCs.

**Dr Lembo:** I was wondering about Cook’s studies showing movement of the isotope with peristaltic contractions. Why is that? Are these nonobliterating luminal contractions that are not picked up?

**Dr Bharucha:** Exactly. The lack of an association doesn’t necessarily mean that there wasn’t an association between peristaltic contractions and transit. Because the distance between the sensors was 10 cm, it is conceivable that contractions that were propagated...
across shorter distances were not identified by manometry. Furthermore, in addition to the nature of the contraction (ie, propagated or not), other factors such as fecal viscosity, colonic tone, and capacitance probably also influence propulsion.

**Dr Chang:** I’m trying to translate this into clinical practice. Because there can be a heterogeneous treatment response in constipated patients, are there certain colonic motility patterns that would be associated with particular symptoms or treatment response? For example, do patients who develop severe pain on a prokinetic agent have increased nonpropagating contractions that are being further intensified by the drug? What about patients with constipation who have multiple bowel movements with a small amount of stool and never really feel evacuated versus those with infrequent bowel movements?

**Dr Bharucha:** The relationship between symptoms and colonic motility patterns has not been formally assessed.

**Dr Chang:** Do you think there are decreased HAPCs or is propagation not necessarily related to motility?

**Dr Bharucha:** Clearly, colonic HAPCs can and do propagate colonic contents. As I mentioned earlier, patients with idiopathic constipation and constipation secondary to antidepressants have fewer HAPCs. However, because the number of HAPCs per 24 hours in healthy subjects ranges from 1 to 15, it is difficult to ascertain whether reduced HAPCs are causing constipation. Therefore, we don’t do ambulatory colonic motility studies, but Dr Rao has good data from the ambulatory studies he’s done. Instead, we assess colonic motor function with a combined barostat-manometric assembly. Although manometric sensors predominantly assess phasic pressure activity, a barostat balloon can also assess colonic tone. Our accumulating, but as yet unpublished, data suggest that an impaired tonic contractile response to a meal (ie, <25% increase in colonic tone over a 60-minute period after a 1000-kcal meal, particularly in association with an impaired response to neostigmine) is a very useful criterion for identifying colonic motor dysfunction.

**Dr Chang:** Did that subgroup of patients have any particular symptoms?

**Dr Bharucha:** We don’t know.

**Dr Hasler:** I presume that most colonic manometry studies are done on prepared colons, in which there has been some sort of lavage. What sort of information can we glean from those studies because it’s obviously a very unphysiologic setting? Are we altering their responses to meals? Are we altering their responses to drugs, such as neostigmine? Do we see the same HAPC pattern in a colon full of stool?

**Dr Bharucha:** There is a study of colonic manometry before and after colonic cleansing that found that only HAPCs occurred more frequently after colonic cleansing, but other motor parameters were unchanged. 27

Another study found, not surprisingly, that colonic transit was accelerated after colonic cleansing. 28 However, cleansing also accelerates colonic transit in normal subjects. Therefore, cleansing does not influence the characterization of constipated patients as normal or delayed colonic transit.

**Dr Rao:** Let me respond to Dr Chang’s question about symptoms, which really is an important clinical observation. When we put some patients on a 5-HT4 agonist, they do report cramping. I haven’t tested for this, but my hunch is that they probably have increased segmental contractions. The predominant colonic motor pattern is localized segmental contractions, and it is decreased in those patients with chronic constipation. However, segmental motor activity is increased in some, particularly those patients who are on the IBS side of chronic constipation; they will probably experience more pain and discomfort because of the excessive segmental contractions.

As for flow of stool, I think it’s a balance between segmental and propulsive activity; one of them has to give way for things to move. The best example is the effect of acute exercise on colonic motor activity. Our hypothesis was that exercise will increase colonic motility. However, we found that colonic motor activity decreased significantly as the intensity of exercise increased. 29 In part, that was because blood was being stolen from the gut to the exercising muscles.

Interestingly, when motor activity returned after exercise, many subjects showed a few HAPCs and good propulsive activity. I think the propulsive colonic activity that returns after exercise accounts for the significant shift of material in the colon.

**Dr Schnelle:** Does the stimulatory effect of a meal imply that increasing the frequency of meals may be potentially good advice?

**Dr Bharucha:** It also ties into the caloric intake required to induce a colonic contractile response to a meal.
Dr Rao: There is no question that if you increase the frequency of meals you will definitely increase colonic motor activity. If you have 6 meals a day, you'll have a lot more colon activity than if you have only 1 or 2 meals because every meal triggers colonic motor activity. Coffee also triggers colonic motor activity.

Dr Schnelle: Therefore, it's plausible, but has anybody studied that and do we know what happens?

Dr Bharucha: Most phasic motor activity after a meal is irregular and nonpropagated; HAPCs don't often occur after a meal. Depending on its caloric content, a meal will also increase colonic tone.

Dr Hasler: If you look at the subset of patients with CC who have an inadequate gastrocolonic response with 3 meals a day, you are probably not going to get much propagation with 6 meals a day.

Dr Schnelle: I saw the reduced response, but I didn't know how much of a reduced response it was.

Dr Hasler: We've done some studies in our institution and found a broad range of gastrocolonic responses. Some people have a normal or near-normal response, but a sizable subset with slow-transit constipation have absolutely no measurable response. In those people, we would not expect a meal to have any effect.

Dr Chang: I'm still interested in the effects of exercise on the gut. Why do runners get diarrhea when they are running?

Dr Rao: The main reason is that they have inhibited all of their segmental contractions. All they need is 1 or 2 little pushes and then everything will move.

Dr Leung: I have a different hypothesis. The extreme example of runner's diarrhea is, in fact, ischemic colitis. That's the extreme; a patient comes in with bloody diarrhea after a marathon. However, even less extreme ischemia of the colon can still produce diarrhea. We haven't written much about this, but it's a real entity.

I suspect many of the things we've been talking about can or should be examined with this hypothesis in mind. Ischemia-induced changes may affect motility sensations, and a patient's perception. For example, patients with cardiovascular disease who exert themselves often complain of chest pain. The same principle can be applied to the gut. Treat the gut like the heart—unless there is an adequate blood supply to sustain exercise, symptoms will occur. Perhaps not extreme symptoms, such as cardiac arrest, myocardial infarction, or ischemic colitis, but the so-called functional symptoms that you can't quite put your finger on.

Dr Chang: I have a comment about 5-HT, the serotonin signaling mechanisms, and trying to correlate that with the clinical presentation. Serotonin is an extremely important neurotransmitter for gut function, but we tend to focus on EC cells as if serotonin is the only substance they contain. EC cells also contain a host of peptides and other substances, such as calcitonin gene-related peptide, cholecystokinin, bradykinin, and vasoactive intestinal peptide, which may account, at least in part, for gut problems. Although we expect diarrhea rather than constipation when more 5-HT is available, that isn't always the case because serotonin is not the only mediator in the gut.

REFERENCES