From the physiology of gastric emptying to the understanding of gastroparesis

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PHYSIOLOGY OF NORMAL GASTRIC EMPTYING

The stomach is the segment of the gastrointestinal tract in which the main secretory functions and digestion in the alimentary canal begins. However, it’s most critical and important function in digestive physiology is gastric motility (GM).

Normal GM is controlled by diverse extrinsic and intrinsic stimuli. The main extrinsic regulation comes from the vagal nerve. Although the majority of vagal efferents that arrive at the stomach are excitatory, some vagal nerve endings are inhibitory. They produce stimuli through neurotransmitters such as nitric oxide and vasoactive intestinal peptide (VIP). Intrinsic stimuli come from the enteric nervous system and are important in the coordination of gastric motility with more distal segments of the digestive tract especially during the interdigestive period (Figure 1). These myenteric neurons also communicate with the different pacemaker cells of the digestive tract. They are also known as interstitial cells of Cajal (ICCs) and are located in the circular muscle layer of the stomach and the proximal intestine.

GM has three basic components. Even though each one of these phenomena has independent moments and mechanisms, normal gastric emptying is only achieved when there is a functional integration of the three activities (1-4).

Gastric reservoir

This motor activity has the objective of storing nutritional content so that it can be processed by the stomach and passed on to the duodenum in suitable quantities so that the intestine’s mechanisms for digestion and absorption are not overwhelmed.

When the ingested food enters the gastric cavity, a vagovagal reflex is generated. Its effector is mediated by nitric oxide liberation and VIP. It diminishes the tone of the muscular walls, especially the wall of the proximal stomach, by inhibiting the maintained slow waves. This allows accommodation of food without increasing intragastric pressure. Maximum relaxation of the stomach allows storage of up to 1.5 liters of content (Figura 2a).

Gastric distension also generates reflexes that contribute to the beginning of physiological processes in distal segments of the digestive tract. This is important for generating the sensation of satiety.
Mixing and postprandial emptying

During this phase, different mixing and crushing mechanisms act on nutrients to form chyme. The evacuation of chyme towards the intestine occurs at a rate adjusted to digestive and absorptive capacity. Under normal conditions the stomach delivers approximately 200 Kcal per hour.

In response to distension waves of peristaltic contractions begin in the proximal region of the gastric body. With a frequency of 3 to 4 per minute they are weak at the beginning, but propagate distally. They progressively increase their intensity until they reach a maximum when they arrive at the antrum where almost complete contraction of the pylorus occurs. As a result of this contractile activity, the food moves distally until arriving at the pylorus which is already contracted. This generates retropulsion that is fundamental in the process of mixture, crushing and homogenization of foods which continues until they reach the consistency of chime (Figure 2b).

During this postprandial contractile activity, particles that have reached the consistency of chyme pass through the pylorus in which a 2mm to 3mm opening remains. Similarly, despite the tetanic contraction of the pylorus, there is a large enough opening to allow evacuation of liquids during the postprandial period. This occurs as the result of the gastro-duodenal gradient pressure that is generated.

The amount of food that is transformed into chyme and evacuated out of the stomach during the postprandial period depends on the ingested volume, its solubility, the amount of ingested liquid, gastric secretion and the degree of mixing and crushing reached.

The duration of postprandial motor activity varies according to the volume ingested and the physicochemical characteristics of the ingested foods. The maximum duration of postprandial motor activity is approximately 120 minutes.

Interprandial emptying

Once the postprandial period has ended, GM occurs under the control of migratory motor complex (MMC), similar to other segments of intestinal activity (Figure 3).

Motor activity of the MMC occurs in cycles that last approximately 100 minutes. They consist of three phases. In Phase I (50% to 60% of the cycle) there is almost total inactivity with occasional contractile waves that do not generate propulsive movements. In Phase II (20% to 30% of the cycle) there is increased frequency of contractions, but they continue to be irregular and do not generate propulsive phenomena. During Phase III of MMC, which lasts approximately 10 minutes, regular propulsive contractile waves are generated at a frequency of 3 cycles per minute. During this phase the pylorus remains totally relaxed. This allows emptying of any gastric contents that had not been transformed into chyme (indigestible solids).

The mechanism of neurohumoral control of MMC is not yet understood with total clarity. However, we do know that the contractile activity in phase III continues in spite of the activity of the vagus and the splanchnic innervation. This suggests that this control is independent of stimuli.
from sympathetic and parasympathetic nervous systems. In contrast, the beginning of phase III is correlated with high plasma levels of motilin, confirming the importance of this hormone for MMC control even though we do not know the mechanism by which motilin is freed by the duodenal mucosa during fasting, nor how its production is blocked by ingestion (17).

**Physiological mechanisms inhibiting gastric emptying**

When the volume of chyme entering the duodenum surpasses the capacities of the digestive and absorption mechanisms, a chain of multiple reflexes beginning in the duodenal wall is triggered by the enteric nervous system to inhibit gastric emptying. The mechanisms most frequently involved in generation of inhibition of enterogastric reflexes are the degree of duodenal distension, the presence of some degree of irritation of the duodenal mucosa, the degree of acidity and chyme osmolarity, and the presence of products of protein and fat digestion.

In addition to inhibition of gastric emptying induced by nervous reflexes, hormones released in the proximal intestine (primarily in response to the fat content of the chyme) can also produce negative feedback that slows gastric emptying. The most important inhibiting hormones are cholecystokinin (CCK), secretin and the gastric peptide inhibitor (GPI).
GM, and therefore gastric emptying, can be altered at different levels and by diverse causes. They result in clinical and paraclinical alterations that have been grouped together as the clinical syndrome called gastroparesis.

Gastroparesis is a chronic alteration of gastric motility in which a delay of evacuation occurs when there is no mechanical obstruction. It is characterized by disorganization of antral peristalsis. Antral peristalsis, electrophysiology and neural transmission are important components of the emptying of solids. Gastroparesis can be idiopathic or attributable to neuropathy or myopathy (as in the case of the diabetes mellitus), postvagotomy syndrome or scleroderma. The symptoms of gastroparesis are variable and include postprandial fullness, precocious satiety, nausea, vomiting, abdominal discomfort and a sensation of distension. Even so, delayed gastric emptying is not always the cause of these symptoms. In addition, there may be complications such as esophagitis, Mallory-Weiss syndrome and the formation of bezoars (7).

Epidemiology

The true prevalence of gastroparesis is currently unknown, but it is assumed that approximately 4% of the general population experience symptoms of gastroparesis. There are series that show 30% to 50% rates of prevalence among diabetic patients and rates of 24% to 40% in patients diagnosed with functional dyspepsia (a disease that affects 20% of the population). Higher prevalences have been observed among women than among men. In fact, 82% of patients with gastroparesis are women, and the majority of them are less than 45 years old. This has been attributed to the fact that progesterone reduces the contractility of the gastric musculature. However, some therapeutic tests performed with progesterone, or without estrogens, do not demonstrate changes in gastric motility (6, 8).

Etiology and physiopathology

The etiology of gastroparesis includes any alteration that induces neuromuscular dysfunction of the gastrointestinal tract since gastric emptying reflects the coordination of different regions of the stomach and duodenum as well as the extrinsic modulation of the central nervous system. This includes fundic relaxation for food accommodation, antral contractions, pyloric relaxation and the coordination of the antrum, pylorus and duodenum. 36% of all cases of gastroparesis are idiopathic (3) while 29% are related to diabetes mellitus. Postsurgical gastroparesis accounts for 13% of all cases including those occurring after vagotomies, bariatric surgery, Nissen fundoplication, and lung and heart-lung transplants. Parkinson’s disease accounts for 7.5% of these cases, while other causes include collagen disease, chronic intestinal pseudo-obstruction, drugs, endocrinopathies (including thyroid, parathyroid and adrenal dysfunction), anorexia nervosa and bulimia. In rare cases it has been identified as part of a paraneoplastic phenomenon in lung, esophageal, stomach, pancreas and breast cancer. Other gastrointestinal upheavals can be associated with gastroparesis including gastroesophageal reflux disease (GERD), hypertrophic pyloric stenosis and constipation.
Gastric emptying results from interactions among forces that facilitate the movement of the food through the stomach. Normally, antral hypomotility is potentially a key component in delaying gastric emptying. Other abnormalities of motility that may contribute to gastroparesis include increased pyloric and duodenal resistance caused by uncoordinated contractions or spasms, intestinal pseudo-obstruction and reduction of gastric fundus tone. The functions of stomach motility require the interaction of the neuronal, humoral and mechanical inhibition and stimulation processes. These are controlled by the vagus nerve and the myenteric plexus. An inhibiting mechanism that apparently plays an important role in delaying gastric emptying is stimulation of the dopamine receptor. It has been demonstrated that stimulation of the dopamine receptor increases relaxation of the gastric fundus, diminishes gastric tone, induces absence of peristalsis and loss of the contraction between gastric and duodenal contractile activity. Dopamine also stimulates the bulb receptors that induce nausea and vomiting.

It has been observed that diabetic patients have an absence of phase 3 contractions and an interrupted migrating motor complex. This has led to consideration of hypotheses such alterations of liberation or bonding with motilin. The stimulation of cholecystokinin (CCK) by fat in the diet produces an inhibition of gastric emptying as pyloric tone increases gastric tone diminishes.

In idiopathic gastroparesis we have described associations with postviral neuropathy, subclinical autonomic dysfunction, alterations of the electrical rhythm, sensitivity of the smooth gastric muscle and/or the enteric nervous system to estrogens and progesterone, diminution of the function of the enteric nervous system (congenital or acquired), and psychogenic. Amongst the infectious etiologies associated with gastroparesis we have found acute viral infections such as varicella zoster (chickenpox and herpes zoster), Epstein-Barr virus, cytomegalovirus, rotavirus virus, Norwalk virus and Hawaii virus. We have described delays of gastric emptying in one third of patients with HIV infection. It especially occurs in those with advanced disease evidenced by low CD4 lymphocyte counts, marked weight loss and enteric infection. In this group of patients, gastroparesis follows infection by MAC (mycobacterium avium intracellulare). We have also seen autonomic neuropathy induced by HIV.

In recent years a relation between H. pylori infection and delayed gastric emptying has been proposed. Some studies have demonstrated that gastric emptying is slowed in H. pylori positive patients although other studies have found that gastric emptying in these patients is similar to that of H. pylori negative patients. Some studies have demonstrated that gastric emptying improves after treatment to eradicate H. pylori, but other studies have not demonstrated this effect. The relation between H. pylori infection and idiopathic gastroparesis is still controversial.

It has been postulated that Prostaglandin E2 (PGE2) could be important in the physiopathology of gastroparesis. It is known that PGE2 is mostly synthesized in the gastric antrum and can affect the amount of slow waves from the migratory motor complex in certain circumstances. It is believed that its local release in response to inflammation in the antrum may be responsible for some gastric dysrhythmias.

**Diagnosis**

After radiological and/or endoscopic study exclude other possible etiologies like intestinal obstruction, it is possible to diagnose gastroparesis if a patient has delayed gastric emptying and symptoms of gastric retention. These include nausea, vomiting, precocious satiety, postprandial fullness, sensation of abdominal distension and abdominal pain.

The detailed anamnesis should include an evaluation of symptoms suggestive of gastric retention. In one study, nausea was reported by 93% of the patients, whereas precocious satiety and vomiting were reported by 86% and 68% respectively. In a second series, nausea, vomiting, postprandial distension and precocious satiety were reported by 92%, 84%, 75% and 60% respectively. Many patients in both series (89% and 49% respectively) also reported abdominal pain. The clinical picture can look similar to symptoms for functional dyspepsia. Measuring gastric emptying is for making a differential diagnosis.

Measuring the severity of gastroparesis symptoms is important for evaluating the effectiveness of therapies at any given moment. Some symptom measuring scales...
have been developed for doctors to perform in order to evaluate gastroparesis outcomes. The most widely used is the Gastroparesis Cardinal Symptom Index (GCSI). This questionnaire is a scale of symptoms tested in seven clinical centers in the United States. It also correlates grading of gastric symptom severity by patients and doctors. The GCSI is made up of three subscales. Each has several items selected to measure important symptoms related to gastroparesis. There are three items to measure nausea and vomiting, four items to measure postprandial fullness and precocious satiety, and two items to measure abdominal distension. A Likert scale of six points is used to classify the severity of each symptom with a period of memory of 2 weeks. The total score of the GCSI is obtained as the average of the three subscales of symptoms. The total scores are ranked from 0 to 5, where the highest scores reflect greater severity of symptoms. Using these questionnaires, investigators are beginning to classify patients with gastroparesis into different subgroups based on profiles drawn from predominant symptoms. It has been proposed that in the future these surveys can fulfill a clinical role very similar to the Rome Criteria in helping doctors select treatment approaches based on symptoms (18).

The physical examination plays two roles in evaluation of patients suspected of having gastroparesis. First, it is used to evaluate the gravity of the present complaint, and second it facilitates diagnosis. The presence of tachycardia or orthostatic hypotension indicates dehydration of the patient or an alteration in the underlying independent nervous system. Poor skin or eye turgidity and dry mucus also suggest dehydration and indicate hospitalization and an urgent need for reanimation. In advanced phases we find clinical indications of undernourishment. In some patients we observe halitosis and gastric sucession in the abdominal exploration resulting from gastric retention of liquids. This is not a pathognomonic sign of gastroparesis since it is a sign that is also present in intestinal obstruction. Abdominal distension and tympanism with or without sensitivity in the epigastrium may also be found.

Anamnesis and physical examination also are important for finding the cause of gastroparesis. We need to look for history, symptoms and signs of DM 1, DM 2, gastric surgery, neuropathy, neoplasia, diseases of the connective tissue like systemic sclerosis, LES and neurodegenerative diseases such as Parkinson’s.

In cases where obstruction of the small intestine is suspected, a simple x-ray of the abdomen and the intestinal transit is useful. If history suggests possible obstruction of the gastric outlet, we need to perform an esophagogastroduodenoscopy or a series of images with barium of the esophagus, stomach and duodenum. In patients with gastroparesis, and in the absence of mechanical obstruction, the esophagogastroduodenoscopy generally reveals the presence of retained nutritional content in the body or gastric fundus after 6 hours of fasting. It is sometimes associated with the absence of antral motor activity. In some patients it is possible to find bezoars. In patients with exacerbated gastroparesis symptoms, mucosal injuries such as esophagitis from reflux or Candida may be found.

In order to establish diagnostic certainty it is necessary to perform specific tests to demonstrate delayed gastric emptying. The most accepted technique is gammagraphy of gastric emptying (19). It consists in determination of the time a radioactive, nonabsorbent marker related to one of the components of a meal remains in the stomach. It measures the gastric storage and gastric emptying. The measurement of gastric emptying with solids is more sensitive than measurement with liquids since emptying liquid content can be normal until later phases of gastroparesis. In order to perform this test a meal is marked with a radioactive isotope. Usually in Colombia a half solid egg tortilla is used. It is marked with 99mTC. Radioactivity in the stomach is detected with an abdominal gamma camera throughout the postprandial period. Images are taken 0, 1, 2 and 4 hours after ingestion. With this technique gastric retention greater than 60% two hours after ingestion, and greater than 10% four hours after ingestion, is consistent with a diagnosis of gastroparesis. Before exploration a patient must temporarily discontinue any medicine that might interfere with gastric emptying during a period adapted to the average life of the medicine (See Table 1). Prokinetic medicines and opioid analgesics must be suspended 2 days before the study.

### Table 1. Medicines that influence gastric emptying.

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<thead>
<tr>
<th>Delay of Gastric Emptying</th>
<th>Acceleration of Gastric Emptying</th>
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<tbody>
<tr>
<td>Opioid analgesics</td>
<td>Progesterone</td>
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<td>Anticholinergics</td>
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<td>Tricyclic antidepressants</td>
<td>Proton pump inhibitors</td>
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<td>Calcium antagonists</td>
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REFERENCES