Clinical Gastroenterology
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Henry P. Parkman
Richard W. McCallum *Editors*

Gastroparesis

Pathophysiology, Presentation and Treatment

Humana Press

CLINICAL GASTROENTEROLOGY

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Preface

Gastroparesis has become a well-recognized gastrointestinal disorder. Patients with gastroparesis can be particularly challenging; the disorder has limited treatments that are effective in reducing symptoms and/or are FDA approved for use in this condition. There also appears to be an increasing number of patients being diagnosed with this condition, either due to increased recognition of this disorder, or possibly due to an increased prevalence of the disorder. One contribution to this observation is due to the increase of diabetes in the general population. There are often many areas of treatment to address with these patients. Many types of health care providers may need to care for these patients, including gastroenterologists, nutritionists, endocrinologists, internists, pain management specialists, psychiatrists, and surgeons. Fortunately, gastroparesis is being increasingly studied over the last decade from a variety of areas with a marked increase in information on gastric motility and gastroparesis. This is an ideal time to develop a book on the many aspects of gastroparesis.

This book reviews the epidemiology, pathophysiology, symptomatic presentation, diagnosis, and treatments for gastroparesis. This book discusses what is currently known about this disorder, pointing out areas of controversy, discussing unmet needs, and areas for future research to help improve our understanding of gastroparesis.

Despite the high prevalence of gastroparesis, the etiology and pathophysiology of this heterogeneous disorder remain incompletely understood. Why does this disorder occur more often in women – not only for idiopathic gastroparesis, but also for diabetic and postsurgical gastroparesis? Symptoms can be varied in this condition – some present with abdominal fullness, some with nausea, and others with abdominal discomfort or pain. Why do some patients have abdominal discomfort, or even pain? How should abdominal pain be treated in these patients in whom one wants to avoid medications that can affect gastric emptying or cause new symptoms as side effects. Our knowledge and understanding of what is known, as well as the challenges in treatment, are thoroughly brought to light by the authors who address these aspects of gastroparesis in this book.

Diagnosis of gastroparesis entails demonstrating delayed gastric emptying. Symptoms of gastroparesis can be mildly correlated with gastric retention. Three tests are clinically available for demonstrating delayed gastric emptying: gastric emptying scintigraphy, wireless motility capsule, and gastric emptying breath testing. Gastric emptying scintigraphy has become standardized into a 4 h imaging test. However, many centers are reluctant to perform a 4 h scintigraphy study due to the investment in manpower and use of dedicated imaging facilities. How a shorter test impacts on diagnosis and treatment of patients is not clear. Gastric emptying occurs with proximal gastric accommodation followed by antral contractility and pyloric relaxation. Does assessment of regional gastric motility improve the evaluation and management of the patients? Wireless motility capsule measures gastric emptying of an indigestible capsule. The test provides information also on gastric contractility and information on whole gut transit. In some patients with gastroparesis, there are abnormalities in whole gut transit, suggesting a more diffuse process. Finally, gastric emptying breath testing has been used in many clinical research studies, and is undergoing the FDA approval process for use as an office-based clinical test. All these diagnostic options, the pros and cons, are extensively and objectively presented and discussed in this book by expert contributors.

Treatment of gastroparesis is generally with dietary modification, prokinetic agents to gastric emptying, and antiemetic agents to reduce nausea and vomiting. Unfortunately, at the present time, there is a paucity of agents to treat gastroparesis. Metoclopramide has been used for several decades. Side effects, primarily involving the central nervous system, can occur in patients, necessitating to stop this treatment. Recently, the FDA issued a warning about the long-term side effects of metoclopramide, particularly tardive dyskinesia. The antibiotic erythromycin, which is also a motilin receptor agonist, has been shown to increase gastric emptying. However, the prokinetic effects of erythromycin reduce over time due to receptor tolerance. The serotonin 5-HT_4 receptor agonists, cisapride and tegaserod, were used off label to treat gastroparesis until they were pulled from the market. It is apparent that new prokinetic agents are needed to treat gastroparesis. However, it has been difficult to establish symptomatic benefit with prokinetic drugs in gastroparesis, possibly because of the pathophysiological heterogeneity of the patients, the inconsistent relationships between changes in motor function measured by variable and often nonstandardized methods and symptomatic outcome, and a lack of well-accepted symptom endpoints for clinical trials. Many experienced clinicians are using domperidone for gastroparesis, an agent approved in many countries but not the USA, through the FDA IND process. Therapeutic options, as well as surgical solutions, are extensively reviewed by experts who are practicing gastroenterologists facing the challenges of managing gastroparesis every day in their practices as well as performing cutting edge clinical research.

There have been several organizations behind advancing the field of gastroparesis, for which the authors appreciate their role in increasing our understanding of gastroparesis: the American Neurogastroenterology and Motility Society (ANMS) and the NIH Gastroparesis Clinical Research Consortium.

The ANMS has been particularly active in the field of gastroparesis since it is a relatively common disorder of gastrointestinal motility. The ANMS has had a series

of conferences and consensus manuscripts on gastroparesis. A clinical review was published in 2006 on the treatment of patients with gastroparesis. This was a multidisciplinary effort led by the ANMS with input from gastroenterologists and other specialists who are involved in the care of patients with gastroparesis. A consensus document was developed by members of the ANMS and the Society of Nuclear Medicine recommending a standardized method for measuring gastric emptying by scintigraphy using a low-fat, egg white meal with imaging at 0, 1, 2, 4 h after meal ingestion, which provides standardized information about normal, rapid, and delayed gastric emptying. Adoption of this standardized protocol will help resolve the lack of uniformity of testing, add reliability and credibility to the results, and improve the clinical utility of the gastric emptying test. The proceedings from a 2009 conference sponsored by the American Gastroenterological Association and the ANMS reviewed the advances in the understanding of the epidemiology, pathophysiology, diagnosis, and treatment of gastroparesis and functional dyspepsia. The ANMS also developed a task force for gastroparesis endpoints for clinical trials. In this initiative, the ANMS helped convert a symptom questionnaire for gastroparesis into a daily diary version, which appears to be a useful outcome endpoint for gastroparesis clinical trials. This validation has become necessary as a prelude for new drug applications to the Food and Drug Administration.

The NIH Gastroparesis Clinical Research Consortium (GpCRC) is a cooperative network of seven clinical centers and a Data Coordinating Center funded through the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health. The mission of the GpCRC is to improve the understanding of gastroparesis by conducting multicenter, observational studies on well-characterized patients with gastroparesis. The studies emanating from the consortium involve a large number of patients, which will better define the disorders. Studies have been developed for idiopathic gastroparesis, diabetic gastroparesis, and the comparison between the two types of gastroparesis. Pathologic studies have recently been published showing reductions in the interstitial cells of Cajal and an inflammatory infiltrate in the myenteric plexus. A wealth of information is being evaluated on the clinical course of patients with gastroparesis.

This book, the first to focus on the many aspects of gastroparesis that has been published over the recent years, provides a comprehensive review and in depth critical distilling of our knowledge, covering important areas for physicians, nutritionists, nurses, and paramedical staff as well as clinical investigators and basic scientists interested in this disorder. Each chapter has been written by an expert in the area, specifically selected because they are recognized as national and international leaders. This exhaustive test will place the reader at the cutting edge of the field and prepare them for future advances while permitting this knowledge to be directly applied to their patients suffering with gastroparesis.

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Chapter 1
Historical Perspectives on Gastric Motility

Richard W. McCallum

Keywords Gastrointestinal motility • Enteric nervous system • Gastric emptying • Radiographic techniques • Scintigraphy

Introduction

The recording, quantitation, and understanding of gut motility have been a constant goal during the last century, particularly the study of peristaltic contractions. Remarkable progress has been made in the study of gastrointestinal (GI) motility, particularly gastric motility. This progress results from contributions of a wide range of disciplines with advances in smooth muscle physiology, electrophysiology, neurohormonal regulation of the GI tract, anatomic/mechanical factors, flow dynamics, as well as basic molecular and cellular biology. Increasingly sophisticated instrumentation, biomedical engineering, and pharmaceutical research have also added to this rich harvest over the past 50 years. A central theme to the progress is the greater understanding of the enteric nervous system, where more than 10^6 neurons intercommunicate and integrate messages from the gut and brain to organize and coordinate the control of GI motility.

This chapter provides a historical perspective to help understand how the path has been taken to arrive at our present understanding of gastric motility.

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Measurement of Flow Through the Gastrointestinal Tract

Aside from Beaumont's famous opportunity in the 1830s in his patient with a gastric fistula [1], no one had any way to examine directly the flow of the gut until more than 50 years later. Beaumont could only make a crude evaluation of gastric flow because his patient's fistula extended into the fundus, and so Beaumont's experiments on flow depended on the measurements of residual volumes collected by aspiration. Also, he was more interested in gastric juice and digestion than gastric emptying.

The great impetus to the study of flow came with the development of the X-ray tube at the end of the nineteenth century. Roentgen's development of the concepts, and methods for X-ray soon found application in the study of gastrointestinal flow. The pioneers, Bowditch and Cannon, examined the stomach and intestine by contrast radiography before the turn of the century [2–4]. Cannon and others were mainly interested in gastric motility and adopted contrast radiography as a new means to visualize peristalsis and flow from the stomach. Physicians soon recognized the ability of contrast radiography to demonstrate morphologic lesions in the stomach. Hurst led this advance in the clinical use of radiography [5, 6]. The use of contrast films to observe flow extended to the other organs, including the colon. The biggest problem in the study of flow in the stomach and intestine was the need for rapid changes of film, which was resolved when rapid film-chargers and cineradiography were developed.

By 1933, radiographic techniques had revealed so much that an authoritative textbook could be written on the digestive tract from the point of view of the radiologist [7]. It contained extensive descriptions of flows in all the organs as well as descriptions of peristaltic wall movements and morphologic abnormalities. The descriptions still appear quite modern to the contemporary reader.

Observations by contrast radiography are hard to quantify, cannot easily be repeated for verification, are usually performed with the subject fasting, and use a remarkably unphysiologic material. These problems of radiography to demonstrate motility were overcome with the development of scintigraphy in the 1980s, where physiologic meals are radiolabeled [8]. Scintigraphy made it feasible to perform flow studies in routine clinical practice and made flow study more sensitive.

Before the advent of scintigraphy, Hunt had developed a beautifully simple and direct method to advance understanding of gastric emptying, especially of its regulation [9]. He used test meals – liquid volumes of variable composition – passed through a nasogastric tube in various volumes and aspirated at variable times afterward to discover the residual volume. He used anesthetized human subjects, studying the same subjects repeatedly because habituation eliminates the inhibition produced by anxiety. Thus, he was able to develop data for the rate of gastric emptying as it is regulated by meal composition [10].

Most discussions of flow in the gut have dealt with bulk flows – the mass translocations of fluid. Interest in microflows came about from theoretic considerations of intestinal absorption, in which the presence of an unstirred layer at the luminal surface of the intestine came to be recognized as a limitation to the rate of absorption. Little can be done to study microflows directly, because it requires the use of the

principles of fluid mechanics, a discipline that is largely as foreign to gastrointestinal physiologists as gastrointestinal physiology is to fluid-mechanists. The fluid mechanicist, Mecagno, who had extensive experience on flow in rivers and seas, was curious about flow in a system that seemed unique to him. A fluid-mechanical approach to flow in the small intestine by Christensen and Macagno yielded a foundation for a rigorous rheologic study of gastrointestinal microflow and a host of new methods and ideas in the 1970s [11], an area that remains to be exploited more fully.

Measurement of Pressures in the Gastrointestinal Tract

The idea that one could study wall motions by the measurement of pressures in the gut lumen, by kymography (or manometry, as it came to be called later), arose quite early, even before the development of radiographic methods to study flow. It began largely with the use of balloons inflated in the stomach and intestine, a method used notably by Bayliss and Starling [12], Carlson [13], and Thomas [14], among others. Investigators could record pressure changes in such balloons easily enough, but they had much trouble interpreting the records. They slowly came to confront the problems of balloon recording, which seem so obvious to us today. The size of the balloon, degree to which it stretches the viscous wall, the compressibility of the recording fluid, and the compliance of the system all restrict the reliability of conclusions about the external forces that alter the pressure in such a closed recording system.

The idea of using open-tip catheters rather than balloons to record pressures was explored in the 1920s, but it was most aggressively developed in the 1950s mainly to examine the esophagus. The principal players in this development, which included Code [15] and Ingelfinger, probably sought, at the outset, simply to measure pressures rather than to fully map peristaltic movements. At first, they used air-filled catheters, later changing to water-filled tubes. They adopted catheters with distal openings placed laterally rather than at the tip of the catheters and observed that, in the esophagus, they could measure the characteristics of peristalsis – velocity and force of contraction – with apparent reproducibility and accuracy. The method was soon improved by Dodds [16] and Hogan and many others with the introduction of the continuous perfusion of the catheters with a low-compliance pump (the Arndorfer pump, developed by a colleague of Dodds') and other changes, and the technique soon passed into standard clinical use to describe esophageal motor functions. The technique subsequently has found use in the small intestine, but used much less in the stomach and colon. Subsequent experimentation with methods led to developments of much more complex devices in which pressures are measured from miniature pressure transducers mounted on flexible catheters. These devices, combined with computer-aided analysis of pressure patterns, now provide objective long-term high resolution monitoring of motility in the stomach and distally. A pressure transducer mounted on a radio signal generator, the "wireless motility capsule," has also found use. Such devices hold the prospect for more carefully characterizing gastrointestinal motor disorders throughout the whole GI tract.

Perfusion manometry and other methods for pressure measurement brought a new importance to the concept of sphincters. Physiologists had long debated the existence of sphincters because, aside from external anal sphincter, the structures could not be directly observed and radiography was scarcely able to show them satisfactorily. Manometry, however, made it possible to define them, to describe their dimensions, the timing of their opening and closure, and the force with which they occluded the lumen. Thus, both the upper esophageal sphincter and the esophagogastric sphincter were not clearly described until the mid-1950s. The application of a small balloon, the "Dent sleeve," named for its inventor, John Dent, greatly facilitated the study of sphincters in vivo, and it remains the major clinical and investigative technique to study sphincters, finding use especially in the esophagus, pylorus, and the anal canal.

Gastrointestinal Wall Movements

Magendie knew what little he did know about the movements of the gut wall from the direct observation of the gut in the open abdomen, and this remained a major method until after the end of the century, even receiving extensive discussion by Alvarez [17] as late as 1928. After that, the methods to examine flows and hence to infer wall movements (radiography and manometry) captured most of the attention.

The ability to observe wall movements more directly without the artifacts associated with the opening of the abdomen arose in the 1950s with the development of miniature force transducers that could be sewn to the gut wall. Wires from these transducers leading to chronically implanted cutaneous plugs in experimental animals permitted investigators to record movements (mainly from the stomach and the intestine) over long periods under varying conditions [18, 19]. Investigators further developed the use of electrodes implanted in the gut wall to record the electrical events in muscle associated with contractions. Electrodes had been used much earlier, by Alvarez and Mahoney [20], in the 1920s for example, but they were neglected for four decades, only to be salvaged for use, especially by Bass [21], when it was realized that electromyography tracings greatly supplemented the tracings of wall movements made with chronically implanted transducers. Now, both implanted transducers and implanted electrodes find widespread use in chronic preparations in experimental animals. The obvious problem of providing high resolution is overcome by the use of multiple closely spaced sensors.

The Electric Slow Waves of the Gut

Basic research focused initially on myogenic components of GI motility followed by neural regulation of GI motility. In the 1930s, gut motor activity was believed to occur as a result of opposition between excitatory parasympathetic (cholinergic) and inhibitory sympathetic (adrenergic) nerves. Electrical field stimulation of gut

muscle preparations led to the discovery of nonadrenergic noncholinergic (NANC) nerves as the predominant intrinsic inhibitory nerves of the GI tract. The identity of the NANC neurotransmitters, vasoactive intestinal polypeptide (VIP), and nitric oxide (NO), then evolved. Electrical slow waves were appreciated to govern the rhythmicity of contractions, and slow waves of the stomach and small bowel began to be studied extensively by muscle electrophysiologists in the 1950s and 1960s.

Electrophysiology was a fully developed technical discipline in 1939, yet Wiggers could say virtually nothing of the electrical activity of the gut in his textbook [22] of that year; "Numerous attempts have been made to record action potentials from isolated and intact viscera. Unfortunately, the arrangement of muscular tissue in these organs is so complex and the electrical variations derived are so complicated that they are for the present difficult to interpret in terms of functional activity." But electrophysiology was the great biologic technology of the time (just as molecular biology is the great technology of ours), and therefore it was not long before ideas and methods were more fully transferred from the heart (where electrophysiology began) to the gut.

As early as 1932, investigators could detect the characteristic electromyogram of the small intestine [23, 24], but it remained a seemingly fresh subject when Daniel's thorough review appeared in 1963 [25]. The subject advanced rapidly in the 1960s, especially under the guidance of Code and Prosser in America and of Daniel in Canada. The idea of electrical slow waves developed rather slowly, given the ease with which they are detectable and their obvious importance. Thus, it was three decades after the work of Alvarez, and Puestow that Code, Daniel, and Prosser took up the subject with their characteristic energy. Investigators focused on the small intestine for a long time, only later extending the method and the concepts to the stomach and colon.

From the beginning, investigators recognized that electrical slow waves govern the rhythmicity of contraction, not merely the force of contraction. That is, like clocks, the slow waves restrict contractions in time and space, acting as pacemaking signals to which the muscle may or may not respond. Indeed, they were a new sort of phenomenon in having this strictly pacemaker or clock function, and so investigators gave them a variety of names, seemingly to feel that existing terminology was somehow inadequate. For some years, "electrical slow waves," "basic electrical rhythm," "pacesetter potentials," and "electrical control activity" competed for usage, to the great confusion of outsiders, and they still do to some extent.

The discovery of the electrical slow waves in the gut satisfactorily unified some old observations. For example, Russian physicians had long toyed with the technology of the electrogastrogram, a device to record the electrical signals of the stomach in analogy with the electrocardiogram. This fascination of the Russians with electrical events in the stomach at a time when they were scarcely thought of in other parts of the world or in other organs reflects the legacy of Pavolv which accounts for the fact that so many of the earliest autonomic neuroanatomists were Russians, or from the Eastern part of Europe. Code, Kelly, Szurszewski [26], and the others who later did so much to advance understanding of slow waves in the stomach validated the electrogastrogram, heretofore largely unknown in the West. It has gained renewed currency

if not actual vitality. Similarly, the finding of a declining gradient in slow-wave frequency along the small intestine tied in frequency along the small intestine tied in well with the theory of a metabolic gradient along the intestine, which had brought Alvarez to the forefront [17]. The fact that the theory excited some controversy was partly attributable to the personality of Alvarez and his appeals to the press and to the public. His intestinal gradient theory arose again from the ashes on a firm foundation with the discovery of the intestinal slow-wave frequency gradient.

The electrical slow waves generated by the stomach and intestine were known long before; they did not attract detailed scrutiny by muscle electrophysiologists until the 1950s and 1960s [26]. This was true partly because the early investigators were not, for the most part, themselves highly trained in the electrophysiology of smooth muscle, and partly because the electrophysiology of smooth muscle as studied *in vitro* did not fully develop as a subject until the 1950s. Bozler in the USA and Bulbring in England especially deserve credit for advancing gut smooth muscle forward as a subject worthy of detailed study in vitro by dedicated electrophysiologists. Bozler studied the stomach and intestine. Bulbring chose the taenia coli of the guinea pig as her model. It was some time, until the mid 1960s before students of gastrointestinal motility fully realized the significance of the observations of Bozler and Bulbring in their basic electrophysiologic studies.

The Interstitial Cells of Cajal: The Pacemaking System

Experts agree now that the source of the electrical slow waves are the interstitial cells of Cajal rather than the smooth muscle, as previously thought. Cajal did not "discover" the interstitial cells that bear his name, but he raised them from obscurity at the turn of the century. He viewed these tiny cells as secondary nerve cells forming intermediates in the communication between the axons of enteric nerves and the cells of effectors tissues, like smooth muscles and gland cells [27]. He thought of them as forming a terminal syncytium or network of nerve fibers that allowed integrating communication within the substance of the smooth muscle.

For a long time, neuroanatomists argued about these cells, their function, distribution, and indeed, their very existence. Cajal's ideas as to their nature and function were neither disproved nor fully accepted, and they remained cells without a clear function for almost a century. As early as 1925, some investigators had proposed that the cells might be responsible for "myogenic" rhythmic contractions on little evidence. Thuneberg revived the idea in 1982 [28], on better evidence, and stimulated the immigration of others who, in fact, have gathered good evidence in its support [29].

It is ironic that the best evidence for the idea that interstitial cells of Cajal generate the electrical slow waves comes from the colon (of the cat and dog), one of the latest places where they were described and the organ where motility is less well understood than in any other structure. The interstitial cells of the mammalian colon were only discovered in 1971, by Stach [30], who found them as a neuroanatomist working on the neglected topic of the innervations of the mammalian colon. The electrical slow waves of the mammalian colon first described in detail only

about the same time, not by design but by accident, the discoverer simply choosing an unexplored tissue in which to demonstrate the use of a new kind of electrode he had devised [31]. The small intestine and stomach remain the organs in which electrophysiology has been concentrated.

Fasting and Postprandial Rhythmic Activity of the Gut

The idea that the pattern or quantities of rhythmic contractions in the gut vary as the animal is fed or fasted goes back a long time. Beaumont, with his limited capacity to see gastric motions in his patient with a fistula to the gastric fundus, concluded that gastric contractions occur only in the fed state and the stomach becomes quiet after it has emptied itself into duodenum. The idea persisted for a long time, but not universally held. Carlson [13] cites the writings of an eighteenth century physiologist, Haller, who believed that hunger represents contractions of the empty stomach, and referred to others who agreed, especially Boldyreff, who had published his observations in 1905 [32]. Recording from balloons inflated in the stomach of conscious dogs, Boldyreff saw alternate periods of powerful rhythmic contractions and absolute or relative quiescence over a period of 3–4 days of starvation. The periods of contractions lasted for 20–30 min, the periods of relative quiescence, 1¼ h or more. Boldyreff noticed that periodic contractions of the intestine accompanied those of the stomach. Hurst later proposed that these periodic contractions give rise to the sensation of hunger, an idea that Boldyreff had rejected because he saw the contractions become weaker as starvation prolonged.

Carlson and his colleagues, after further experiments, concluded that hunger is indeed caused by these periodic powerful contractions of the stomach. He described his studies (which involved yet another patient with a gastric fistula) in 1916 [13] and the idea of "hunger contractions," of a particular force and regularity, remained part of standard teaching in gastrointestinal physiology until about the 1940s, when it appears to have died out. Boldyreff's original work and Carlson's observations both have been fully reviewed by Wingate [33].

Although periodicity in gastrointestinal contractions in the fasting animal was established by these studies, the matter soon fell into neglect and was forgotten. The picture of vastly different motility in feeding and fasting did not reemerge until the work of Ruckebusch [34] in France and of Szurszewski [35] in America. Szurszewski and his colleagues confined themselves to man and the dog, Ruckebusch ranged widely across the animal kingdom. Ruckebusch was able to show that periodicity is constant in many herbivores that eat constantly, and that eating interrupts the periodic cycle mostly in carnivores that normally eat meals at wide intervals of time. Ruckebusch's broad interests in comparative animal functions are indicated in his textbook [36].

Thus, the idea of periodicity of gastrointestinal contractions in fasting arose, apparently from casual observation, very long ago, but it found little use then except by Carlson to explain hunger. It was finally and firmly rediscovered and the periodic activity of the gut in fasting (newly christened the "migrating motor complex"), has become deeply entrenched in the body of knowledge [35].

W.B. Cannon and F.T. Murphy in 1906–1907 reported that gastric emptying and intestinal motility may be inhibited by both central and peripheral mechanisms. In 1943, Wolf and Wolff suggested that certain emotional states can alter gastric motility, secretion, and blood flow. Ongoing research defined the influence of GI peptides and hormones on the migrating motor complex (MMC). In a review 10 years after the demonstration of the migrating complex, Wingate noted that neural and hormonal factors are involved in regulation, but "specific details remain blurred" – an observation which is slowly being unraveled.

Gastric Sieving of Solids and Receptive Relaxation

Magendie recognized that the stomach contracts to shift its contents, and by 1886 Hofmeister and Schütz described gastric peristalsis. Only after the advent of radiography could Cannon really visualize it in vivo. Beaumont had proposed that food entering the stomach follows a pathway along the greater curvature to reach the pylorus. Cannon was able to disprove that idea. He could see different motor functions of the antrum and fundus and visualized retropulsion of contents with antral contractions. Cannon's views on gastric contractions prevailed for a long time. The full complexity of gastric flows, including sieving, the separation of solids from liquids by the antrum, became clear only after 1960 with Meyer's review and full account of this development [37, 38].

Cannon recognized the reservoir function of the proximal stomach, and realized that it expanded (accommodation) with swallowing by the process now called receptive relaxation. But it was not until 50 years later that vagal inhibition of the stomach received careful study, when Harper [39] observed that the electrical stimulation of the central stump of the severed vagus-induced gastric relaxation by way of the other intact vagus. In the 1960s, Janson [40] and Abrahamson [41] extended the concept of vagally mediated gastric relaxation by demonstrating several reflexes. The excitation of noncholinergic, nonadrenergic inhibitory nerves mediates these reflexes, for the most part, but Miolan and Roman [42] showed that receptive relaxation also involves the suppression of activity in tonic excitatory fibers to the gastric fundus.

Reverse Peristalsis in the Small Intestine

The idea of reverse peristalsis as a phenomenon underlying vomiting and dyspepsia goes back a long time. Various early writers considered it a well-established pattern of peristalsis in the esophagus, stomach, small intestine, and colon, even though the evidence then existed only from the study of the stomach and colon. Many who studied the small intestine had looked for it in vain. In 1961, Smith and Brizzee [43], investigating vomiting by cineradiography in the cat, observed that apomorphine-induced vomiting produced reverse peristalsis in the small intestine. Weisbrodt and Christensen saw it again in 1972 [44]. They used electrodes implanted in the small

intestine of the cat. They noted that vomiting was preceded by a complex change. First, the electrical slow waves diminished in amplitude to the point of extinction. Then a prolonged burst of spikes appeared first at the most distal electrode and moved very slowly, 2.8 cm/s, cephalad through the whole segment under study. The animal then vomited. The electrical slow waves returned soon thereafter, running cephalad at first, slowly orienting themselves to the normal cephalocaudal progression.

Conclusion

These historic perspectives on gastric motility provide a framework for appreciating the following chapters of this book that describe the current knowledge of gastric motility and gastric dysmotility, particularly gastroparesis.

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Chapter 2
Epidemiology of Gastroparesis

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Keywords Gastroparesis • Gastric emptying • Postinfectious gastroparesis • Diabetic gastroparesis • Idiopathic gastroparesis • Quality of life

Introduction

Despite the enormous public health impact of gastroparesis (GP), several gaps in our knowledge still exist. This chapter focuses on the epidemiology of GP with particular attention to those studies which have attempted to shed light on the conflicting definitions of the disorder, its most common etiologies, the incidence, prevalence, and the changing secular trends. The socioeconomic burden of GP in terms of costs, morbidity, and impact on patients' quality of life (QOL) are also explored.

Definitions

Patients with GP can exhibit a broad spectrum of clinical manifestations, but symptom severity correlates poorly with the degree of delay in gastric emptying [1]. The clinical manifestations of GP include nausea, vomiting, postprandial pain and early satiation in the absence of mechanical obstruction. The American Gastroenterological Association (AGA) consensus has stated that pain is not a common concern in

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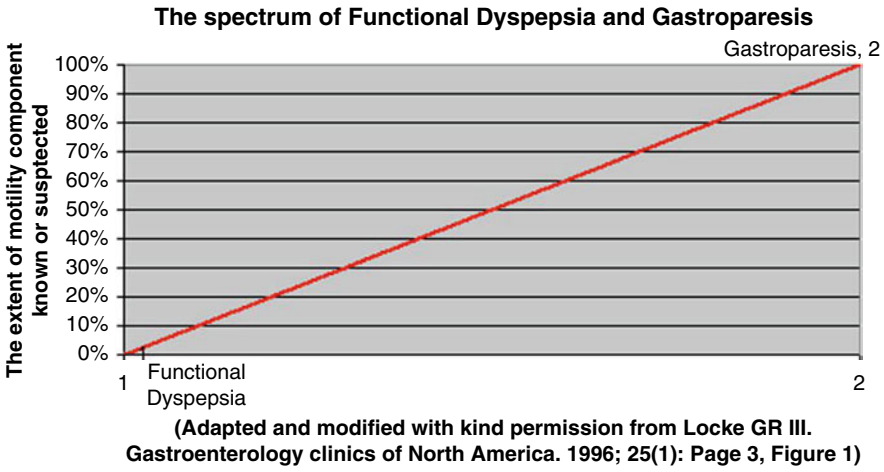

Fig. 2.1 The continuum of dyspepsia and gastroparesis

patients with GP, but two studies have observed that the prevalence of pain in GP can be as high as 89% [2]. However, the severity of abdominal pain does not seem to correlate with the degree of delay in gastric emptying [2].

GP is thus defined as upper GI symptoms in the setting of delayed gastric emptying; obstruction must be excluded before making a firm diagnosis. However, this broad simple definition is problematic for a number of reasons.

Mildly delayed emptying overlaps with functional dyspepsia (FD). Some experts in the field have proposed that delayed gastric emptying and GP are two different entities, and that the diagnosis of GP should be restricted only to those with grossly delayed gastric emptying [3]. Others have proposed the confusing term "gastroparesis-like" syndrome to describe patients with dyspepsia but normal emptying, which for all intents and purposes is FD [4]. Although there is a significant overlap of symptoms, still others have argued that it is the extent of disordered motility that differentiates FD from true GP [5] (Fig. 2.1).

GP may be acute, or chronic if symptoms persist for more than three months [6]. The two most common causes of GP are idiopathic and diabetes mellitus. Even in the absence of symptoms of GP, in those with insulin-treated diabetes, delayed gastric emptying may predispose to poor control of glucose concentrations, particularly hypoglycemia in the early postprandial period [7]. In contrast, in patients with type 2 diabetes (T2DM) who are not managed with insulin, delayed gastric emptying may represent an advantage providing better glucose homeostasis. Whether the definition of GP should be broadened to include these patients with disordered glycemic control attributable to GP is unresolved.

Variation in defining what constitutes GP is also limited by the absence of standardization in interpreting scintigraphy, i.e., the cut off applied, variations across centers in the volume and composition of test meals, the posture of patients during GES, duration of testing, and calculations of emptying as t½ or % retention [8]. Despite recent efforts to standardize GES, many institutions still use 2 h scanning which may have lower sensitivity and specificity than 4 h scanning; this may potentially underestimate patients with GP and thus the true prevalence of the disorder [8]. A 4-h gastric emptying scan showing a delay in gastric emptying three standard deviations above normal using a standard test meal, regardless of symptoms, seems to represent a practical definition of GP that is at least specific.

Causes of Gastroparesis

GP is important but is uncommon; while some estimates suggest that up to 4% of the American population may be affected, this is likely an overestimate (see below) [9]. The etiology of GP is multifactorial with over 90 causes identified in the literature [10] (Table 2.1). The mean age of onset of GP is 34 years (range: 15–72) [11]. Soykan et al. studied a cohort of 146 patients finding 36% were idiopathic, 29% diabetic, 13% postgastric surgery, 7.5% Parkinson's disease, 4.8% collagen vascular disorders, 4.1% due to intestinal pseudoobstruction, and 6% from other miscellaneous causes [9]. Although chronic causes of GP are usually irreversible, the acute cases often resolve after correction of the underlying etiology. Idiopathic gastroparesis (IGP) comprises the largest group of patients and when further subdivided, 23% may have a suspected viral etiology [9].

Table 2.1 Secondary causes of gastroparesis in the population

Probable cause of gastroparesis, *n* (%)	Definite gastroparesis (*n* = 83)	Definite plus probable gastroparesis (*n* = 127)	Definite plus probable plus possible gastroparesis (*n* = 222)
Idiopathic	41 (49.1)	55 (43.3)	70 (31.5)
Diabetes mellitus	21 (25.3)	39 (30.7)	103 (46.4)
Connective tissue disease	9 (10.8)	12 (9.4)	15 (6.8)
Hypothyroidism	1 (1.2)	2 (1.6)	5 (2.3)
Malignancy	2 (2.4)	4 (3.1)	11 (5.0)
Gastrectomy/ fundoplication	6 (7.2)	10 (7.9)	12 (5.4)
Drugs	19 (22.9)	29 (22.8)	54 (24.3)
End-stage renal disease	4 (4.8)	7 (5.5)	19 (8.6)

Note: Three diagnostic definitions were used: definite gastroparesis – delayed gastric emptying and typical symptoms: probable gastroparesis – typical symptoms and food retention on endoscopy or upper GI study; possible gastroparesis – typical symptoms alone or delayed gastric emptying without GI symptoms. Causes of gastroparesis are not mutually exclusive

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Prevalence of Gastroparesis

Data on the prevalence of a disease often sheds light on the burden of disease to society, but for GP, this is difficult to ascertain. Population-based data assessing the extent of GP are scarce. As symptoms do not identify GP, questionnaires alone do not provide robust estimates [1]. Furthermore, population-based studies applying GES are not available.

The most robust data relating to the prevalence of GP are based on a large historical cohort, the Rochester Epidemiology Project (REP), a medical record linkage system in Olmsted County, Minnesota. The REP was used to identify community residents with GP based on strict definitions of definite GP (delayed gastric emptying by standard scintigraphy and symptoms of GP), probable (symptoms of GP and food retention on endoscopy or upper GI study) and possible GP (typical symptoms alone or delayed gastric emptying by scintigraphy). Among the 222 eligible cases of GP studied between 1996 and 2006, only 83 patients met the strict criteria for definite GP with 82% being female (with 44 probable and 95 possible cases) [10]. The most common cause of definite GP was idiopathic (49.4%), followed by diabetes (25.3%) [10]. The overall age-adjusted prevalence of definite GP per 100,000 persons in January 1, 2007 was 37.8 (95% CI, 23.3–52.4) for women and 9.6 (95% CI, 1.8–17.4) for men. Overall, this study indicated that although GP is an uncommon condition in the community, it still represents a major disease burden given the poor prognosis, lower survival and requirement for continuous chronic medical care (see below).

Effect of Ethnicity on Prevalence

No data exist on the prevalence of GP in Hispanics or blacks and therefore whether ethnic differences may influence the epidemiology of GP is unknown. The prevalence of dyspepsia in studies from Europe and North America is reported to be 3–40%, but the rates of GP cannot be determined [12–14]. Generally, studies indicate that the prevalence of chronic GI symptoms, including dyspepsia, is lower in Asian countries as compared to the West [15]. However, Chang et al. reported delayed gastric emptying in 59% of male Chinese subjects with T2DM presenting with upper GI symptoms [15].

Prevalence by Etiology of Gastroparesis

Given the causes of GP are multifactorial, the prevalence of GP in the general population is best assessed by considering the potential risk factors and underlying pathophysiology of the disorder.

Prevalence of Diabetic GP

The prevalence of GP in tertiary referral centers is reported to be 30–50% of type I diabetes (T1DM) and 15–30% of T2DM based on cross-sectional studies [16–18]. For example, in one referral center delayed GES was present in 50–65% of patients with diabetes [16]. However, the selection bias inherent in this approach may seriously overestimate the true prevalence in the community. A large population-based study done by Bytzer et al. evaluated 423 subjects randomly selected from the community with diabetes; they observed that "gastroparesis-like" symptoms were more common in diabetic (11–18%) than nondiabetic people [19]. Moreover, those diabetic subjects reporting poor glycemic control had higher rates of upper GI symptoms (OR 2.45; 95% CI, 1.50–3.98). Hence, conflicting evidence exists as to whether GI symptoms are more common in T2DM which comprises 90–95% of cases of diabetes [20].

Still other studies have failed to establish an association between GI symptoms and DM [21]. For example, one study using records through the REP in subjects with T1DM and T2DM suggested that the prevalence of GI tract symptoms (other than constipation) in patients with DM in the community was similar to persons without DM and, in particular, symptoms of GP are not more common in diabetics than in the general population [21]. However, this database (REP) has some shortcomings, including its predominantly Caucasian and homogeneous population. Another population-based study of 15,000 Australian adults found that those with T1DM treated with oral hypoglycemic medications with or without insulin therapy and those with poor glycemic control were more likely to suffer from nausea/vomiting and upper GI or dysmotility symptoms [22].

The natural history of GP is explored in a subsequent chapter, however, in a longitudinal study done by Jones et al. of 20 patients with DM followed over 12 years, only a minimal change in gastric emptying and GP symptoms was seen over time, despite evidence for progression of autonomic neuropathy [23]. Acute hyperglycemia delays emptying and may worsen symptoms such as nausea and vomiting by this mechanism, while insulin-induced hypoglycemia accelerates gastric emptying substantially, even when the latter is abnormally delayed [24]. Studies on the prevalence of GP during euglycemia are lacking.

Prevalence of Idiopathic Gastroparesis

The proportion of patients with gastroparesis with IGP in a study at a referral center by Soykan et al. was 35.6%, comprising the largest group of GP patients in the cohort; 23% reporting acute viral gastroenteritis preceding their symptoms [9]. Strikingly, a history of physical and sexual abuse was reported in 62% of females with IGP but the relevance of this association remains unclear.

Incidence of Gastroparesis

The true *incidence* of GP in population-based settings is uncertain. However, a recent study done in Olmsted County, Minnesota evaluated incident cases of GP diagnosed either at Mayo Medical Center or Olmsted Medical Center between January 1, 1996 and December 31, 2006 [10]. Through the Mayo Clinic's common medical record system, data on 80% of the entire population in this county are made available with 96% of the population seen at least once during any given 4-year period thus providing the capability for population-based studies. Investigators in the study defined incident case of GP as any new case diagnosed over the 10-year period. When GP is defined by symptoms and delayed gastric emptying (definite GP), the age adjusted (to 2000 US whites) incidence of definite GP per 100,000 person-years for 1996–2006 in Olmsted County, Minnesota, was 9.8 (95% CI, 7.5–12.1) for women and 2.4 (95% CI, 1.2–3.8) for men [10]. The incidence of definite GP was significantly greater in women than in men and, as expected, the prevalence rates were higher among women than men, age-adjusted being 4:1 [10]. Patients with advanced age over 60 years or older had a peak incidence of 10.5 per 100,000 person-years, suggesting that the incidence of gastroparesis may increase with advancing age [10] (Fig. 2.2). These numbers remained similar irrespective of the different diagnostic criteria used [10].

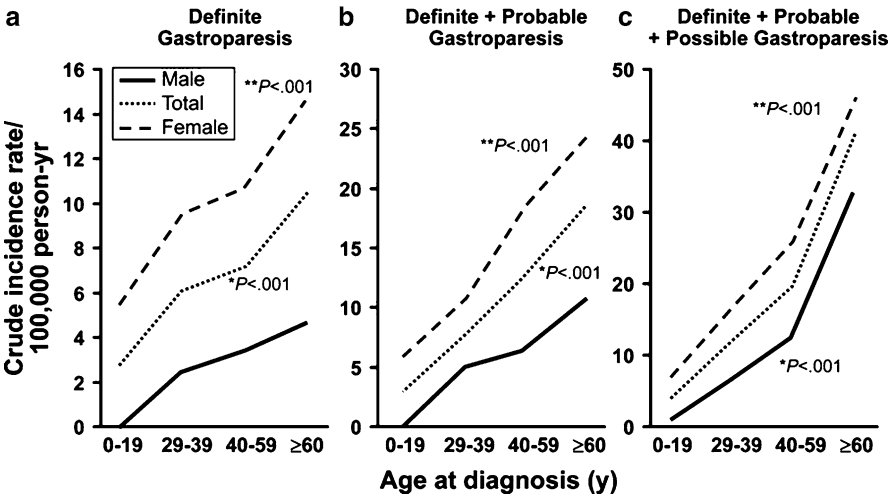

Fig. 2.2 Age-specific incidence of gastroparesis in Olmsted County, Minnesota, 1996–2006 (From ref 10, with permission)

Risk Factors and Predictors of Disease Progression in GP

One aim of epidemiology is to identify homogeneous subgroups in the population who are either at a particularly high or low risk for developing GP. A problem inherent in cross-sectional studies is that the etiologic risk factors cannot be differentiated from associations with no causal relevance.

Influence of Gender and GP

Based on studies done in referral centers, a female predominance of GP exists with a female to male ratio of 4:1 [10]. Some studies have shown that gastric emptying is slower in females compared to males and may also be related to the phase of the menstrual cycle with slower gastric emptying seen during the luteal phase of the menstrual cycle (when progesterone levels are high) versus the follicular phase or menopause (when progesterone levels are low) [25]. However, other studies have failed to show correlations between prolonged gastric emptying and phases in the menstrual cycle, instead demonstrating only postlag gastric emptying rates were slower in women than in men [26]. Furthermore, Monas et al. argue that the greater prevalence of GP in females may reflect the difference in health care seeking behavior, with females seeking health care more frequently than men in general [26].

Hyperglycemia in Diabetics and Gastric Emptying

In diabetes, delay in gastric emptying may be due to elevations in the plasma glucose concentrations [7]. Blood glucose concentration of >8 mmol/l versus 4 mmol/l in healthy subjects and diabetics are associated with delay of both solid and liquid emptying [7]. A profound effect on motor function throughout the GI tract can be seen with any acute change in the blood glucose concentration, which is independent of any intrinsic neuropathy [24].

Hospitalizations

The number of hospitalizations for GP has been increasing in the past decade [27]. In the USA, hospitalizations for a primary diagnosis of GP have been increased, especially among the elderly from 1995 to 2004 [27] (Table 2.2). The data are based on all-payer inpatient care database, the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) in the USA covering 20% of hospitals. Strikingly, hospitalizations for GP as the primary diagnosis increased from 3,977 in 1995 to 10,252 in 2004 (+158%) and using GP as the secondary diagnosis there was an increase of 136%. These statistics represent an overall increase of 138% in the

Table 2.2 National estimates of length of stay, total charges, and number of in-hospital deaths due to gastroparesis as the primary diagnosis, gastroparesis as the secondary diagnosis or a common upper GI condition as the primary diagnosis in the USA, 1995 and 2004

Year	1995			2004		
Outcome	Length of stay	Total charges	In-hospital death	Length of stay	Total charges	In-hospital death
Gastroparesis related hospitalizations						
Primary diagnosis	29,187	47,726,558	60	62,296	208,263,570	57
Secondary diagnosis[a]	455,234	863,291,147	1,454	849,667	3,291,756,583	1,709
Other upper GI conditions as primary diagnosis[a]						
GERD	268,302	569,048,424	122	258,741	1,266,554,967	53
Gastric ulcer	604,436	1,295,370,569	3,096	478,210	2,233,560,923	2,120
Gastritis	592,254	1,008,033,754	1,269	507,760	2,078,923,132	839
Nausea/vomiting	132,182	200,905,164	326	208,139	685,351,009	304

Table reproduced with permission from Wang et al. Gastroparesis-Related Hospitalizations Am J Gastroenterol. 2008 Feb;103(2): Page 321, with permission

GERD gastro esophageal reflux disease

[a] Some hospitalizations had GERD, gastric ulcer, or nausea/vomiting as the primary diagnosis and gastroparesis as the second diagnosis. These hospitalizations were included in both groups

USA during 1995–2004. Moreover, when GP was compared to other GI diseases, such as gastroesophageal reflux disease (GERD), gastritis, and peptic ulcers, GP patients had the longest length of hospital stay and the second highest total charges in 1995 and 2004 [27]. GP patients, as compared to patients with predominantly nausea and vomiting, experienced more inpatient procedures, a longer length of stay and higher total charges. Similarly, the likelihood of in-hospital death was lower for patients with GERD as the primary diagnosis than for those with GP. The dramatic increase in hospitalizations for GP seen after 2000 is unexplained, but may be reflective of an increasing incidence of GP and DM, changes in the GP diagnostic criteria and modes of diagnosis, the lack of treatment options subsequent to the removal of cisapride from the US market 2000, and approval of the gastric electrical stimulator by the Food and Drug Administration.

Economic Impact of GP

While GI diseases in the USA cost over 40 billion dollars in health care expenditures, the inpatient cost of GP as primary diagnosis increased dramatically from $48 million in 1995 to $208 million in 1998 [28]. Moreover, this upward trend in costs may continue, as GP increases with the increased incidence of DM [27].

Based on the North Carolina Hospital Discharge Database from 1998, Bell et al. found that patients with diagnoses of both DM and GP were hospitalized for an average hospital stay of 5.3 days per admission and accumulated an average cost of $7,709 per hospital visit with medicare as the primary payer (52.1%) [29]. Most of these patients were admitted directly from the emergency department (56.2%) [29]. As a result, patients with both DM and GP incurred about US $11 million in charges in that year with 7,800 hospital days for 1,500 discharges.

Impact on Health-Related Quality of Life

Health-related quality of life (HRQOL) is an important outcome for patients with chronic illnesses, in general, and has recently gained much interest in the epidemiological literature. Although studies in GP patients are limited, HRQOL is reduced in patients with gastroparesis [30, 31]. Systematic reviews in patients with FD suggest that impairment of HRQOL exists in patients with moderate to severe FD treated in a referral setting, and El-Serag et al. suggest that the same would be true for GP [32]. Talley et al. studied whether delayed gastric emptying in “meal-related” dyspepsia impairs QOL, finding that although QOL is impaired in patients with FD as demonstrated by the SF 36 (generic HRQOL instrument) and Nepean Dyspepsia Index (NDI) , only female sex, epigastric pain, and nausea, but not delayed gastric emptying, were associated with an impaired total QOL score [30]. We speculate that an effective therapeutic response in patients with GP will lead to a corresponding improvement in HRQOL, although large randomized controlled trials would be necessary for a definitive determination.

Mortality

Long-term studies in patients with GP indicate that GP is probably not a benign disease, and has considerable morbidity with a poor prognosis given the limited current therapeutic options [33]. Mortality from GP is highest in the decompensated GP patients more at risk of developing complications [9]. For example, Soykan et al. found over a 6-year follow-up period that 7% of those with GP had died with 22% of patients with GP needing either long-term enteral or parenteral feeding. Twenty-six percent of these patients did not respond to medical therapy and 6% underwent gastric electrical stimulation. Mortality in the 10 patients that died was attributable to metabolic derangements, cardiac complications, renal failure, suicide, and/or bowel ischemia due to adhesions.

Other data suggest that in diabetics, GP is associated with higher risk of morbidity, but not mortality. Australian patients with type 1 and 2 diabetes were assessed by scintigraphy, GI questionnaires and autonomic nerve function testing at the Royal Adelaide Hospital [17]. The subjects were followed up 9 years later and of 86 patients, 21 had died (24%) with causes of death related to renal and cardiovascular disease. Those patients who had died had longer duration of diabetes, higher scores based on autonomic testing, retinopathy, and slower esophageal transit than those who were alive, but no differences in solid or gastric emptying were evident. A large study by Hyett et al. of a cohort of patients in a tertiary care referral center, conducted from 2000 to 2008, evaluated whether delayed gastric emptying in diabetics predicted morbidity and mortality [33] (Fig. 2.3). The study compared diabetics with symptoms of GP and delayed emptying based on gastric emptying scintigraphy to those with only symptoms of GP, and found that delayed GES was a predictor

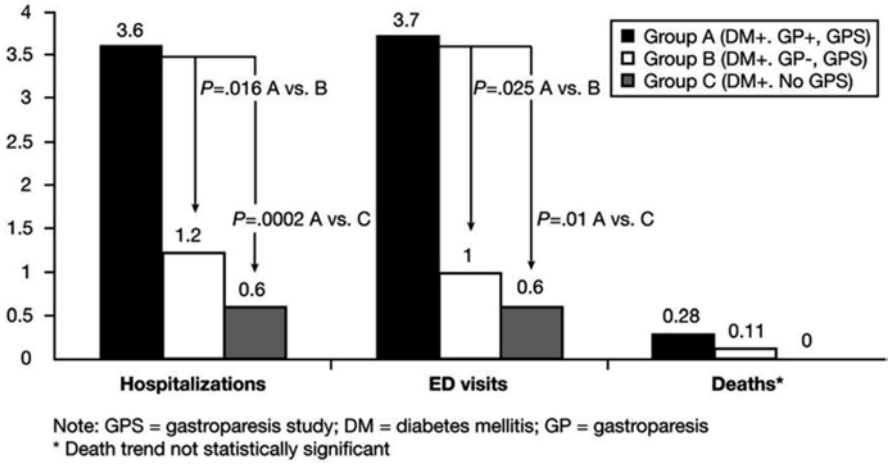

Fig. 2.3 Outcomes between groups per 1000 patient days (Reproduced with permission from [33])

of worse prognosis with more hospital days per 1,000 patient days (25.5 vs. 5.1), emergency room visits, more office visit procedures, such as upper endoscopy performed and increased prevalence of other comorbid conditions, such as coronary artery disease, and hypertension. However, delayed gastric emptying alone in diabetics was not associated with higher mortality. More work is needed to define whether diabetic gastroparesis impacts on mortality.

The 5-year estimated survival of Olmsted County residents with definite GP (symptoms and diagnostic testing consistent with GP) was 67% (95% CI, 60–75%), significantly less than that expected in that population of 81% [10]. Among the causes of death in this cohort were cardiovascular diseases (24.6%), respiratory failure (23.2%), and chronic renal failure (15.9%). Older age at diagnosis was associated with decreased survival. Nondiabetic GP in this cohort was also associated with a better survival than diabetic GP. Other data suggest that postviral GP has a better prognosis and a shorter duration of disease than IGP [34].

Future Studies

Several gaps exist in our current knowledge on the epidemiology of GP. Some of these deficiencies are attributable to the suboptimal definition of GP and a lack of differentiation from FD. We lack a clear understanding of ethnic differences in patient populations with GP. Furthermore, an understanding of the natural history of GP as it relates to the pediatric population is unknown. The NIDDK created a GP registry in 2006 to undertake an observational study to clarify the epidemiology, natural history, clinical course, and outcomes of GP, and this should answer some of these questions. Future technologies, such as swallowed wireless motility capsule using telemetry (SmartPill, SmartPill, Inc., Buffalo, NY), offer a nonradioactive method for assessing gastric transit time in the ambulatory setting [35]. Once such tests become affordable and widely available for use in the general population, the current estimates of incidence and prevalence of GP in the general population may change significantly.

Conclusions

GP represents a major disease burden associated with increased emergency room visits, hospitalizations, complications and poorer survival, especially in the elderly. Because the natural history of GP has been investigated only over the past decade, the long-term outcome is not clearly defined. More aggressive strategies to screen diabetics for GP, and better defined management strategies for all affected are necessary to reduce the morbidity and mortality associated with this usually chronic and debilitating condition.

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Chapter 3
Clinical Presentations of Gastroparesis

Shilpa C. Reddy and John M. Wo

Keywords Gastroparesis • Clinical presentation • Nausea • Vomiting • Abdominal pain • Regurgitation

Introduction

The clinical presentation of gastroparesis is very heterogeneous. Some patients present with predominant symptoms of nausea and vomiting resulting in weight loss, dehydration, and frequent hospitalizations. Some may present with early satiety, postprandial fullness, epigastric pain, and abdominal distension suggestive of postprandial distress syndrome of functional dyspepsia while others may report effortless regurgitation and heartburn resembling gastroesophageal reflux disease (GERD).

It is important to recognize that the presence of delayed gastric emptying by scintigraphy or breath testing does not always imply a diagnosis of gastroparesis. Gastroparesis is a clinical syndrome with chronic and recurrent symptoms. Establishing the cause and effect between gastric emptying impairment and symptom generation can be difficult because the pathophysiology of the development of upper gastrointestinal symptoms is multifactorial. These symptoms involve gastric motor and sensory function, the enteric nervous system, and the interaction between the central nervous system and the stomach. This may explain why the severity of gastric emptying impairment, a measurement of motor dysfunction only, correlates poorly with severity of symptoms. There is an urgent need to identify specific markers or characteristics which can predict prognosis and improve the management strategy of this heterogeneous syndrome. In this chapter, the many facets of the clinical presentation of gastroparesis are presented.

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Symptoms Associated with Gastroparesis

Gastroparesis has been associated with nausea, vomiting, early satiety, bloating, and epigastric pain. These symptoms are very common in the general population. They may or may not be related to gastroparesis. Forty-five percent of the adults in the US report at least one of these upper gastrointestinal symptoms over a 3-month period [1]. A detailed clinical history is important to determine if symptoms are associated with delayed gastric emptying. Symptoms should be exacerbated with eating, especially after fatty foods and indigestible solids, such as salads and leafy vegetables. However, persisting symptoms for many hours after meal ingestion are common.

The symptoms and pathophysiology of gastroparesis and functional dyspepsia overlap. Patients with postprandial distress and/or epigastric pain with mild gastric emptying impairment may be considered to have functional dyspepsia by some physicians and gastroparesis by others. Patients with a marked delay in gastric emptying should be considered to have gastroparesis instead of functional dyspepsia [2].

Nausea, Retching, and Vomiting

Nausea is a subjective symptom and difficult to define. Patients often feel they are about to vomit, and they use terms, such as "sick to the stomach" or "queasy." Severity of nausea is difficult to measure as it depends on subjective reporting by the patient. Different aspects of nausea, such as frequency, intensity, and duration, have been quantified in past studies of patients with chemotherapy-induced nausea [3]. In gastroparesis, nausea should be postprandial, but morning nausea or persistent nausea may be present. The intensity of nausea may become debilitating enough to become the chief complaint in some patients with gastroparesis, but it should not be out of proportion to the other upper gastrointestinal symptoms.

Emesis is an event associated with retching and forceful evacuation of gastric content in a retrograde fashion from the stomach up to and out of the mouth. Some patients may have retching without expulsion of gastric contents. Emesis and retching are usually postprandial and occur soon after eating, but they can occur hours after meal ingestion in patients with very poor gastric emptying. Emesis immediately after starting a meal should suggest other causes other than gastroparesis. The term "vomiting" is more subjective than emesis because "vomiting" is often used by the patient to describe both emesis and effortless regurgitation of undigested foods. This distinction between emesis and effortless regurgitation may be important. Emesis is an event resulting from visceral afferent input from the abdominal vagus nerve to the central nervous system [4]. Emesis may be absent if these pathways are not activated, such as in patients with postvagotomy gastroparesis, who may present with effortless regurgitation of undigested foods without retching. However, the pathophysiologic difference between emesis and effortless regurgitation in gastroparesis has yet to be determined.

Postprandial Fullness, Satiation, and Early Satiety

Postprandial fullness is an unpleasant sensation of stomach fullness after meals. Patients may describe postprandial fullness as a prolonged sensation of food remaining in the stomach. Satiation is the disappearance of the hunger sensation after consuming food. It is the opposite of hunger and appetite. Early satiation is the early disappearing of appetite during food ingestion and before nutrient absorption. Patients of gastroparesis may describe early satiation as loss of appetite or disappearing of appetite while eating. Early satiety is a feeling of stomach fullness soon after starting to eat, out of proportion to the size of the meal.

It is difficult to distinguish between the complaints of postprandial fullness, satiation, and early satiety in patients with gastroparesis. These three complaints are grouped together in the postprandial fullness/early satiety subscale of the gastroparesis cardinal symptom index (GCSI) [5]. Patients with gastroparesis often report a prolonged period of stomach fullness after eating, unable to finish a normal sized meal, and a loss of appetite. However, these are the same symptoms associated with functional dyspepsia, where about one-third of the patients have delayed gastric emptying of solids [6, 7]. Female gender, postprandial fullness, and vomiting seem to predict a greater prevalence of delayed gastric emptying in patients with functional dyspepsia. It has been suggested that symptoms beginning immediately or within 30 min after food ingestion are less likely due to gastroparesis. However, in a study of symptom measurement during 4-h gastric scintigraphy, the sensation of stomach fullness occurs and peaks immediately after ingestion of the standardized meal in patients with documented delayed gastric emptying [8].

Bloating and Abdominal Distension

Bloating is also a very subjective sensation of increased abdominal pressure. Bloating can occur without eating and should be differentiated from postprandial fullness. It may or may not be related to food ingestion. In a population survey of upper gastrointestinal symptoms of over 20,000 adults, the sensation of bloating was identified as a separate symptom-subgroup distinct from nausea/vomiting and postprandial fullness by statistical cluster analysis [1]. In patients with functional dyspepsia, the association between bloating and delayed gastric emptying has been mixed [9, 10].

Bloating should also be distinguished from abdominal distension, where the abdomen is visibly larger with an increase of abdominal girth by measurement. In some patients, abdominal distension is minimal in the morning but progressively gets worse throughout the day. Significant abdominal distension may suggest the presence of small intestinal bacterial overgrowth or chronic intestinal pseudoobstruction of the small bowel [11].

Abdominal Pain

Abdominal discomfort or pain is common, occurring in 46–90% of the patients with gastroparesis [12–15]. Prevalence of abdominal pain in gastroparesis is comparable to functional dyspepsia [7, 14]. Patients with idiopathic gastroparesis may have more frequent abdominal pain than those with diabetic gastroparesis [14]. Postprandial epigastric pain is perceived by physicians as the most common presentation of gastroparesis, more than retching/vomiting and heartburn/regurgitation [16]. Abdominal pain is an important complaint for the patient, and it correlates with impairment of quality-of-life [14].

The characteristics of abdominal pain are variable. About 40% of patients have localized epigastric pain, but it can be diffused in some patients [14]. Pain is usually characterized as postprandial, but it can be constant, occur at night, and interfere with sleep. The cause and effect between delayed gastric emptying and abdominal pain is poorly understood. The impairment of gastric emptying does not correlate with the intensity of abdominal pain [14, 17]. Persistent epigastric pain not related to meal ingestion should suggest epigastric pain syndrome of functional dyspepsia, rather than gastroparesis [18]. In patients with gastroparesis, the presence of abdominal pain predicts poor response to gastric electrical stimulator placement [19].

Heartburn and Regurgitation

Gastroparesis has been considered a potential cause for GERD. However, the precise mechanism on how delayed gastric emptying cause acid and nonacidic reflux has been difficult to determine [20]. Studies have shown that 33–45% of patients with GERD also have delayed gastric emptying [21–23], but this may be an overestimation due to patient selection in studies from tertiary centers. Nearly 20% of patients with gastroparesis present with heartburn and/or regurgitation as their chief complaints [24]. It is essential to obtain a detailed history in patients who are refractory to proton pump inhibitors. The presence of effortless regurgitation of undigested foods, nausea, postprandial distress, or early satiety should suggest the possibility of gastroparesis, and the diagnostic evaluation should be redirected. Fundoplication should be avoided to prevent postfundoplication gas-bloat syndrome.

Psychological Issues Associated with Gastroparesis

It is important to consider the psychological state in patients with gastroparesis. Nearly half of patients referred to tertiary centers have evidence of moderate to severe depression, and more than half have clinically significant temporary and prolonged symptoms of anxiety [25]. These psychological illnesses are often unrecognized and untreated in many patients. The presence of depression and anxiety are

associated with more frequent hospitalizations and severe gastroparesis by physician and patient assessments [15, 25]. However, psychological dysfunction is not associated with the etiology or severity of gastric retention [25].

It is unclear if the psychological illness is contributing to symptom generation or is a result of the chronic disease burden of gastroparesis. As in irritable bowel syndrome and functional dyspepsia, past physical and sexual abuse may be present in some patients with gastroparesis [12]. Psychologic issues should be addressed, and appropriate pharmacologic therapy and consultation should be initiated, especially in patients with refractory gastroparesis.

Predominant Symptom Presentation

The term "gastroparesis," which implies a paralyzed stomach, does not describe the whole spectrum of this heterogeneous clinical syndrome. The severity of gastric emptying impairment does not correlate with the severity of symptoms. Physicians often feel overwhelmed because patients with gastroparesis present with multiple functional symptoms with varying intensity. It is essential to identify the most important chief complaints of each patient to focus the clinical history and to formulate a management strategy. It may be useful to conceptualize patients with gastroparesis into three distinct subgroups based on predominant symptom presentations (Table 3.1) [24]. However, there is no data at this time to support the clinical usefulness of any classification in predicting outcome or to improve clinical management.

Vomiting-predominant gastroparesis consists of patients with chief complaints of nausea, retching, and vomiting, often resulting in dehydration, weight loss, and hospitalization (Table 3.1). Regurgitation-predominant gastroparesis consists of patients often described as having GERD, but they also have symptoms of nausea, postprandial fullness, and early satiety. These patients report regurgitation of undigested foods without retching, occurring many hours after meal ingestion or at night while they are asleep. Rumination, which is the immediate regurgitation of

Table 3.1 Proposed classification of gastroparesis based on predominant-symptom presentation

	Definitions
Vomiting-predominant gastroparesis	Vomiting with retching and nausea are the most bothersome symptoms
Dyspepsia-predominant gastroparesis	Unpleasant or troublesome sensation (discomfort or pain) centered in the upper abdomen is the most bothersome symptom; this sensation may be characterized by or associated with upper abdominal fullness, fullness after small meals, bloating, or nausea
Regurgitation-predominant gastroparesis	Effortless regurgitation of acid or undigested food or heartburn is the most bothersome symptom

partially digested food that is subsequently reswallowed, should not be associated with gastroparesis. Dyspepsia-predominant gastroparesis consists of patients indistinguishable from those with postprandial distress syndrome of functional dyspepsia [18].

Subscale scores of nausea/vomiting and heartburn/regurgitation, using the patient assessment of gastrointestinal symptom (PAGI-SYM) severity index, have been associated with the vomiting-predominant and regurgitation-predominant gastroparesis subgroups, respectively [24, 26]. However, the patients in the dyspepsia-predominant gastroparesis subgroup have multiple symptoms with variable intensity. This subgroup was unable to be characterized by any of the PAGI symptom subscales.

Symptom Patterns

Patterns of presentation and progression in gastroparesis are variable. Patients should be inquired regarding any presence of acute respiratory or gastrointestinal infection before developing the symptoms of gastroparesis. A post-infectious gastroparesis syndrome has been described in retrospective series with isolation of both the cytomegalovirus and Epstein-Barr viruses [27, 28]. In these patients, symptoms may improve with time, but longitudinal cohort studies to confirm this assumption is limited. However, most patients with gastroparesis report gradual onset of symptoms without any particular triggering event.

Gastroparesis is a chronic and recurrent syndrome, but symptom progression is variable. Some patients have chronic stable postprandial symptoms with minimal fluctuations. Others may report progressive worsening of their symptoms. Periodic exacerbation may be common, especially in patients with vomiting-predominant symptoms. In a retrospective review of patients with gastroparesis, poor glycemic control in diabetics, infection, poor compliance, and intolerance of medications have been identified as the culprit for an acute exacerbation requiring hospitalization [29]. A cyclic pattern with recurrent nausea and vomiting with symptom-free intervals has been described in some patients with diabetic gastroparesis [30]. These patients tend to have a higher incidence of migraine headache, greater impairment of gastric emptying, and more abnormalities by electrogastrography (EGG).

Assessment of Disease Severity

Measurement of Symptom Severity

Several symptom scales have been developed to quantify a patient's own assessment of gastroparesis symptoms [31–34]. However, only the GCSI has been extensively validated and found to be reliable and responsive to changes, and correlate with

Table 3.2 Gastroparesis cardinal symptom index[a]

Subscales	Symptoms
Nausea/vomiting	• Nausea (feeling sick to your stomach as if you were going to vomit or throw up) • Retching (heaving as if to vomit, but nothing comes up) • Vomiting
Postprandial fullness/ early satiety	• Stomach fullness • Not able to finish a normal-sized meal • Feeling excessively full after meals • Loss of appetite
Bloating	• Bloating (feeling like you need to loosen your clothes) • Stomach or belly visibly larger

[a]Graded from 0 to 5 (0 = none; 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) with a 2-week recall period

physician and patient assessment (Table 3.2) [34]. The GCSI is a multinational instrument with a 6-point Likert response scale ranging from 0 (none) to 5 (very severe). The GCSI consists of nine symptoms with three subscales (nausea/vomiting, postprandial fullness/early satiety, and bloating) that are graded by the patient with a symptom recall of 2 weeks (Table 3.2). Daily evaluation of the GCSI appears to maintain its validity and reliability [35]. Bloating is differentiated from postprandial fullness/early satiety and nausea/vomiting in the GCSI, in a similar manner that bloating was identified as a distinct symptom subgroup by statistical cluster analysis [1].

The GCSI was developed as a part of the PAGI-SYM severity index, which was designed as a single instrument for patients with GERD, functional dyspepsia, and gastroparesis [26]. The GCSI does not include the heartburn/regurgitation (7 items), upper abdominal pain (2 items), and lower abdominal pain subscales (2 items) of the PAGI-SYM severity index. Since the symptoms of gastroparesis overlap with GERD and functional dyspepsia, it is reasonable to use the full PAGI-SYM index in assessing the clinical spectrum of gastroparesis and its predominant-symptom presentation.

Measurement of Quality-of-Life

Assessment of quality-of-life (QOL) is important in understanding the patients' symptom severity and implications on their life. The SF-36 Health Survey is a self-administered 36-item questionnaire designed to measure generic health status of the patient. It comprises eight multi-item subscales: physical function, role limitation due to physical health problem, vitality, general health perceptions, bodily pain, social functioning, role limitation due to emotional problems, and mental health. The physical component summary (PCS) and the mental component summary (MCS) scores are calculated using these subscales. The SF-12 is a simplified,

self-reported 12-item questionnaire which measures perceived health. The SF-12 correlates very well with the PCS and MCS of the SF-36. Both the SF-36 and SF-12 have been utilized to assess the QOL in patients with gastroparesis [15, 24, 36, 37]. The advantage of using the SF-36 and SF-12 is the ability to compare the QOL of gastroparesis with the normal population and other disease states.

The patient assessment of gastrointestinal quality-of-life (PAGI-QOL) is developed as a single instrument for patients with GERD, functional dyspepsia, and gastroparesis [38]. It is a valid, reliable, and sensitive instrument for assessing the QOL in these patients. The PAGI-QOL is a 30-item questionnaire with five domains: daily activities, clothing, diet/food habits, relationship, and psychological well-being/distress. It correlates well with the generic health-related SF-36.

Physician Assessment of Disease Severity

Unlike GERD, where erosive esophagitis, peptic stricture, and Barrett's esophagus are objective endoscopic and pathologic identifiers for complications of GERD, there are no objective markers specific for complications of gastroparesis. Some patients may have severe nausea and emesis resulting in dehydration, documented by orthostatic hypotension and acute renal insufficiency. Frequent emergency room visits and hospitalizations may be related to dehydration, but subjective severe abdominal pain is also common in hospitalized patients. Some patients with severe gastroparesis have significant weight loss and nutritional deficiency requiring small bowel feeding access to bypass the stomach. Intolerance of nasojejunal feeding should alert the possibility of a chronic intestinal pseudoobstruction of the small bowel. A gastric food bezoar is a common finding during upper endoscopy despite overnight fasting, but a gastric bezoar causing gastric outlet obstruction is rare.

A physician-assessment severity scale for gastroparesis has been proposed by a consensus panel of experts (Table 3.3) [2]. It is based on the response to treatment, ability to maintain nutrition orally, and frequency of hospitalizations. However, this

Table 3.3 Proposed classification of gastroparesis based on severity

	Definitions
Grade 1: Mild gastroparesis	• Symptoms relatively easily controlled • Able to maintain weight and nutrition on regular diet or minor dietary modifications
Grade 2: Compensated gastroparesis	• Moderate symptoms with partial control with pharmacological agents • Able to maintain nutrition with dietary and lifestyle adjustments • Rare hospital admissions
Grade 3: Gastroparesis with gastric failure	• Refractory symptoms despite medical therapy • Inability to maintain nutrition via oral route • Frequent emergency room visits or hospitalizations

From the American Motility Society Task Force on gastroparesis [2]

Table 3.4 Gastroparesis severity based on 4-h gastric scintigraphy [2]

	% Retention at 4-h
Mild	<20%
Moderate	20–35%
Severe	35–50%
Very severe	>50%

grading scale has not been validated, and criteria may be subject to interpretation by the physician. An objective grading of gastroparesis severity has been proposed based on the amount of gastric residual at 4-h by gastric scintigraphy using the standardized international method (Table 3.4) [39, 40]. However, this scintigraphy grading scale does not correlate with symptom scores by GCSI [25]. Future studies are needed to determine if these grading scales can predict prognosis and improve management strategy in patients with gastroparesis.

Conclusion

The clinical presentation of gastroparesis is very heterogeneous. The presence of gastric emptying impairment does not always imply a diagnosis of gastroparesis. The cause and effect between delayed gastric emptying and symptoms may be difficult to prove. The symptoms of gastroparesis should be associated with meal ingestion. Both predominant symptom presentation and symptom pattern should be identified. In addition to the upper gastrointestinal symptoms, the psychological state of the patient has to be considered. Symptom severity and quality-of-life impairment can be quantified using currently available validated instruments. Severity grading scales for gastroparesis have been proposed, but future studies are needed to determine if they can predict prognosis and improve management strategy in patients with gastroparesis.

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Chapter 4
Gastric Dysmotility at the Organ Level in Gastroparesis

Michael Camilleri and Maria I. Vazquez-Roque

Keywords Gastroparesis • Gastric emptying • Gastric accommodation

Introduction

Gastric motor functions represent a complex series of events that are regulated by circulating blood glucose and hormones, such as the incretins, extrinsic neural control from the brain and spinal cord, the enteric nervous system, the interstitial cells of Cajal (ICC), smooth muscle cells, and locally released neurotransmitters. The normal function of the two major regions of the stomach, the fundus and antrum, depend on these neural and muscular mechanisms. The major motor function of the gastric fundus is to receive and store food, and the antrum triturates ingested food into chyme. To maximize nutrient absorption and digestion, the antrum and pylorus empty chyme into the duodenum through carefully regulated functions. Alterations in these functions lead to delayed gastric emptying and clinical symptoms, such as nausea, vomiting, early satiety, anorexia, bloating, or pain. To better understand the underlying mechanisms that characterize gastric dysmotility at the organ level, it is important to understand the normal gastric motor physiology.

Control of Gastric Motor Function

Gastric motor functions depend on neuromuscular control mediated by enteric (intrinsic), parasympathetic, and sympathetic nervous system (extrinsic), ICC, and by smooth muscle cells [1] (Fig. 4.1).

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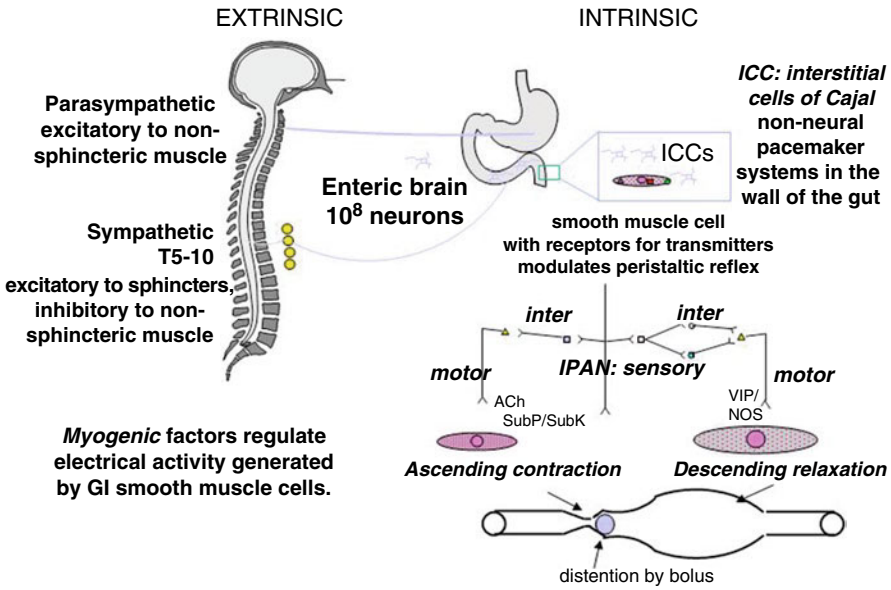

Fig. 4.1 Schematic representation of the extrinsic and intrinsic control of gastric motor function. The extrinsic pathway is composed of vagal efferents and splanchnic efferents. The intrinsic pathway is composed of interstitial cells of Cajal and the motor function unit

The enteric nervous system (ENS), sometimes called the "gut brain," is a collection of more than 100 million neurons organized in ganglia that function independently but they also integrate signals from the autonomic and central nervous system. The ENS is a network of ganglia arranged in the myenteric, deep mucosal, and submucosal plexi. The myenteric or Auerbach plexus is involved in control of gastrointestinal motility. The submucosal or Meissner plexus is involved the control of absorption, secretion, and mucosal blood flow. The ICC, located between the circular and longitudinal muscle layers in the stomach wall in the deep mucosal plexi, serve as a nonneuronal pacemaker system that creates the basic electrical rhythm for gastric propulsion, the migrating motor complex, and sensation [2, 3]. The ICC's communicate signals between the ENS plexus and smooth muscle cells. Electrical control activity spreads through the contiguous segments of the gut through neurochemical activation by excitatory (e.g., acetylcholine [Ach], substance P) and inhibitory (e.g., nitric oxide [NO], somatostatin, vasoactive intestinal peptide [VIP]) transmitters.

The autonomic regulation of gastric motor functions consists of extrinsic control by the parasympathetic and sympathetic nervous systems. Parasympathetic pathways reach the stomach through the vagus nerve. Vagal efferents arise in the dorsal motor nucleus of the vagus nerve and, to a lesser extent, from the nucleus ambiguus and tractus solitarius, the latter being predominantly involved in afferent (sensory) functions.

The sympathetic nervous system connects to the stomach from the intermediolateral columns of the spinal cord at the T5 to T10 levels, synapsing in the celiac ganglia. Splanchnic efferents, in the celiac ganglia, supply the myenteric ganglia mostly innervating the pyloric sphincter [4, 5].

Myogenic factors regulate the electrical activity generated by gastrointestinal smooth muscle cells [6]. The smooth muscle cells that control gastric motility have specific receptors for amines, peptides, and other transmitters that reach the smooth muscle membrane by neurocrine, endocrine, or paracrine routes. The ICCs are in close proximity to the smooth muscle cells and are responsible for integration and coordination of the electrical slow wave spreading through the smooth muscle syncytium to produce circumferential contractions.

The motor function unit in the gastrointestinal tract responsible for the transfer of food from the stomach into small intestine is the peristaltic reflex (Fig. 4.1). This reflex is initiated either by luminal distention (mechanical stimulus) or by a chemical stimulus. Mucosal sensation is transmitted by intrinsic primary afferent neurons and leads to a contraction in the orad (more proximal) segment that is mediated by excitatory transmitters, chiefly Ach, substance P and serotonin. Relaxation in the aborad segment allows transport of the incoming bolus, and this is mediated by inhibitory neurotransmitters, such as NO and VIP. Interneurons, such as opiates or somatostatin, coordinate these functions.

Physiology of Gastric Motor Functions

The fasting and postprandial periods have unique motility patterns in healthy individuals. The fasting period is characterized by a highly regulated cyclic motor pattern in the body and antrum called the migrating motor complex (MMC) [7, 8]. There are three phases in an MMC cycle, with approximate total duration of 60–90 min in healthy individuals. Phase I is a period of quiescence, with no contractile activity recorded, and phase II is characterized by intermittent irregular contractions. Phase III, the activity front, is contractile activity that occurs at frequency of up to 3 per minute in the stomach and up to 12 per minute in the upper small intestine. Phase III migrates for a variable distance through the small intestine. There is a gradient in the frequency of Phase III contractions from ~12 per minute in the duodenum to ~8 per minute in the ileum. During fasting, the stomach participates in the cyclical activity front that propagates through the antrum, thereby emptying nondigestible solid residue into the duodenum. Approximately 50% of phase III activity fronts originate in the stomach during fasting [7, 9]. Since nondigestible solid is not found in the stomach after 8 h fasting, antral contractions during phase III of the MMC are efficient in clearing nondigestible solids from the stomach despite the fact that only 50% of MMCs have an antral component.

The two functional regions of the stomach, that is the fundus and antrum, are responsible for the reservoir and pump activity in the postprandial period (Fig. 4.2). The stomach muscle is organized in three layers with fibers organized

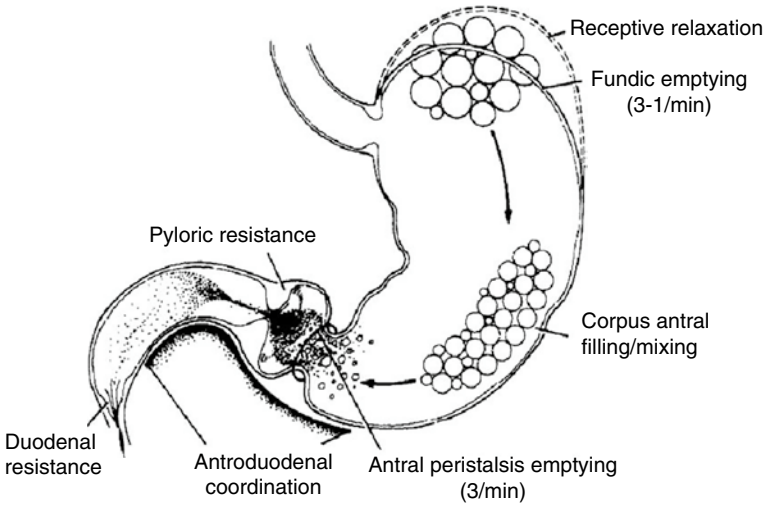

Fig. 4.2 The different regions of the stomach and specific functions in the digestion of a meal. Modified from Koch KL. Electrogastrography: Physiological Basis and Clinical Application in Diabetic Gastropathy. Diabetes Technology and Therapeutics Vol. 3. Issue 1, July 5, 2004. Mary Ann Liebert, Inc., Publishers

on different axes: circular, oblique, and longitudinal. These are innervated by excitatory and inhibitory motor neurons of the ENS. The mid-portion of the greater curvature of the stomach is considered the functional site of the gastric electrical pacemaker, although ICCs which have spontaneous firing and reflect the cellular pacemaker activity that coordinates rings of contractions that sweep through the stomach.

During fasting, the fundus is tonically contracted; after food is ingested, a neurally mediated reflex relaxes the proximal stomach to receive the meal. Food is then transferred from the esophagus into the fundus, which acts as a reservoir to accommodate the ingested meal, also called gastric accommodation. The decreased tone in the fundus allows large amounts of solid or liquid food with little or no increase in intragastric pressure, thus avoiding postprandial symptoms, such as fullness and pain [10]. The initial phase of fundic relaxation is a reflex called receptive relaxation which occurs during swallowing. During receptive relaxation and stimulation of mechanoreceptors by the arrival of food in the stomach, vagal afferents, and vagovagal reflexes are activated, stimulating the intrinsic inhibitory neurotransmitters NO and VIP. Adaptive relaxation is triggered by distention of the gastric reservoir [11]. This process facilitates the initial chemical digestion of food by acid and proteases before contents are transferred to the antrum. Fundic relaxation is impaired in patients with fundoplication due the mechanical effects of the operation, as well as a result of

vagal injury [12]. Such patients are likely to have a lower threshold for postprandial fullness and pain.

Another important function of the fundus is to contract and transfer the contents of the gastric reservoir into the antral pump [11]. Thus, the fundus produces contractile events that are most easily demonstrable as phasic volume changes by using a barostatically-controlled balloon [10, 13].

The antrum produces high amplitude contractions that grind solids by physical and liquid shearing forces. Chyme, which is composed of solid particles that have been reduced to 1–2 mm in size suspended in gastric juice, is then able to empty through the pylorus [14]. Particles that have not been reduced to this size are continually forced toward, and retropulsed from the distal stomach by an occluded pylorus until liquid shearing and chemical digestion achieve adequate trituration. In contrast, interdigestive antral motor function clears the stomach of nondigestible solid particles whose size has not been reduced by trituration.

The pylorus is mostly composed of thickened circular muscle and presents a zone of high resting pressure controlled by Ach and NO. Through antropyloroduodenal coordination, 2–4 mL of chyme is emptied into the duodenum through phasic contractions that occur at a maximum rate of 3 per minute. Antropyloroduodenal coordination coordinates antral peristalsis with decreased duodenal pressure and pyloric resistance to ensure optimal emptying of gastric contents [6].

Physical characteristics, volume, and macronutrient content of ingested food determine the gastric emptying rate of a meal. Gastric emptying of liquids is faster than the emptying of solids, and it follows a simple exponential model for nonnutrient liquids [14]. The emptying of high-nutrient liquids or fully homogenized solids approximates a linear model. The gastric emptying half-time for noncaloric liquids is approximately 20 min for healthy individuals. Nonnutrient liquids empty from the stomach exponentially [15], but with increasing caloric content of liquids, the gastric emptying rate is approximately of 200 kcal/h [16, 17].

Gastric emptying of solids is characterized by two stages; an initial lag phase during which no food is emptied from the stomach, followed by a postlag emptying phase which tends to be linear [6, 18] (Fig. 4.3). The lag phase is associated with the time when there is accommodation of solids in the fundus and the transfer of food into the corpus and antrum for trituration and grinding. The duration of the lag phase depends on several meal factors, such as macronutrient content (e.g., it is longer with higher fat or calorie content of the meal) [19, 20], the chewing process or the degree to which the food is homogenized before ingestion, or is easily digestible or triturated. The lag phase duration typically may last up to 60 min. In healthy volunteers, a positive correlation between antral motility and overall emptying of solids has been demonstrated [15]; the lag time duration is inversely related to the antral motility index, consistent with the concept that more effective antral contractions facilitate trituration and the commencement of emptying. The emptying of liquids is significantly associated with antral contractility only after the lag time for trituration of solids has been completed and pyloric closure coincident with antral contractions is no longer required [15].

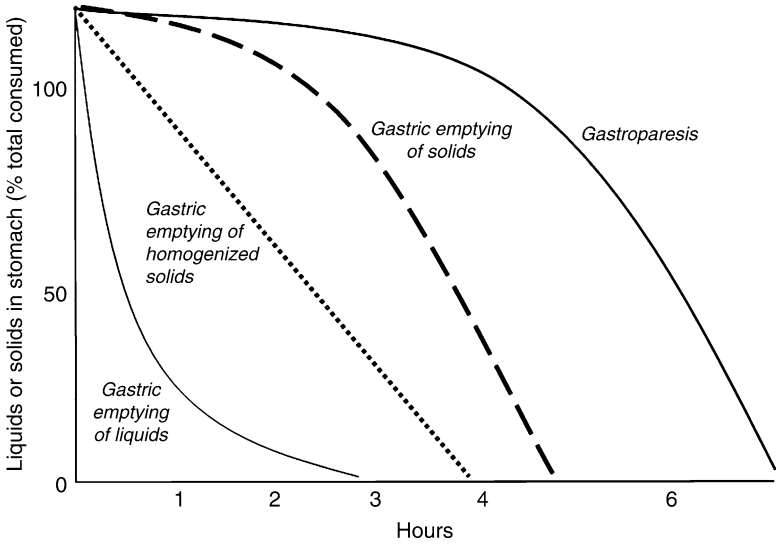

Fig. 4.3 Gastric emptying of solids and liquids in health and in gastroparesis. Note the exponential emptying of liquids, in contrast to the initial retention of solids (lag phase) which is followed by a generally linear postlag emptying rate

Gastric Dysmotility

Gastric motor dysfunction or dysmotility is typically characterized by an abnormality in one or more of the different gastric functional regions. Alterations in the ENS, pacemaker cells (ICCs), or smooth muscle cells [1] have been described in gastric dysmotility. Neuropathic or myopathic disorders can affect the mechanisms that control gastric motor functions leading to gastric dysmotility, such as diabetes mellitus, sarcoidosis, and amyloidosis, among others. Similarly, there are data suggesting the ICC pathology may cause the impaired motor function. Different pathophysiological processes may cause impaired intragastric distribution of food, and delayed emptying of the stomach, and they include impaired fundic relaxation (or accommodation), antral hypomotility, and pylorospasm.

Fundus

Impaired postprandial fundic accommodation occurs in patients after vagotomy and partial gastric resection [21]. Patients with vagotomy have gastric emptying studies that show delayed emptying of solids (resulting from impaired vagal input to the antrum) and accelerated emptying of liquids (resulting from impaired vagal

supply to the inhibitory innervation that normally relaxes the fundus). Patients with fundoplication may have impaired fundic accommodation, in part as a result of vagal injury [22]. Patients with diabetes mellitus and refractory gastroparesis may experience impaired gastric accommodation and visceral hypersensitivity [23], whereas others have increased compliance [24], thus leading to a longer lag phase in emptying of solids, with prolonged retention of a meal in the proximal stomach. Increased compliance in patients with diabetes mellitus and autonomic neuropathy compared to normal volunteers was reported to be associated with increased visceral sensation; these data suggest that hypersensitivity is related to increased symptoms, such as nausea, bloating and abdominal pain [25]. Conversely, patients with diabetes with no evidence of autonomic neuropathy may have increased fundic phasic contractions that explain the observed accelerated emptying of liquids observed in recently diagnosed diabetes mellitus [13].

The underlying pathophysiology in impaired accommodation is not well understood, but in theory abnormalities in the sensory apparatus, the vagovagal reflex pathway, the intrinsic inhibitory innervation or the smooth muscle in the proximal stomach may all be affected and result in reduced gastric accommodation [26].

Antrum

Abnormalities of antral motor function lead to delayed gastric emptying. Antral hypomotility has been associated with a prolonged lag phase and half-time of gastric emptying of solids and delayed emptying of liquids in patients [27]. In most patients, this is due to a reduced frequency of antral contractions in the postprandial period. Although some patients demonstrate irregular, low-amplitude antral contractions [28, 29], the more common situation is a reduced frequency of distal antral contractions. In secondary or idiopathic hypomotility of neuropathic origin, less than 1 antral contraction per minute during the first hour after a solid meal correlates with significant antral hypomotility [30]. Antral hypomotility is associated with postsurgical gastroparesis, diabetic gastroparesis, and idiopathic gastroparesis [28]; it has also been described in functional dyspepsia [31, 32]. These findings contrast with observations in patients with systemic sclerosis, in which the average amplitude of antral contractions was ~35 mmHg, significantly less than controls [33].

Pylorus

During the postprandial period, the pylorus typically opens during an antral peristaltic wave to ensure emptying of nutrients into the duodenal bulb in a coordinated fashion. However, dysfunction of the pylorus in the form of pylorospasm can cause delayed gastric emptying in diabetic gastroparesis likely secondary to a deficiency in inhibitory nitrergic neurons to relax the tonically contracted pylorus. In manometric studies,

diabetic patients had prolonged and intense pyloric contractions compared to controls [34]. Pylorospasm was diagnosed with peak amplitude of tonic activity of 13 mmHg and duration of 7 min.

Small Bowel Dysmotility

Small bowel dysfunction may also impair gastric emptying. A study of 14 patients with clinical and manometric confirmation of neuropathic chronic intestinal pseudoobstruction and normal antral motility demonstrated that gastric emptying of solids was significantly slower compared to healthy controls [35]. Similar findings have been described in paraneoplastic dysmotility, were histologic findings confirmed a disorganized ICC network in a patient with newly diagnosed small cell lung cancer [36]. The underlying mechanism of how small bowel dysmotility affects gastric motility is not well defined, but may be secondary to a diffuse process, such as a myopathy, neuropathy, or autoimmune-mediated disturbance of the ICCs rather than an isolated phenomenon.

Gastric Electrical Dysfunction

Gastric electrical dysfunction is another mechanism of gastric (antral) dysmotility. The normal pacemaker rate is approximately 3 per minute. Gastric dysrhythmias range from reduced (bradygastria, 1–2 per minute), increased (tachygastria, 4–9 per minute) frequency, or a mixed bradytachygastria. Gastric dysrhythmias have been described in diabetic gastroparesis, functional dyspepsia, anorexia nervosa, and vomiting of pregnancy [28]. Although the precise mechanisms on how these dysrhythmias cause symptoms is unclear, normalization of the gastric electrical rhythm has been described in patients with diabetic gastroparesis after long-term treatment with domperidone [37].

Conclusion

Stomach functions are regulated by a complex series of events that are controlled by extrinsic nerves, the enteric nervous system, excitatory and inhibitory neurotransmitters, and hormones. The stomach has distinct functional regions that result in the initial storage and subsequent trituration of food. Abnormalities of these regions are seen in specific disease states, such as diabetes mellitus, in which several factors lead to gastric dysfunction (including autonomic neuropathy and significant hyperglycemia), systemic sclerosis or amyloidosis. Thorough understanding of the pathophysiology in these disease states is important for selection of therapy.

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Chapter 5
Cellular Pathogenesis of Gastroparesis

Tamas Ordog

Keywords Interstitial cells of Cajal • Enteric nervous system • Smooth muscle • Slow wave • Nitric oxide • Gastric emptying • Gastroparesis • Receptor tyrosine kinase • Macrophage • Stem cell

Introduction

The gastric neuromuscular apparatus plays important roles in the digestive process by accommodating and retaining meals for initial digestion, mixing food with gastric secretions, reducing particle size, controlling the delivery of contents into the duodenum, and producing signals regulating meal termination. Gastric neuromuscular dysfunction is often associated with symptoms which, when chronic or frequently recurrent, cause considerable morbidity [1]. Gastroparesis, defined as slow emptying in the absence of mechanical obstruction, is one of the most significant manifestations of gastrointestinal dysmotility, particularly in females [2, 3]. It often accompanies diabetes and gastric surgery, but its cause remains obscure in about one-third of the cases [4]. While gastroparesis per se may not increase mortality, it can adversely affect the quality of life and lead to nutritional insufficiency, electrolyte imbalance, impaired glycemic control, and frequent hospitalizations [1]. Current treatment modalities, which focus on symptom control and stimulation of residual function, are not curative and frequently ineffective [2, 3, 5]. The purpose of this chapter is to review recent advances in defining the cellular pathogenesis and potential new therapeutic targets in this disorder. It is proposed that gastroparesis

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arises from an interplay between factors causing cellular stress or other functional challenges and tissue dystrophy causing reduced functional capacity and reflecting an imbalance between degeneration and regeneration of cells of the neuromuscular apparatus [6]. In order to be curative, future therapeutic approaches need to focus on restoring tissue integrity by the alleviation of cellular stress, trophic support of surviving cells, and, in cases where regeneration from endogenous sources is not possible, replacement of the missing cells from exogenous sources.

Pathophysiology of Gastroparesis

Gastric emptying is a highly complex function reflecting several aspects of gastric motor physiology, including fundic and antral tone and motility, slow-wave activity, pyloric function, and antropyloroduodenal coordination [7, 8]. Gastroparesis may manifest in delayed emptying of both digestible and indigestible solids and nutrient liquids and may be preceded by accelerated emptying [1, 9]. Emptying of liquids depends mainly on the fundic "pressure pump" mechanism controlled by pyloric opening. Loss of normal pyloric relaxation has been demonstrated both in patients and mouse models of gastroparesis [3, 10, 11]. In contrast, emptying of solids is more closely related to phasic antral motility [6]. Indeed, delayed solid emptying is caused primarily by antral hypomotility and dilation [2]. Reduced antral contractions may arise from abnormal smooth muscle function, inadequate or abnormal pacing by slow waves or impaired electromechanical coupling [6, 12]. The latter may develop from reduced (net) neural excitation [13], impaired smooth muscle responsiveness to neural and humoral input [14], or when slow-wave frequency is abnormally rapid and plateaus are too short to permit sufficient Ca^{2+} influx into smooth muscle cells [6, 12]. Since the orderly corpus-to-antrum propagation of peristaltic contractions depends on the organized spread of slow waves [13, 15], dysrhythmias developing along the propagation pathway disrupt the normal pattern of slow-wave propagation and peristalsis after meals causing delayed gastric emptying and also during phase III of the interdigestive migrating motor complex, which may lead to bezoar formation [7, 8]. These motor functions are orchestrated by a complex interplay between several cell types whose specific contributions are discussed below.

Cellular Mechanisms Underlying Gastric Motility

Gastric motor functions are controlled by cells both intrinsic and extrinsic to the stomach. The gastric neuromuscular apparatus consists of smooth muscle cells, enteric neurons and glia, interstitial cells of Cajal (ICC) and other mesenchymal cells. Extrinsic cells include vagal and sympathetic efferent and sensory neurons, as well as endocrine cells of the gut and the pancreas, which are responsible for caloric load-dependent feedback inhibition of gastric emptying. Under pathological

conditions, inflammatory and immune cells also influence gastric motor functions by regulating other cell types. In this chapter, we consider neural and mesenchymal cell types with particular emphasis on the generation of phasic motor activity critical for solid emptying.

Cross-bridge cycling underlying smooth muscle contraction is facilitated and inhibited by phosphorylation and dephosphorylation, respectively, of the 20-kDa myosin light chain (MLC20) [16]. Phosphorylation status of MLC20 is mainly determined by the relative activities of MLC kinase (MLCK) and phosphatase (MLCP). Under physiological conditions, smooth muscle contraction is initiated by calmodulin-dependent activation of MLCK by increased free cytoplasmic calcium ($[Ca^{2+}]_i$), which also inhibits MLCP indirectly. The increase in $[Ca^{2+}]_i$ largely depends on Ca^{2+} entry via voltage-sensitive Ca^{2+} channels (e.g., $Ca_v1.2$) although Ca^{2+} release from the sarcoplasmic reticulum via inositol 1,4,5-trisphosphate receptor-operated Ca^{2+} channels (IP_3R) also contributes. The latter are activated by G-protein-coupled membrane receptors, which also stimulate mechanisms leading to inhibition of MLCP and consequent increased cross-bridge cycling in a Ca^{2+}-independent manner. Smooth muscle membrane depolarization above the threshold for voltage-dependent Ca^{2+} entry can be brought about by myogenic, ICC-mediated, and neuronal mechanisms and the efficacy of excitation-contraction coupling can be further regulated by altering the responsiveness of the smooth muscle to input signals [16]. Stretch can depolarize smooth muscle cells via regulation of mechanosensitive ion channels, including $Ca_v1.2$, $Na_v1.5$, a tetrodotoxin-insensitive Na^+ channel; $K_{2P}2.1$, $K_{2P}10.1$, and $K_{Ca}1.1$ potassium channels and various nonselective cation channels (NSCC) [17]. Since gastrointestinal smooth muscle cells are interconnected into larger functional units by gap junctions, depolarization at one point will spread to neighboring cells and activate entire bundles.

A second layer of regulation is provided by ICC, an evolutionarily preserved, heterogeneous group of mesenchymal cells identifiable by ultrastructural features and the dependence on stem cell factor signaling via Kit, a receptor tyrosine kinase [18, 19]. ICC can be classified by their primary function as some are mainly involved in electrical rhythm generation (e.g., multipolar ICC in the myenteric region of phasic muscles) [20], whereas others (e.g., spindle-shaped, intramuscular ICC) mainly contribute to regulation of contractile activity by generating tone [21] and by mediating neuroeffector inputs [22] and afferent mechanical signals [17, 22, 23]. ICC regulate smooth muscle membrane potential via electrical coupling and the hyperpolarizing gaseous mediator carbon monoxide [24].

Electrical slow waves that drive phasic contractile activity mainly originate from pacemaker ICC in the myenteric region of the gastric corpus and antrum, although intramuscular and septal ICC also contribute [15, 20, 25]. In mutant rodents lacking pacemaker ICC in parts of the gastrointestinal tract, peristalsis and survival depend on the emergence of a secondary pacemaker activity resembling Ca^{2+} action potentials [13]. However, this activity cannot support propulsive motility at the same efficacy as slow waves [13, 26] and may not be able to fully compensate for ICC loss developing postnatally [27]. The mechanisms of slow-wave generation by ICC are not fully understood. According to the most comprehensive model [15, 20, 28],

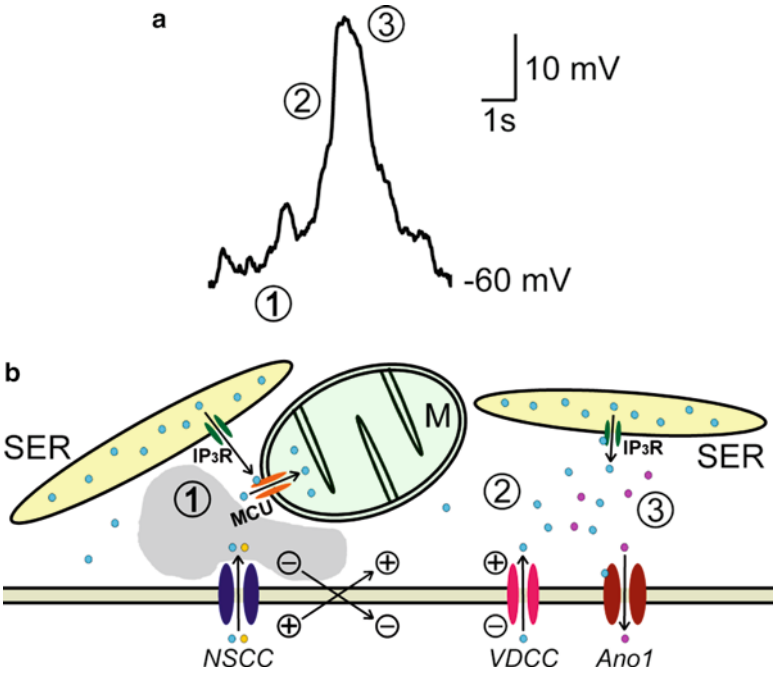

Fig. 5.1 Model for slow-wave generation by ICC. (**a**) Time course of an electrical slow wave recorded from a pacemaker ICC. ①: Unitary potentials; ②: upstroke; ③: slow-wave plateau. (**b**) Model of main events underlying slow-wave generation based on refs. [19, 27–30]. *SER* sarco-endoplasmic reticulum; *M* mitochondrion; *IP_3R* inositol 1,4,5-trisphosphate receptor-operated Ca^{2+} channel; *MCU* mitochondrial Ca^{2+} uniporter; *NSCC* nonselective cation channel; *VDCC* voltage-dependent, dihydropyridine-resistant Ca^{2+} channel; *Ano1* anoctamin 1 Ca^{2+}-activated Cl^- channel; *blue dots*: Ca^{2+}; *ocher dots*: Na^+; *purple dots*: Cl^-. *Arrows* indicate direction of ion fluxes. *Circled numbers* correspond to slow-wave phases in (**a**); *circled* + and − *signs* indicate membrane polarity. ①: Unitary potentials are initiated by the release of a small quantum of Ca^{2+} from the SER via IP_3R, which activates closely apposed MCU. Since mitochondrial [Ca^{2+}] is not in equilibrium with cytoplasmic [Ca^{2+}], this results in Ca^{2+} influx into the mitochondrion and a net decrease in [Ca^{2+}] within a perimitochondrial microdomain (*shaded area*). NSCC within this microdomain are activated by reduced [Ca^{2+}], which leads to membrane depolarization. ②: Membrane depolarization causes the opening of VDCC, which leads to the upstroke of the slow wave. ③: Ca^{2+} entering via the VDCC together with Ca^{2+}-induced Ca^{2+} release from the SER activates Cl^- efflux via Ano1, the main inward current underlying the slow wave. Mitochondrial, cytoplasmic and SER [Ca^{2+}] are restored by the mitochondrial Na^+/Ca^{2+} exchanger and the SER Ca^{2+} pump (not shown)

they involve spontaneous elementary events arising from Ca^{2+} cycling between the sarco-endoplasmic reticulum and mitochondria, voltage-sensitive, dihydropyridine-insensitive Ca^{2+} currents, and Ca^{2+}-activated, and inward-rectifying Cl^- conductances (Fig. 5.1). The elementary event underlying slow-wave activity is the so-called unitary potential; a small, random depolarization reflecting openings of NSCC regulated by periodic release of small quanta of Ca^{2+} from the smooth sarco-endoplasmic

reticulum via IP_3R. $[Ca^{2+}]_i$ indirectly governs the openings of the NSCC by stimulating the influx of Ca^{2+} into energized mitochondria [29] causing a net decrease in $[Ca^{2+}]_i$ in the immediate vicinity of NSCC. Since increased $[Ca^{2+}]_i$ inhibits these channels by a calmodulin-dependent mechanism, the periodic decreases in local $[Ca^{2+}]_i$ lead to corresponding increases in NSCC open probability. The generation of slow waves requires the synchronization of many such pacemaker units. This is achieved by the summation of unitary potentials and subsequent activation of voltage-sensitive, dihydropyridine-insensitive Ca^{2+} currents [20], which, directly or indirectly by facilitating Ca^{2+} release from intracellular stores, raise $[Ca^{2+}]_i$ to a level that activates an inward current via a Ca^{2+}-activated Cl^- conductance likely mediated by anoctamin 1 (Ano1 or Tmem16a or DOG-1) [30], a protein uniquely expressed by ICC within the gastrointestinal musculature [28, 31, 32]. Other conductances described in ICC may also contribute to these mechanisms [30].

Since activation of the voltage-sensitive, dihydropyridine-resistant Ca^{2+} currents by depolarization of electrically coupled, neighboring ICC can phase-advance slow waves, these channels are also responsible for slow-wave propagation by sequentially triggering the pacemaker mechanisms in networks of electrically coupled ICC [20]. In the stomach, slow waves originate in the orad corpus along the greater curvature [33] and spread both circumferentially, across the thickness of the musculature and aborally. Propagation in all three directions can be sufficiently explained by a decreasing gradient in the intrinsic frequencies of pacemaker ICC [13, 34, 35], which permits sequential entrainment of spontaneously active cells [34]. Experiments utilizing high-resolution mapping of electrical activity have indicated that slow-wave propagation in the circumferential direction may only occur as part of the initial, isotropic propagation away from the primary pacemaker area, and all subsequent propagation reflects the anal spread of the resultant circumferential band of activation [13, 33]. An alternative hypothesis proposed for the circumferential propagation of gastric slow waves is that it may occur along a low-resistance pathway provided by intramuscular ICC that are embedded within, and run parallel to, the circular smooth muscle cells [15]. This model can also explain why slow waves can be recorded close to the lesser curvature, where myenteric ICC networks are sparse or missing [34].

Slow waves regulate phasic contractile activity by periodically bringing the smooth muscle membrane potential close to the activation threshold for voltage-dependent Ca^{2+} entry which, if sufficiently large, results in a mechanically productive contraction [16, 20]. Electromechanical coupling, i.e., the force of slow-wave-driven contractions, depends on the magnitude and duration of suprathreshold depolarization and the presence or absence of slow-wave-associated, regenerative Ca^{2+} action potentials. Thus, despite the continuous presence of slow waves, mechanically significant contractions may not occur at the frequency dictated by the pacemaker input. Phasic contractions that have the characteristic frequency of the pacemaker ICC do occur postprandially or during an interdigestive migrating myoelectric complex [13, 19] in response to increased electromechanical coupling, which can arise from distension causing smooth muscle depolarization via the activation of mechanosensitive ion channels [17], net neuronal excitation, or smooth muscle sensitization by humoral factors.

The third level of regulation is provided by the enteric nervous system (ENS) and the systemic autonomic nervous system [36]. The latter exerts efferent control via the ENS by parasympathetic input from the vagal nuclei and the sacral spinal cord and by sympathetic postganglionic nerves from the prevertebral ganglia. There is also direct postganglionic sympathetic innervation of certain smooth muscle cells and blood vessels. Both the vagus and sympathetic nerves carry afferent axons as well. The ENS in humans contains ~10^8 neurons that include primary afferent neurons, excitatory and inhibitory motor neurons, ascending and descending interneurons, secretomotor, vasomotor, and intestinofugal neurons [36]. ENS neurons are organized into functional circuits that execute reflex responses, some of which involve even intestinofugal neurons and the prevertebral ganglia [37]. The ENS may also have "hard-wired" circuits similar to central pattern generators that may be responsible for repetitive behaviors [38]. Neural control is exerted by action potential-driven neurotransmitter release and, depending on the neurotransmitters, can be excitatory [e.g., acetylcholine, serotonin, substance P (SP)] or inhibitory [nitric oxide (NO), vasoactive intestinal polypeptide (VIP), ATP] [36].

Neural control of smooth muscle function is either direct or indirect via spindle-shaped intramuscular ICC [22] and Kit^-, platelet-derived growth factor receptor α (alpha)-expressing mesenchymal cells [fibroblast-like cells (FLC)] [39, 40]. In fact, NO-dependent control of gastrointestinal smooth muscle relaxation in the mouse is entirely indirect and likely mediated by both ICC and FLC [40]. ICC may transmit the effects of both excitatory and inhibitory neural inputs to the smooth muscle cells and also to pacemaker ICC by electrical coupling or paracrine mediators. For example, prostaglandins, which have been shown to mediate the arrhythmogenic effects of hyperglycemia [41], may elicit antral tachyarrhythmias by activating dominant pacemaker activity in intramuscular ICC via EP_3 receptors [42]. A role for intramuscular ICC in efferent neural control is supported by reduced postjunctional responses in tissues of rodents lacking these cells due to pharmacological Kit blockade or mutations in *Kit* or its ligand, the presence of synapse-like specializations in closely apposed nerves and ICC, expression in intramuscular ICC of genes/proteins related to neurotransmitter-mediated signal transduction, and receptor-mediated internalization of neurotransmitters [19, 22, 31, 39, 40]. Intramuscular ICC may also help maintain the proximal-to-distal slow-wave frequency gradient by contributing to the metabolism of acetylcholine [43] and thereby preventing excessive chronotropic stimulation in the antrum during vagal stimulation. Whereas ICC contribute to cholinergic and nitrergic responses, purinergic inhibition and non-cholinergic (peptidergic) excitation are rather preserved in their absence [22, 43]. In mice deficient in intramuscular ICC, partial preservation of nitrergic neuromuscular neurotransmission [19, 21] is likely due to the overlapping functions of FLC [39, 40]. The consequences of selective FLC loss remain to be investigated.

Intramuscular ICC also contribute to afferent neural signaling. Similarly to smooth muscle cells, ICC can sense mechanical stimuli, e.g., by expressing mechanosensitive ion channels (e.g., $Ca_v1.2$ and $Na_v1.5$) [17] and mediate the effects of distention to neuronal circuits [23]. Interestingly, maintenance of the latter function depends on a mutual trophic support between ICC and certain vagal nerve terminals [19, 23].

Intramuscular ICC can also transduce passive stretch into excitatory input to pacemaker ICC in the stomach without the involvement of enteric neuronal activity, possibly by releasing prostaglandins [22].

In summary, higher order motor functions such as gastric emptying are supported by an intricate and highly redundant control system with significant functional reserve [13]. In the next section, we review changes to the key regulatory cell types which could reduce the functional capacity of the motor apparatus and contribute to the development of gastroparesis.

Cellular Degeneration in Gastroparesis

Degenerative changes affecting extrinsic nerves, the ENS, smooth muscle cells, and ICC have been described both in patients and animal models of gastroparesis, particularly in diabetes (Fig. 5.2). Herein, we provide a brief summary of the key cellular changes and their functional consequences; for more detailed descriptions, the reader is referred to recent reviews [3, 6, 8, 12, 44].

Extrinsic Nerves

Vagotomy itself can result in delayed solid emptying [2] by eliciting slow-wave arrhythmias and uncoupling [45] and by blocking the gastric accommodation reflex [46]. However, the latter spontaneously recovers with time due to the emergence of an ENS reflex utilizing a pharmacologically indistinguishable nitrergic efferent mechanism [46]. Vagal neuropathy has been proposed as a major factor in other forms of gastroparesis as well. Early studies focused on myelinated axons of the thoracic vagus but most of those fibers do not innervate abdominal viscera. In a patient with intractable gastroparesis, Guy et al. described severe reduction in the density and diameter of unmyelinated axons [47] and similar findings were reported in spontaneously diabetic BioBreeding (BB) rats [48]. However, others failed to detect vagal involvement in larger series [6]. The degeneration described in the dorsal motor nucleus of the vagus of rats 3–7 days after streptozotocin (STZ) treatment [49] is difficult to ascribe to diabetes because of the rapid development of the changes and the well-known neurotoxic effects of STZ [50]. Thus, while degenerative changes in the vagus nerve may occur in nonsurgical gastroparesis, their true significance remains unclear. Diabetic autonomic neuropathy also affects sympathetic nerves. In patients and animal models, enlarged distal axons and nerve terminals were described in prevertebral ganglia [51] and decreased tyrosine hydroxylase immunolabeling was reported in a relatively small subset of patients with gastroparesis [52, 53]. While these are compelling results, their relevance to gastroparesis is uncertain [3].

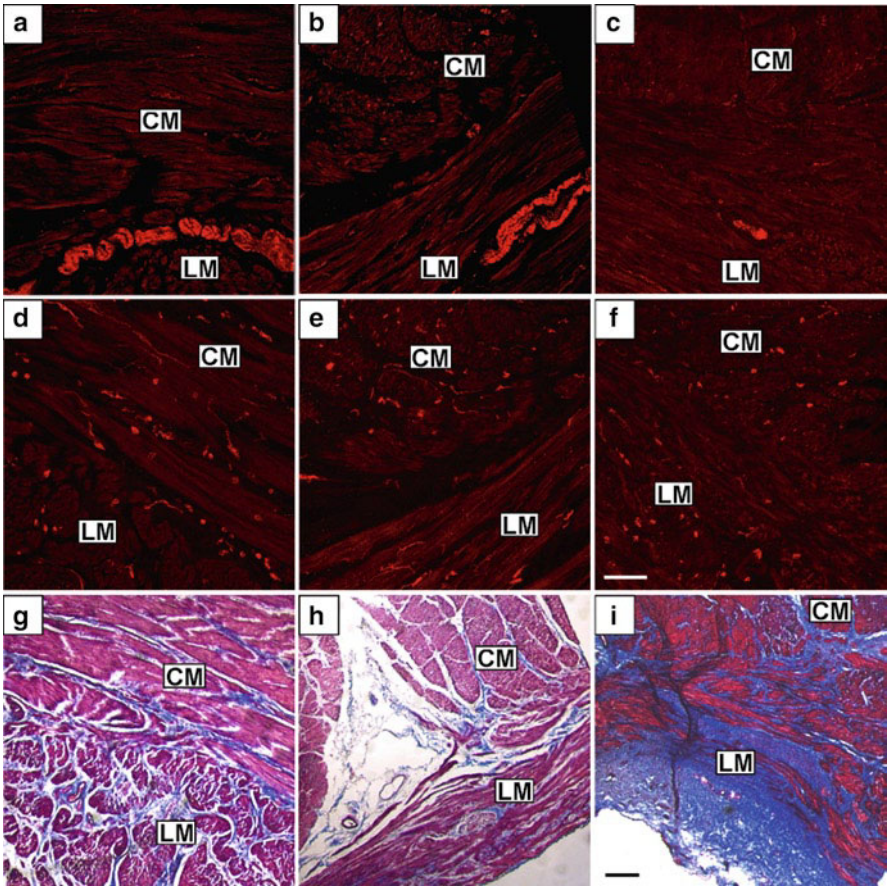

Fig. 5.2 Cellular dystrophy in the stomach of patients with diabetic gastroparesis and refractory symptoms. Full thickness specimens from the anterior wall of the mid-corpus above the incisura. Reprinted from [51] under terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0). *Left panels*, control tissues obtained from nondiabetic obese patients undergoing gastric bypass surgery. *Middle panels*: 37-year-old female patient with a history of well-controlled type 1 diabetes for about 3 years (case 1). *Right panels*: 32-year-old white female patient with a history of poorly controlled type 1 diabetes for about a decade (case 2). *CM* circular muscle; *LM* longitudinal muscle. (**a**–**c**) Immunoreactivity for neuronal nitric oxide synthase (nNOS). Normal immunoreactivity for nNOS in control (**a**) and case 1 (**b**). nNOS immunoreactivity was markedly decreased in case 2 (**c**). (**d**–**f**) Kit expression as a marker for interstitial cells of Cajal. Control (**d**) and case 1 (**e**) showed normal Kit immunoreactivity while in case 2 (**f**) there was a loss of Kit immunoreactivity suggesting a decreased number of ICC. Round cells lacking processes and present in all tissues are Kit^+ mast cells. *Scale bar* in (**f**), is 100 μm and applies to (**a**–**f**). (**g**–**i**) Masson's trichrome staining (connective tissue: *blue*; nuclei: *dark red/purple*; cytoplasm: *red/pink*). The control (**g**) and sections from case 1 (**h**) showed no increase in fibrosis, whereas sections from case 2 (**i**) showed an increase in fibrosis in both muscle layers and along the myenteric plexus. *Scale bar*, 200 μm

Enteric Nervous System

Degenerative changes in myenteric neurons and axons, as well as reduced nerve fibers or perikarya have been described in the stomachs of patients with severe diabetic [52, 54, 55] and idiopathic gastroparesis [55, 56]. However, others failed to detect similar changes in patients with long-standing diabetes [57, 58] and no general neuron degeneration was observed in several animal models, including BB/W rats, STZ-diabetic, and NOD mice [10, 59, 60]. In a recent study conducted in 60 patients (20 patients each with diabetic and idiopathic gastroparesis and 20 age- and sex-matched controls) by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Gastroparesis Clinical Research Consortium (GpCRC), a small but significant decline in intramural nerve fibers, abnormal ultrastructure of nerve endings, and degeneration of enteric glial cells were found [53]. A more consistent finding in gastroparesis, particularly in females [61], is a specific reduction in nitrergic signaling. Decreased NO production likely contributes to impaired accommodation and pyloric relaxation [10, 11, 59]. Reduced expression of neuronal NO synthase (nNOS) mRNA or protein, as well as lower numbers of nNOS-expressing neurons were observed in BB/W rats [59], STZ-diabetic rats and mice [10, 62, 63] and NOD mice [9, 10]. However, in STZ-diabetic rats others found no change in the number of $nNOS^+$ neurons [64] and nNOS expression was actually increased in male rats [61, 64]. Loss of nNOS-expressing nerve fibers or neurons were reported in the stomach of type 1 [52, 55] and type 2 diabetic patients [65] and also in patients with idiopathic gastroparesis [55]. In the NIDDK GpCRC study, reduced nNOS expression was found in 40 and 20% of patients with idiopathic and diabetic gastroparesis, respectively [53]. However, similarly to VIP and SP expression, nNOS immunolabeling did not change significantly [53]. While dropout of $nNOS^+$ neurons may dominate late in gastroparesis, reduced nitrergic signaling seen in early phases may reflect impaired axonal transport [11], nNOS dimerization [61], or function from reduced cofactor levels [66] rather than reduced expression.

Smooth Muscle

Degeneration of smooth muscle cells has been described in patients with therapy-resistant gastroparesis and severe weight loss arising from long-standing, complicated diabetes [52, 54, 58]. Histological findings included scattered, homogeneous, eosinophilic bodies (“M” bodies) and atrophy with intercellular collagen accumulation. Similar changes were also noted in a patient with severe idiopathic gastroparesis [56] but not in larger series of diabetic and/or gastroparetic patients [53, 55, 57]. In the absence of overt smooth muscle degeneration, impaired smooth muscle function associated with gastroparesis may be due to more subtle abnormalities seen both in patients and animal models, such as impaired cellular responses to muscarinic or

tachykininergic stimulation [14, 67], reduced expression of stem cell factor [60, 68], myosin heavy chain [60], and smoothelin [53], as well as markedly increased connective tissue stroma surrounding smooth muscle cells and separating them from ICC and enteric nerves [53, 69]. Thus, deterioration of intracellular pathways mediating neurotransmitter responses and a decrease in contractile protein expression may precede the more profound changes detected in advanced, therapy-resistant cases.

Interstitial Cells of Cajal

Since the first reports on the role of ICC in diabetic gastroenteropathies [69, 70], ICC loss has been found not only in type 1 and type 2 models [9, 60, 68, 71–74], but also in patients with idiopathic [56, 75], diabetic [52, 55, 65, 76, 77], and postsurgical gastroparesis [76, 77]. Recently, the NIDDK GpCRC [53] identified ICC loss, found in 50% of patients with either diabetic or idiopathic gastroparesis, as the most consistently occurring histological abnormality. In rodents, ICC depletion usually becomes noticeable several weeks after the onset of diabetes coinciding with the development of delayed emptying of solids, electrical dysrhythmias, and reduced postjunctional electrical responses [9, 60, 68, 69, 71, 73]. The ICC injury has been reported to be focal [69] or diffuse [68] and more severe in distal stomach [69, 73]. In NOD and *db*/*db* mice, all ICC classes were affected [60, 68, 69], whereas in STZ-diabetic rats, damage was restricted to intramuscular ICC and submucous border ICC of the antrum [73]. Besides reducing neuromuscular neurotransmission [69], loss of intramuscular ICC may also predispose the antral pacemaker ICC to tachygastria under tonic cholinergic excitation [43]. Major ultrastructural abnormalities in the remaining cells were only reported in STZ-diabetic rats [71, 73] and, more recently, in gastroparetic patients [53]. A loss of close association between ICC and enteric nerves was noted both in drug-induced and spontaneous diabetes [53, 69, 73]. Invasion of myenteric ICC into the fundus and appearance of ectopic electrical rhythmicity were also described in NOD mice [69] and may have contributed to reduced accommodation. In four larger studies involving 14–41 gastroparetic patients, major loss of ICC was detected in 21–50% of the subjects [53, 55, 76, 77]. Patients with severe ICC loss had less normal slow waves, more tachygastria both in fasting and fed state, and showed less improvement to electrical stimulation than patients with normal ICC [76, 77]. However, the loss of ICC did not correlate with the degree of gastric emptying or symptoms [77]. In another study involving 42 diabetic patients, Iwasaki et al. [65] detected a significant reduction in intramuscular ICC in 8 patients with severe diabetes. No ICC loss was found in the myenteric region or in patients with milder forms of the disease. Thus, ICC loss is commonly associated with gastroparesis of any etiology in both patients and animal models. The degree of cellular dystrophy seems to be related to the severity of diabetes [9, 52, 60, 65, 69]. Importantly, ICC loss also predicts resistance to conventional therapy or electrical stimulation [76, 77].

Cellular Mechanisms of Gastroparesis and the Road to Curative Therapy

The foregoing indicates that the complex pathophysiology underlying gastroparesis reflects not only impaired organ function, but also profound changes in the cellular composition of the *tunica muscularis*. This is in contrast with currently available therapies, which focus on symptom control and stimulation of residual function. Clearly, for better results, therapeutic efforts should focus on restoring tissue integrity. However, several questions need to be answered before curative therapies could be designed.

How Exactly Does Cell Loss Lead to Gastroparesis?

Studies in animal models and reduced systems have identified specific functions of key cell types of the gastric musculature. However, as discussed above, these individual functions add up to a highly complex and redundant control system, where the relationship between cell deficit and loss-of-function is not linear due to the existence of significant functional reserves. Thus, within the range of compensation, damage to any particular component is likely to result in dysfunction that is less than predicted; whereas beyond a certain limit, injuries may become catastrophic. It can be assumed that in a compensated but functionally limited stomach, new challenges, such as hyperglycemia, electrolyte imbalances, infections, stress, and other psychological factors [1, 8, 78, 79], can more easily precipitate dysfunction and symptoms [2, 58] (Fig. 5.3). This concept is supported by recent findings in progeric mice deficient in the anti-aging peptide Klotho [80] and in aging humans [81], which revealed progressive, diffuse, age-related loss of ICC throughout the gastrointestinal tract (~13% per decade of life) occurring in the absence of gastroparesis. However, detailed studies in the progeric mice demonstrated reduced functional reserves, including reduced inhibitory neurotransmission and slow waves. It is, therefore, likely that for gastroparesis to manifest, diffuse cellular dystrophy must be accompanied by factor(s) triggering decompensation. For example, gastroparesis may be precipitated by dominant ectopic pacemakers [82] developing in the depleted ICC networks in response to a focal damage [25], abnormal response to excitatory neurotransmitters [43], hyperglycemia [41], and increased prostaglandin secretion [42]. Models, such as Klotho-deficient mice, will allow direct testing of this hypothesis.

Is There a Common Mechanism of Cell Deficit in Gastroparesis?

A variety of mechanisms, including hyperglycemia, oxidative/nitrosative stress, reduced trophic factors, impaired differentiation from precursors, viral infections, autoimmunity, and inflammation, have been proposed to underlie cell loss in gastroparesis [2, 6]. Some of the best understood mechanisms, such as the loss of nitrergic

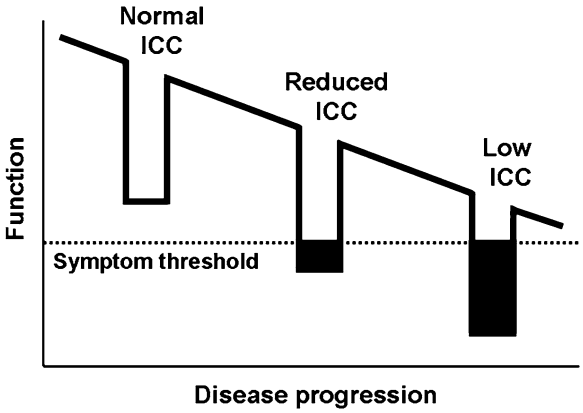

Fig. 5.3 Proposed interaction between cellular dystrophy and acute functional challenges in the generation of organ dysfunction and associated symptoms using ICC as an example. The *sloping line* on *top* depicts gradually declining cell numbers during the course of a disease. *Downward deflections* from this *line* indicate the effects of acute functional challenges (hyperglycemic episodes, infections, stress, etc.). *Closed areas* indicate symptomatic episodes. While diffuse cell loss itself may not lead to detectable dysfunction or symptoms, it enables acute challenges to precipitate clinical disorder

neurons from oxidative/nitrosative stress and consequent apoptosis [11] are, however, specific for diabetes and cannot explain gastroparesis developing in the absence of elevated blood glucose, e.g., in anorexia nervosa [83]. In various etiologies, cell depletion may be precipitated by entirely different factors or mediated by common downstream mechanisms. Recent reports suggest that inflammatory/immune mechanisms and/or reduced signaling from trophic factors may serve as "common denominators" of gastroparesis. Autoimmune processes are known to contribute to the pathogenesis of gastrointestinal neuromuscular disorders [84] and inflammatory mediators, such as interferon-γ may also cause depletion of various cells, e.g., ICC [85]. Accumulation of $CD45^+$ leukocytes (mainly macrophages) was noted in 40 and 45% of biopsies from patients with idiopathic and diabetic gastroparesis, respectively; [53] and a mild lymphocytic infiltrate of the myenteric region was detected in 43% of diabetic tissues in another cohort [55]. However, other clinical and experimental studies failed to detect similar changes and in some models, inflammatory infiltrates appear to be a confounding variable rather than a true pathogenetic factor [6]. Recently, Choi et al. [72] found that an increase in M2 macrophages expressing heme oxygenase-1 may protect ICC from oxidative stress in diabetes and loss of these cells could precipitate gastroparesis. Thus, gastroparesis may indeed involve immune-related mechanisms although recruitment of immune cells per se may not necessarily signal a pathogenetic event.

Since many cells depend on signaling from various receptor tyrosine kinases (RTKs) for survival, loss of RTK ligands may also mediate the effects of disparate

etiological factors. For example, smooth muscle cells, ICC precursors and even peripheral neurons utilize insulin and insulin-like growth factor I (IGF-I) as differentiation, survival, and growth factors [6], and they are reduced or ineffective in diabetes, caloric restriction, and other forms of stress [86]. Stem cell factor/Kit signaling critical for maintenance of ICC is also dependent on insulin/IGF-I [60] and the trophic effect of vagal innervation on ICC [23] may also be mediated by RTK ligands. RTK actions may be negatively influenced by hyperglycemia and oxidative stress via the upregulation of forkhead box O (FOXO) transcription factors [63], which can compete with other transcription factors for signaling intermediates [87]. Increased nuclear accumulation of FOXO3a has been shown to play a role in hyperglycemia-induced apoptosis of enteric neurons [63]. Thus, studying RTK signaling in different forms of gastroparesis may lead to the discovery of novel therapeutic targets.

Strategies to Restore Tissue Integrity and Function

Gastric functions involve both storage-promoting and propulsive functions and ICC, nitrergic nerves, and smooth muscle cells contribute to both. For example, loss of nitrergic inhibition (or loss of ICC that mediate this effect) in the fundus may cause accelerated gastric emptying, whereas similar changes in the pylorus may cause delayed emptying. It also follows that pharmacological treatments to increase NO levels or effects will influence both aspects of gastric motility and may not result in the desired outcome. Indeed, trials with nitroglycerin and sildenafil in patients with gastroparesis have been disappointing, likely due to the opposing effects of NO on gastric emptying via stimulating proximal gastric relaxation (which encourages storage) and pyloric relaxation (which increases emptying) [88]. A better therapeutic approach may be to improve or restore the integrity of the ENS and/or ICC. Depending on the stage of disease, this may be accomplished by different means: At an early stage, cellular injury likely manifests exclusively at the level of impaired gene expression and intracellular signaling and eliminating factors causing cellular stress should permit cellular repair and prevent further progression [9, 89]. Sustained insult eventually precipitates cell dystrophy and depletion, but opportunities for restoring tissue integrity from local stem/progenitor cells, such as those described in postnatal mice for enteric neurons [90] and ICC [85], or by axon regeneration [91] probably persist for extended periods of time. Supporting endogenous defense mechanisms and replacing missing trophic factors would still be expected to lead to recovery from this stage. Major cell loss and remodeling with an accumulation of extracellular matrix only occur after repeated insults. At this point, endogenous progenitor cells may also be affected and if so, tissue regeneration may require stem cell replacement [92–94] coupled with treatments supporting their survival in the diseased host tissues.

Summary

A joint effort of basic and clinical research groups over the last decade has resulted in a significant increase in our understanding of the cellular basis of gastroparesis. While many unsolved issues remain, particularly in the context of translating the new findings into novel therapies, the availability of relevant animal models and clinical research infrastructure, including opportunities for collaborations raise the hope for finding a cure for gastroparesis.

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Chapter 6
Sensory Dysfunction in Gastroparesis

Jan Tack and Pieter Janssen

Keywords Gastroparesis • Visceral hypersensitivity • Gastric barostat • Chemosensitivity

Introduction

Gastroparesis is a chronic, symptomatic, gastrointestinal disorder characterized by delayed gastric emptying of food solids, in the absence of mechanical obstruction of the stomach. Symptoms of gastroparesis are variable and include nausea, vomiting, abdominal pain, postprandial fullness, bloating, early satiety, and weight loss. Diabetes mellitus and prior surgery are considered the two major organic causes of gastroparesis, but in a large subset of patients no obvious underlying cause is found. This condition is referred to as idiopathic gastroparesis [1–3]. Traditionally, motor dysfunction, and especially delayed emptying of solids, was considered the principal underlying pathophysiological mechanism. Recent studies have indicated a role for visceral hypersensivity in symptom generation in gastroparesis.

Role of Delayed Gastric Emptying

Traditionally, delayed gastric emptying is considered the major pathophysiological mechanism underlying the symptoms in patients with gastroparesis. However, the correlation between symptom pattern and severity, and the rate of gastric emptying or severity of gastroparesis, has traditionally been poor.

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Table 6.1 Association between delayed gastric emptying and the symptom pattern in patients presenting with dyspeptic symptoms

Study (ref.)	*N*	Prevalence of delayed emptying (%)	Correlation
Wegener et al. [5]	43	30%	No correlation
Jian et al. [6]	28	59%	No correlation
Talley et al. [7]	32	30%	No correlation
Waldron et al. [8]	50	42%	No correlation
Klauser et al. [9]	69	35%	No correlation
Scott et al. [10]	75	28%	No correlation
Stanghellini et al. [11]	343	34%	Associated with female sex, postprandial fullness, vomiting
Maes et al. [12]	344	30%	Not studied
Perri et al. [13]	304	33%	Associated with postprandial fullness, nausea, and vomiting
Talley et al. [16]	551	24%	No correlation
Sarnelli et al. [17]	392	23%	Associated with postprandial fullness, nausea, and vomiting
Talley et al. [18]	864	34%	Associated with postprandial fullness

Table 6.2 Association between delayed gastric emptying and the symptom pattern in diabetic patients

Study (ref.)	*N*	Prevalence of delayed emptying (%)	Correlation
Ziegler et al. [20]	34	35%	No correlation
Jones et al. [21]	101	65%	Associated with female sex and abdominal bloating/fullness
Punkkinen et al. [22]	27	26%	No correlation
Faraj et al. [23]	31	68%	Associated with abdominal fullness

Several studies assessed the presence of delayed gastric emptying and the symptom pattern in patients presenting with functional dyspepsia symptoms [4–18]. Depending on the study, the prevalence of delayed gastric emptying in functional dyspepsia ranges between 20 and 50%. In the largest studies, the prevalence of delayed emptying of solids ranges around 30% [4–18]. Most studies failed to find a convincing relationship between delayed gastric emptying and symptom pattern (Table 6.1). More recently, three large scale single-center studies from Europe found associations between delayed gastric emptying for solids are more prevalent symptoms of postprandial fullness, nausea, or vomiting [11, 13, 17]. On the other hand, two large multicenter studies from the USA found no or only a very weak association [16, 18] (Table 6.1). Almost all studies focused on solid emptying rate only. Only few studies looked at delayed emptying for liquids, reporting a fairly high prevalence and association with symptoms of postprandial fullness [17, 19].

Similarly, in diabetes, the relationship between the presence of delayed emptying and epigastric symptom pattern or severity is inconsistent [20–23] (Table 6.2). Two studies reported an association of delayed emptying with the severity of abdominal bloating/fullness.

Role of Visceral Hypersensitivity

In a large subset of patients with functional gastrointestinal disorders, including functional dyspepsia, increased visceral sensitivity is present, allowing physiological stimuli to induce symptoms. Several studies have clearly established that, as a group, patients with functional dyspepsia have enhanced sensitivity to gastric distension, and this is considered an important mechanism underlying symptom generation [4, 24–29].

It has only been recently appreciated that epigastric pain is also an important symptom in patients with gastroparesis [30]. As none of the studies mentioned above have shown an association between delayed gastric emptying and symptoms of abdominal or epigastric pain, the underlying pathophysiology remains to be fully elucidated. In functional dyspepsia, hypersensitivity to gastric distention was associated with symptoms of epigastric pain, belching, and weight loss [29]. The possibility that visceral hypersensitivity is present in gastroparesis, and its potential contribution to symptom pattern and severity, is only being beginning to be investigated.

In a study of 58 patients with idiopathic gastroparesis, the relationship between the symptom pattern, gastric emptying rate and sensitivity to gastric distention was studied. Hypersensitivity to gastric distention was found in 29% of the patients (Fig. 6.1), and they reported a higher prevalence of epigastric pain, early satiety, and weight loss [31]. Symptom scores for epigastric pain and belching were significantly higher in the hypersensitive subgroup (Fig. 6.2). In the same study, visceral sensitivity was also a significant determinant of symptom severity [31].

Two studies in diabetes confirmed that diabetic patients, as a group, are more sensitive to gastric balloon distention compared healthy volunteers [32, 33]. More recently, Kumar et al. reported that 55% of 18 patients with diabetic gastroparesis were hypersensitive to gastric balloon distention, but no association with the symptom pattern was reported [34]. The contribution of impaired glycemic control in gastric hypersensitivity to balloon distention is unclear, as conflicting results have been reported on the importance of hyperglycemia in sensitization of the stomach to balloon distention [33, 35].

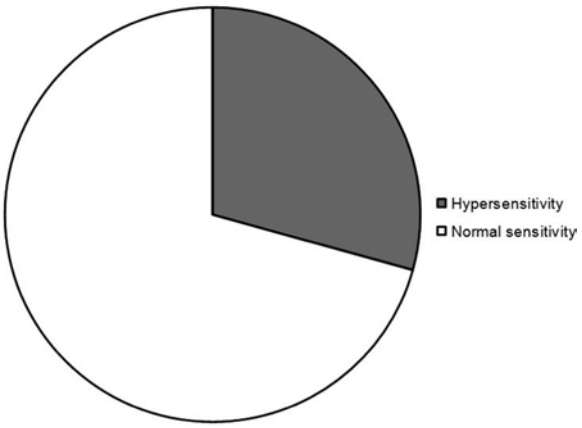

Fig. 6.1 Prevalence of visceral hypersensitivity in 58 consecutive patients diagnosed with idiopathic gastroparesis in Leuven

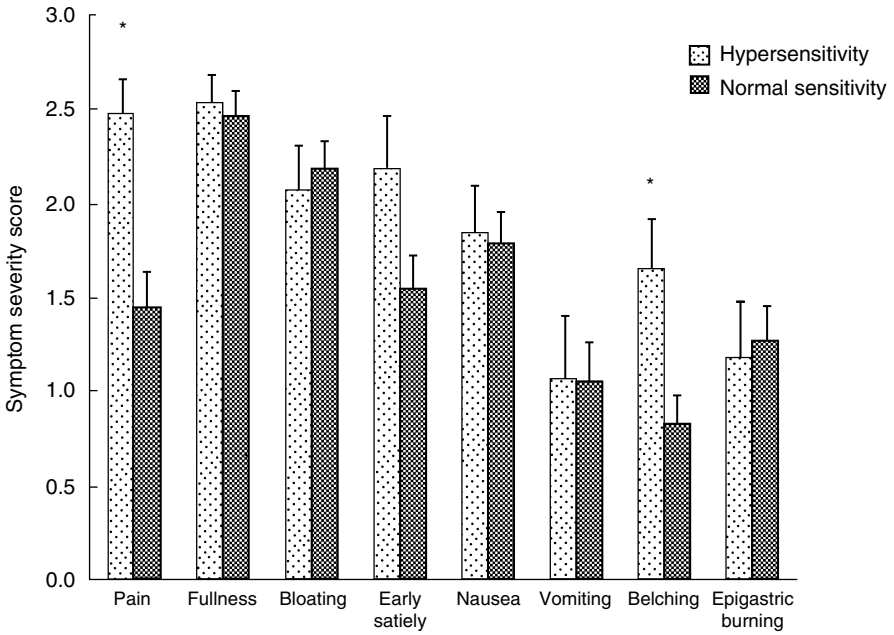

Fig. 6.2 Symptom severity scores for dyspeptic symptoms in 17 patients with idiopathic gastroparesis and visceral hypersensitivity compared to 41 patients with idiopathic gastroparesis and normal visceral sensitivity in Leuven. * $p<0.05$ compared to normosensitive patients

In functional dyspepsia, visceral hypersensitivity is not limited to mechanosensitivity of the proximal stomach, but there is also evidence of hypersensitivity to antral and duodenal distention, and increased duodenal chemosensitivity to acid, lipids, and capsaicin [11, 36–40]. Whether these are also present in (a subset of) gastroparesis patients remains to be studied.

Associated Features of Visceral Hypersensitivity

In functional dyspepsia, visceral hypersensitivity is associated with a number of psychosocial features, such as anxiety, a history of abuse and somatization [41–43]. Emerging evidence from brain imaging studies suggests that these psychopathological events may alter visceral pain processing at the level of the brain [44, 45]. Based on these associations in FD, psychosocial comorbidity could also contribute to increased symptom severity in gastroparesis, through changes in visceral sensitivity. Indeed, a number of studies have reported on comorbidities and their impact in gastroparesis patients.

In a single-center cohort of 146 patients with gastroparesis, high prevalences were reported of a history of physical or sexual abuse (62% of women with idiopathic gastroparesis), and physical abuse was significantly associated with abdominal pain, somatization, depression, and lifetime surgeries [46]. In 299 gastroparesis patients enrolled in the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium database, higher depression and anxiety scores were associated with more severe symptom gastroparesis symptom severity while the degree of delayed emptying was not a major determinant of severity [47]. While it still needs to be established that these are potential markers of visceral hypersensitivity in gastroparesis, the associated psychopathology and its impact on symptom severity clearly indicates that the pathophysiology of gastroparesis involves more than a delayed gastric emptying rate.

Therapeutic Implications: Summary

It is likely, but unproven, that visceral hypersensitivity is one of the reasons of the poor correlation between gastric emptying rate and symptom profile, and the lack of good correlation between enhancement of gastric emptying and symptom improvement in gastroparesis [48–51]. This would implicate that treatments directed at visceral sensitivity might be effective in gastroparesis, regardless of their effect on gastric emptying rate or gastric motility.

No optimal treatment approach for visceral hypersensitivity has currently been established. It has been suggested that antidepressants, such as tricyclic agents or selective serotonin reuptake inhibitors, may act through a decrease in visceral sensitivity [52]. However, the available evidence suggests that they may act centrally, not on visceral sensitivity itself, but on the affective component of pain sensation processing [53, 54]. No controlled trials are available of antidepressants in gastroparesis, but most treatment algorithms recommend their use in gastroparesis patients that fail to respond to prokinetic therapy, based on clinical impressions of effectiveness [55].

Levosulpiride is an antipsychotic drug with dopamine-2 receptor antagonistic properties. In functional dyspepsia, levosulpiride was shown to decrease sensitivity to gastric distention [56]. Placebo-controlled trials with levosulpiride are lacking. However, in a double-blind cross-over trial in a small group of patients with idiopathic gastroparesis and dyspeptic symptoms, levosulpiride was superior to cisapride in providing relief of symptoms and decreasing their impact on daily activities [57]. The effects of other drugs potentially affecting visceral sensitivity, such as gabapentin or pregabalin, have not been addressed in gastroparesis.

Altered visceral sensitivity has also been implicated in the therapeutic effect of gastric electrical stimulation in gastroparesis. Active gastric electrical stimulation therapy increased threshold for pain during gastric balloon distention, and was associated with changes in central nervous system blood flow on positron emission tomographic imaging suggest that increased vagal efferent function might be involved [58].

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Chapter 7
Pathology of Gastroparesis

Amol Sharma and Rebecca Thomas

Keywords Gastric emptying patterns • Gastric emptying scintigraphy • Gastric wall • Duodenum • Enteric glial cells

Introduction

While symptoms of gastroparesis are defined [1], the pathogenesis of this condition is poorly understood. Furthermore, gastric emptying scintigraphy, the gold standard for diagnostic testing, does not correlate with symptom severity. Some patients with the classic constellation of symptoms for gastroparesis have normal or near-normal gastric emptying patterns [2]. Uncertainty of underlying pathophysiology underscores the struggle to develop effective therapies. The inability of the stomach to effectively empty its solid and liquid contents into the duodenum in the absence of a mechanical obstruction defines gastroparesis [1]. Gastric emptying is dependent on well-coordinated efforts by multiple components in the gastric wall. Different cells, structures, and mechanisms are hypothesized to be responsible for gastroparesis. Currently, however there is a lack of histopathologic evidence to substantiate most of these hypotheses.

Anatomy

The gastric wall consists of the mucosa, submucosa, muscularis propria, and serosa. The mucosa includes the surface epithelium, gastric glands, lamina propria, and the muscularis mucosae. The surface epithelium consists of tall columnar cells with

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apical neutral mucin. The loosely packed gastric glands in the cardia and pylorus secrete neutral mucin while cardiac glands also produce sialomucin. The glands in the body and fundus are tightly packed and consist of zymogenic/chief cells in the basal portion and parietal cells in the isthmic portion of the glands. The stromal lamina propria separates the gastric glands from the surface epithelium. This layer contains many cell types, including fibroblasts, lymphocytes, plasma cells, macrophages, and mast cells. The muscularis mucosa is a thin layer of muscle forming the boundary of the mucosa. The submucosa lies between the muscularis mucosa and muscularis propria. It is composed of loose connective tissue with blood vessels, lymphatics and the autonomic nerve plexus of Meissner, which consists of ganglion cells and nerve fibers.

The gastric mucosa contains a variety of hormone-producing or neuroendocrine cells. Histamine-secreting enterochromaffin-like (ECL) cells are the predominant neuroendocrine cells found in the body and fundus. The distribution of neuroendocrine cells in the antrum is more diverse. Approximately half of these cells are gastrin-secreting G cells; 30% are ECL cells producing serotonin, and 15% are D cells secreting somatostatin.

The muscularis propria consists of three layers: inner circular, outer longitudinal, and an innermost layer of oblique muscle. The oblique muscle layer is most prominent at the cardia. The inner circular muscle is aggregated into the pyloric sphincter. The outermost layer is the serosa, which is a thin layer of mesothelium, with underlying loose connective tissue, forming the subserosa. The myenteric plexus of Auerbach lies between the inner circular and outer longitudinal layers of the muscularis propria. The Auerbach plexus is similar to the Meissner plexus except that the former has larger ganglia, a greater number of neurons and a more compact, defined network. Ganglia (Fig. 7.1) have ganglion cell bodies, which are large and polygonal with abundant pink cytoplasm, large vesicular nuclei and prominent nucleoli; they can be highlighted on immunostaining with neuron-specific enolase (NSE) (Fig. 7.2). Immunostaining with S-100 also outlines nerve processes connecting adjacent ganglia in the plexuses, as well as Schwann cells (Fig. 7.3) and glia/glia-like cells (Fig. 7.4).

The entire gastrointestinal tract, including the stomach, is richly innervated. Vagal and spinal afferents compose most of the innervation of the stomach. Vagal afferent neurons outnumber efferent neurons in a ratio of 10:1. These neurons terminate either in the lamina propria or the muscularis propria. In the lamina propria, vagal afferents monitor the luminal contents. In the muscularis propria, vagal afferents have two main types of endings: intramuscular arrays (IMA) and intraganglionic laminar endings (IGLE). IMA are distributed parallel to the smooth muscle, whereas the IGLE form basket-like structures around the intermyenteric ganglia [3]. IGLE are in contact with the connective tissue capsule and enteric glial cells that surround the intermyenteric ganglia.

Spinal afferent nerve terminals are located primarily in the serosa and the muscle layer but they also innervate the mucosa. Both vagal and spinal afferents in the muscle are mechanosensitive, but vagal afferents have a lower threshold for activation, and are thought to be involved in physiologic processes. Spinal afferents are often

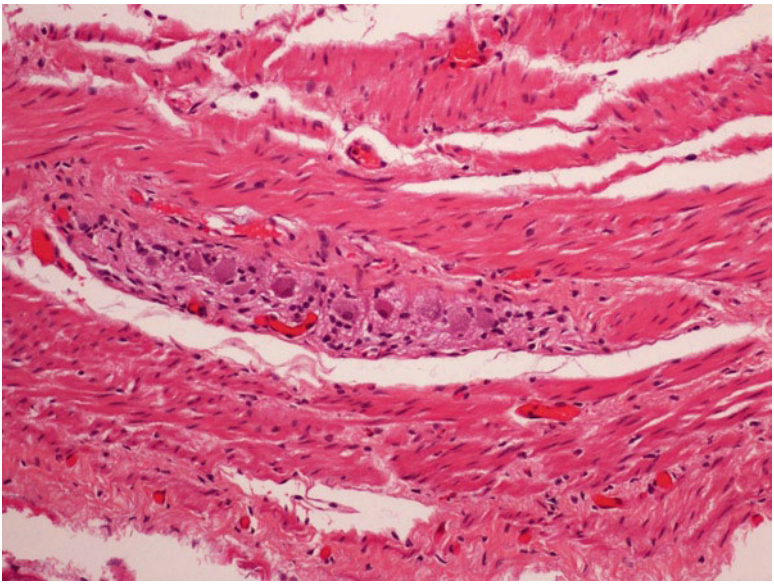

Fig. 7.1 Hematoxylin and Eosin stain; magnification X200: Intermyenteric plexus with ganglion containing ganglion cells and nerve processes

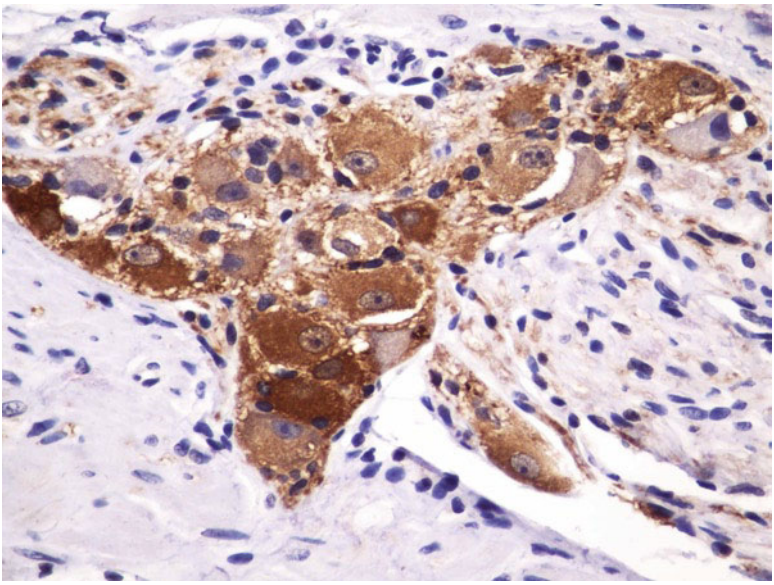

Fig. 7.2 Immunohistochemical stain for NSE; magnification X400: Positively staining ganglion cells

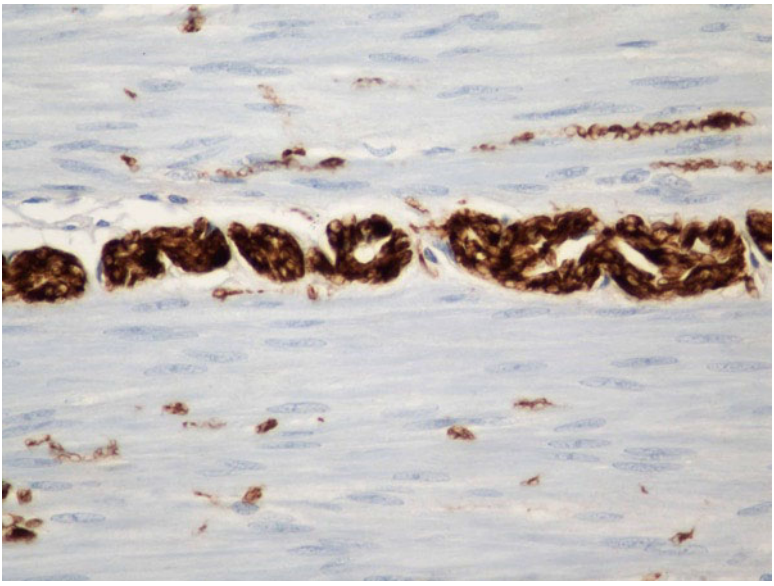

Fig. 7.3 Immunohistochemical stain for S100; magnification X200: Positively staining Schwann cells

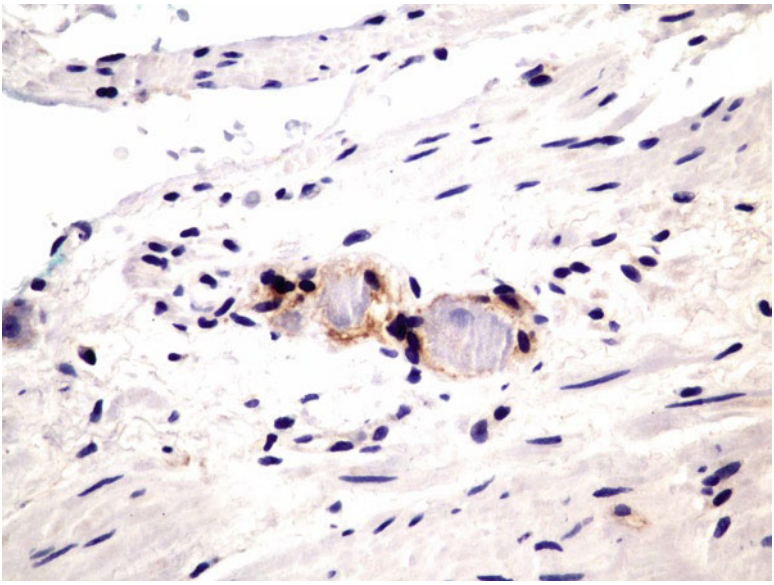

Fig. 7.4 Immunohistochemical staining for GFAP; magnification X400: Positively staining glial cells enwrapping ganglion cells

activated only at levels of distension or contraction that would be considered noxious. Sensory modulation may occur during inflammation, ischemia, injury, or infection such that previously insensitive afferents can develop mechanosensitivity during inflammation, a phenomenon known as plasticity. Different immunomodulators released by various cells, such as platelets, leukocytes, lymphocytes, macrophages, glial or mast cells are thought to influence this process.

Since afferent neurons do not extend into the lumen of the GI tract, their activation may result from substances absorbed from the lumen, or neurotransmitters released into the lamina propria by endocrine cells. 5HT acts as a paracrine agent by activating its own receptor on the afferent nerve terminal. Mechanical or chemical stimuli may trigger the release of 5HT.

In addition to smooth muscle cells, the muscularis propria also contains interstitial cells of Cajal (ICC). These cells are modified myofibroblasts of mesenchymal origin with fusiform cell bodies, a large round nucleus and one or more dendritic processes. There are two distinct layers of ICC: a network of cells lying in the intermyenteric plexus between the inner circular and outer longitudinal layers (ICCmy), and a second group interspersed between the smooth muscle fibers of the muscularis propria (ICCim). The majority of the ICC lies within the muscular coat, where they compose approximately 5% of the cell burden [4]. These cells are present throughout the gastrointestinal tract, where they show distributional variations in the different regions. In the gastric antrum for example, ICCim are generously distributed in the inner circular layer, but are rare in the outer longitudinal layer. In the fundus, ICC are absent in the intermyenteric plexus, but are present in both the inner circular and outer longitudinal layers of the muscularis propria.

ICCmy are most likely the pacemaker cells while ICCim mediate changes in pacemaking activity via enteric neurotransmission. ICCim also play a role in afferent neural signaling in the GI tract. Morphologic and molecular studies have identified ICC in close proximity to enteric neurons. ICC also express receptors that are required for motor neurotransmission. Furthermore, ICC are crucial to the normal development and maintenance of vagal IMA in the stomach. The synaptic-like contacts between nerve terminals and ICCim facilitate rapid diffusion of transmitters to the ICCim. In turn, ICCim transmit electrical impulses to smooth muscle cells via gap junctions [5]. ICCmy spontaneously generate electrical activity; however, only antral ICCim initiate electrical activity, and fundic ICCim do not. The absence of ICCmy in the fundus may be the reason why the fundus is not myogenically active.

ICC express c-kit, a proto-oncogene and tyrosine kinase receptor. Staining of this protein has permitted immunohistochemical identification of the morphology and distribution of these cells, as c-kit is a commercially available antibody (Fig. 7.5). Monoclonal antibodies against this receptor result in loss of ICC and paralytic ileus in mice, implicating the functional importance of c-kit to these cells [6]. Mast cells also stain positively for c-kit. Therefore, it is important to recognize the rounded morphology of mast cells, as opposed to the dendritic ICC, since mast cells may also be present in the muscularis propria (Fig. 7.6).

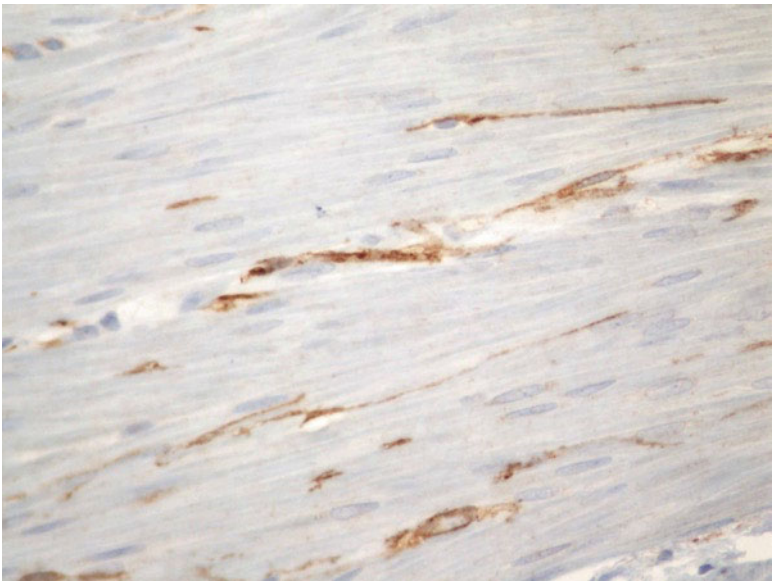

Fig. 7.5 Immunohistochemical staining for c-kit; magnification X400: Positively staining interstitial cells of Cajal with dendritic processes, within muscularis propria

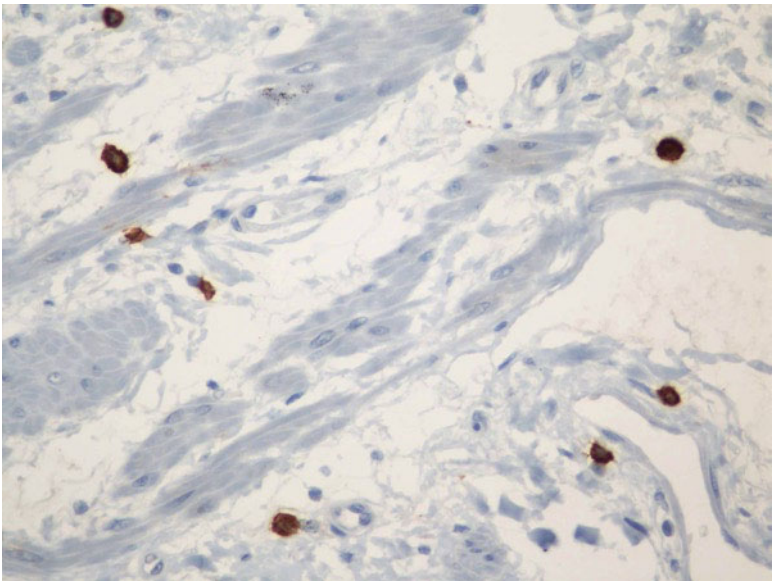

Fig. 7.6 Immunohistochemical staining for c-kit; magnification X400: Positively staining mast cells with rounded morphology, within muscularis propria

Pathophysiology

Nitric oxide (NO) is a free radical signaling molecule generated by nitric oxide synthase (NOS). There are three independent genes encoding neuronal, endothelial, and inducible NOS (nNOS, eNOS, and iNOS, respectively). These NO signaling pathways contribute to motility and vascular regulation in the GI tract, as well as the associated diseases. While the influence of NO on GI motility is generally controlled by nNOS, NO effects on vascular function usually occur through eNOS. The most important role of nNOS-derived NO in GI motility is as an inhibitory nonadrenergic noncholinergic (NANC) smooth muscle relaxant via activation of smooth muscle cell guanylate cyclase [7]. Nerves throughout the GI tract express nNOS with highest levels in the pyloric sphincter. Other transmitters, such as vasoactive peptide (VIP), adenosine triphosphate, and carbon monoxide, also function in conjunction with NO as NANC inhibitory signals. NO promotes gastric accommodation. Pharmacological inhibitors of NOS increase frequency of gastric contractions, hasten gastric emptying, and decrease gastric fundic volume. In contrast, NO donors [7] slow gastric emptying and improve accommodation of the proximal stomach. Hypertrophic pyloric stenosis is also associated with a decrease in nNOS expression within the hypertrophied circular muscle of the sphincter while normal distribution of NOS protein is present in the longitudinal muscle.

Normal gastric emptying requires the coordination of function of several cell types, including extrinsic neurons, enteric motor neurons, ICC, and smooth muscle cells. The pacemaker region of the stomach is located on the greater curvature of the body. In this region, ICC initiate a pacemaker signal, potentiating a slow-wave rhythm of approximately three cycles per minute and dictating the frequency of smooth muscle contraction. Motor neurons are modulated by signals from the CNS, primarily through the vagal nerve. Contractions are coordinated between different parts of the stomach, and between the stomach and small bowel. Sensory information is relayed to the CNS via the vagal and spinal afferent nerves.

Coordinated gastric function requires a combination of stimuli that promote contraction, such as acetylcholine and substance P, and stimuli that inhibit contraction, such as VIP and nitric oxide. Therefore, neuronal NO and the enzyme responsible for its synthesis, nNOS are of great interest in the study of gastroparesis.

Pathology

Two separate animal studies demonstrate an association between impaired gastric relaxation and a decrease in nNOS expression; one study in rats with streptozotocin-induced diabetes and the other study of the antrum of obese diabetic mice, a recognized model for type II diabetes [8, 9]. Factors responsible for the changes in gastric nNOS expression in diabetics are unclear but three mechanisms are hypothesized: neuronal loss or degeneration, inhibition of nNOS transcription, and impaired nNOS function [10]. Subsequently, decreased nNOS expression results in loss of

proximal relaxation and delayed gastric emptying as a combination of intense pylorospasm and disordered nonpropulsive antral motility. In nonobese diabetic (NOD) mice, insulin acting as a trophic factor reverses the decreased expression of NOS [11]. However, if these mice were deprived of insulin for greater than 12 weeks decreased expression of NOS becomes irreversible [12]. Animal studies have also demonstrated decreased numbers of ICC in diabetic models. In NOD mice, a model for type I diabetes, reduced numbers of ICCmy and ICCim were observed in the gastric antrum and corpus compared to controls [13, 14]. In streptozotocin-induced diabetic rats, depletion and degenerative changes were observed in the ICCim while the ICCmy were spared [15]. This reduction of ICC is associated with significant disruption of slow-wave activity and attenuated neuronal responses. In cell cultures, prolonged hyperglycemia results in loss of ICC networks [16], an effect that was prevented by insulin. Nitric oxide may be responsible for the maintenance of ICC and the loss of nNOS could result in depletion of ICC. In animal models with streptozocin-induced diabetes, a vagal neuropathy appears to be present. Both degenerative changes of the sensory [17] and motor [18] nuclei of the vagal nerve and sympathetic axonal dystrophy [19] have been noted in this model. In addition, another study shows that truncal vagotomy significantly decreases the expression of nNOS in rats, which is reversed by nicotinic receptor stimulation [10].

Pathologic assessment of gastric tissue in patients with gastroparesis is limited. Furthermore, human biopsy studies are susceptible to sampling errors due to an inhomogeneous distribution of ICC through the gastrointestinal tract [20]. A recent study that revealed several pathologic abnormalities in the gastric tissue has been shown in some patients with refractory gastroparesis [21]. There was a reduction in nerve cell bodies in both idiopathic and diabetic gastroparesis. A reduced number of ICCs were found in the myenteric plexus. An inflammatory infiltrate was present in nearly half of the patients with diabetic gastroparesis. Thus, histologic abnormalities in gastroparesis are heterogeneous and include myenteric inflammation, decreased innervation, and reduction of ICCs. One study reported that no ICC were found in the gastric antrum of nine of the twenty-three patients with refractory diabetic gastroparesis [22]. Examining the gastric antrum of diabetic patients after gastrectomy for gastric cancer, researchers observed a loss of ICCim, but not ICCmy, in those with severe uncontrolled diabetes [23].

Etiology

The pathogenesis of gastroparesis is poorly understood and probably multifactorial. Although diabetic gastroparesis is the most studied and characterized etiology of gastroparesis, idiopathic gastroparesis is the most common. Less common etiologies include postsurgical, medication-related, postviral, collagen vascular disease, and autoimmune.

Diabetes Mellitus

Our understanding of the pathophysiology of gastroparesis is best in diabetics. From a prospective study over 12 months of diabetics who attended a GI clinic and had gastric emptying studies performed, more than 20% of the patients had delayed gastric emptying. Women had slower gastric emptying, but there was no correlation between gastric emptying and age, type of diabetes, duration of diabetes, fasting glucose concentration, glycosylated hemoglobin level or the presence of other diabetic complications. The pathophysiologic factors thought to contribute to gastroparesis include electrical dysrhythmia (identified by electrogastrography), antral hypomotility and distension, pylorospasm, loss of nitrergic input to smooth muscle, and possible vagal and spinal neuropathies.

Diabetic patients are at high risk of developing gastroparesis. The prevalence of gastroparesis ranges from 25 to 55% in type 1 diabetes [24, 25] and occurs in 30% of type 2 diabetes. It would be hard to overestimate the contribution of diabetes to the pathology of gastroparesis. Increased fibrosis and collagen deposition in the muscularis propria (Fig. 7.7) and a decrease in the number of ICC (Fig. 7.8) seem to be a recurring theme in the literature. Histopathologic analysis of the stomach of four patients with partial gastrectomies for intractable diabetic gastroparesis was performed and revealed severe fibrosis of the muscular layer [26]. The changes in the smooth muscle of diabetics result in a stiffer stomach with lower compliance than in healthy subjects. In a case study, full thickness biopsy from a patient with brittle and poorly controlled diabetes demonstrated muscular fibrosis, and fewer nerves, myenteric neurons, inhibitory neural input, and ICC compared to control [27]. Studies show conflicting results in whether there are structural changes in humans in the vagal nerves, enteric neurons, ICC, and smooth muscle cells. There is probably a spectrum of pathological findings in these patients.

Idiopathic Gastroparesis

Idiopathic gastroparesis is the most common subtype and affects mainly young to middle-aged women. Inherent in its designation, no primary etiology for this subtype has been identified. Many studies suspect a viral etiology. Approximately 30–50% of the patients suffering from idiopathic gastroparesis identify a distinct viral prodrome preceding onset of symptoms of delayed gastric emptying [28]. Pathologic mechanisms include T-cell mediated or antibody-mediated damage to neuronal elements. In one case, a young man had an acute onset of chronic intractable vomiting and weight loss, requiring the placement of a feeding tube. Upon histological evaluation of the gastric wall, a significant infiltrate of CD4 and CD8 T lymphocytes was identified [29] associated with ganglion cells. Treatment of this patient with steroids resulted in a dramatic recovery. Case reports have also demonstrated a marked reduction in ICCmy and ICCim along with decreased numbers of myenteric ganglia in myenteric ganglia in severe idiopathic gastroparesis [30, 31].

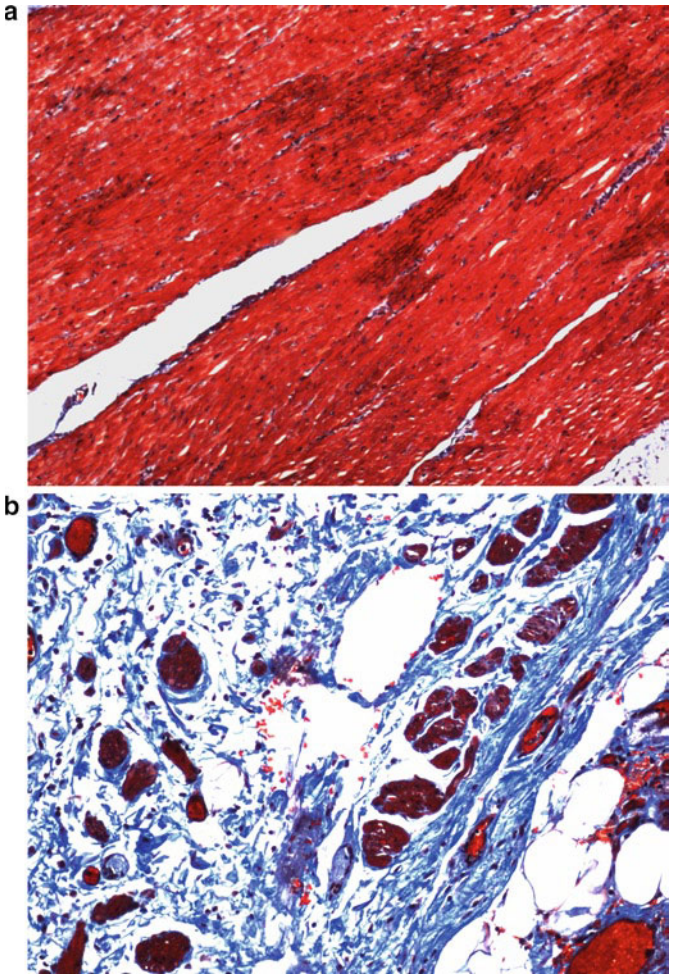

Fig. 7.7 (**a**) Masson Trichrome stain; magnification X200: Normal muscularis propria with no fibrosis. (**b**) Masson Trichrome stain; magnification X200: Muscularis propria with extensive fibrosis surrounding a few residual muscle bundles

Autoimmune

The link between autoimmunity and gastroparesis has been best established for paraneoplastic gastroparesis, most often associated with small cell carcinoma, lymphoma, or ovarian cancer [10]. These patients have an inflammatory infiltrate in the myenteric plexus, and a circulating antibody known as anti-Hu (ANNA-1). Anti-Hu and N-type calcium channel antibodies are the best recognized of numerous autoantibodies in the pathogenesis of gastric dysmotility. Other antibodies include

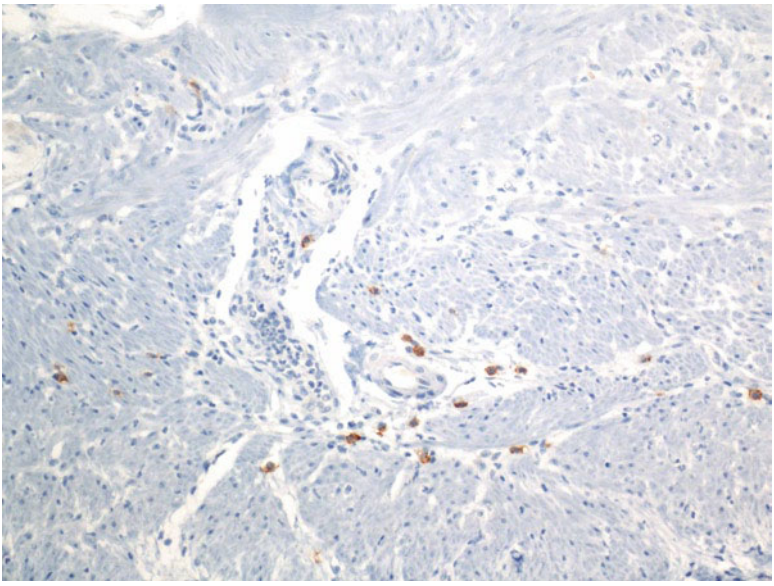

Fig. 7.8 Immunohistochemical staining for c-kit; magnification X200: Absence of interstitial cells of Cajal; mast cells present

ganglionic acetylcholine receptor autoantibody, P/Q-type calcium channel antibody, ganglionic- and muscle-type nicotinic acetylcholine receptor antibody, striational antibody, and rarely (in association with ovarian or breast cancer) Purkinje cell autoantibody type I or anti-Yo [32]. Histological examination of tissue sections often shows a marked inflammatory cell infiltrate of predominantly T lymphocytes (Fig. 7.9) of the myenteric plexus with much less submucosal plexus involvement. Myenteric plexus neurons are decreased in number, but nerve fibers within the muscularis propria appear normal. A case report demonstrates a decreased number and disordered network of ICC in a patient with small cell carcinoma of the lung [32]; the hypothesis being that the autoantibody recognized a cell-surface antigen common to the small cell carcinoma, as well as to the ICC; c-kit is the most likely candidate.

Infectious Causes

Various infectious causes have been implicated in the etiology of gastroparesis, especially in children; they include rotavirus, Norwalk, cytomegalovirus, Herpes simplex virus and vaccinations to hepatitis B and tetanus, as well as Lyme disease. A prior viral infection may well be unrecognized as most cases of viral gastroparesis are self-limiting. Therefore, few studies have isolated viral culprits during periods

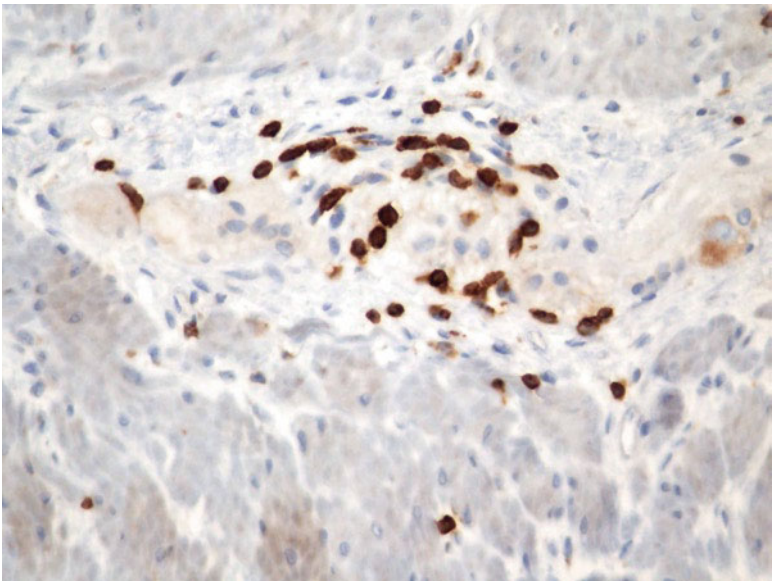

Fig. 7.9 Immunohistochemical staining for CD4; magnification X400; T lymphocytes around and within a ganglion

of active shedding. In one series of 11 children who developed gastroparesis after an acute viral infection, 8 tested positive for rotavirus [33]. In another series of cases of postinfectious inflammatory causes of gastroparesis, all five cases were young women; three were thought to have an association with vaccinations against anthrax, tetanus and hepatitis B while two developed Lyme disease [34]. The authors hypothesize that gastroparesis occurred as a result of inflammation to the enteric nervous system or the autonomic nervous system via immune activation.

Future Directions

Enteric glial cells are an emerging area of interest in gastrointestinal motility disorders. Currently, little is known of these cells. They were originally thought to simply provide a protective microenvironment for the enteric nervous system similar to astrocytes in the central nervous system; however, numerous observations implicate a role of enteric glia in neurotransmission. Additionally, two animal models have shown that ablation of enteric glia by different methods result in inflammatory insults to the mucosa [35, 36]. These studies suggest that enteric glia are integral to gastrointestinal mucosa, which might also imply their significance in mucosal inflammatory diseases, such as inflammatory bowel disease. The study of glial cells will be greatly enhanced by the identification of a sensitive and specific immunohistochemical marker.

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Chapter 8
Natural History of Patients with Gastroparesis

Reza A. Hejazi, Henry P. Parkman, and Richard W. McCallum

Keywords Delayed gastric emptying • Diabetic gastroparesis • Gastric motility disorder

Introduction

Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach [1]. The three most common etiologies of gastroparesis are diabetes, postsurgical, and idiopathic (i.e., of unknown cause). Symptoms associated with gastroparesis include nausea, vomiting, postprandial fullness, early satiety, bloating, and/or abdominal pain. Asymptomatic cases of delayed gastric emptying can be seen; particularly, in diabetic patients where difficult to control glucoses can be associated with the onset of delayed gastric emptying.

The true prevalence of gastroparesis is difficult to estimate due to the relatively poor correlation of symptoms with gastric emptying and the need to apply a diagnostic test to diagnose this condition in a community setting [2]. It is unclear if the majority of patients with gastroparesis seek health care or how often they are referred to gastroenterologists, and therefore the true prevalence of gastroparesis is not known. Community studies of the outcome of gastroparesis are few, and studies conducted in tertiary referral centers may not reflect findings encountered in the general population. Estimates for the prevalence of gastroparesis have been approximately 4% [3], based on the prevalence of functional dyspepsia in the community (20%) and the prevalence of delayed gastric emptying in patients with functional

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dyspepsia (20%). However, in a recent epidemiologic study of Olmsted County, Minnesota, the prevalence of gastroparesis was lower with the prevalence of definite gastroparesis (symptomatic individual with delayed gastric emptying) reported to be 9.6 per 100,000 for men and 37.8 per 100,000 for women [4].

Although gastroparesis was initially described 50 years ago [5], little is known about the natural history, clinical course and outcome of patients with gastroparesis. Natural history of patients with gastroparesis is mostly reported in symptomatic patients seeking health care and treatment. The majority of the published literature in natural history and outcome are in the diabetic gastroparesis population [6, 7]. There are few data in patients with idiopathic and postsurgical gastroparesis. Mild gastroparesis is believed to have a low mortality rate, whereas patients with severe gastroparesis may develop complications from their gastric motility disorder and/or their underlying disorder [4, 8]. Most patients are treated for symptomatic gastroparesis, which might improve symptoms and alter natural history. In patients with gastroparesis referred to tertiary centers with over 6 years follow-up, the majority (74%) required long-term prokinetic therapy, 22% needed long-term parenteral or enteral feeding, and 7% had died, suggesting gastroparesis is not a benign condition [8]. Postsurgical gastroparesis and idiopathic gastroparesis associated with prominent abdominal pain are often more refractory to pharmacologic therapy.

Clinical Course of Gastroparesis

Information on the clinical course of gastroparesis is being obtained in the NIDDK Gastroparesis Clinical Research Consortium which has a registry of patients with gastroparesis that have been followed for several years while receiving clinical care [9]. Recently, 156 patients with gastroparesis with follow-up data after 48 weeks were reported [9]. The most commonly used medications were antiemetics and prokinetics followed by opiates, antidepressants, and neuropathic pain modulators. The clinical severity of gastroparesis symptoms improved at follow-up, with a median reduction in the gastroparesis cardinal symptom index (GCSI) scores from 3.1 to 2.8. Improvements were seen in symptoms of nausea and vomiting with less improvements for early satiety, postprandial fullness, bloating, and abdominal pain. After 48 weeks, quality of life (PAGI-QOL) showed improvement in total scores (2.9 vs. 2.5) with improvements in daily activity subscore (2.5 vs. 2.0), diet subscore (1.9 vs. 1.3), and psychological subscore (3.4 vs. 2.3). Hospitalizations for gastroparesis did not change (47 vs. 40% of patients). During the follow-up period, TPN was instituted in 6.5% of patients, J-tube feeding in 5%, and gastric electrical stimulation (GES) in 30.5%. This study shows that over 1 year, the burden of gastroparesis in patients remains high, despite mild improvements in several parameters. The pattern of improvement is heterogeneous with improvements in nausea and vomiting, but not in bloating and abdominal pain. These results emphasize the chronic nature of gastroparesis and the need for novel therapeutic approaches.

Most treatment studies for gastroparesis have been of only 1–2 months duration. A 12-month trial of the prokinetic agent, cisapride (10 mg three times daily), was assessed in 21 patients with gastroparesis and 12 patients with chronic intestinal pseudoobstruction [10]. For the whole group of 21 patients, gastric emptying of both solids and liquids improved significantly after 1 year of cisapride. Among chronic intestinal pseudoobstruction patients, there was predominantly an improvement in gastric emptying of solids; in contrast, patients with gastroparesis had a greater improvement in liquid emptying. Total symptom score improved significantly in the gastroparesis group (median score: 8 at baseline vs. 6 at 1 year) but not in the chronic intestinal pseudoobstruction patients (median score at baseline 10 vs. 9 at 1 year). In this 12-month open trial, the prokinetic agent, cisapride, was effective in improving gastric emptying in patients with gastric stasis and consistently improved symptoms in those with gastroparesis. Long-term treatment studies with other prokinetic agents, when available, are needed.

Long-term treatment studies with gastric electric stimulation are being reported. Abell et al. reported long-term data using GES for drug-refractory gastroparesis [11, 12]. Two hundred and fourteen consecutive drug-refractory patients with the symptoms of gastroparesis were assessed: 156 patients implanted with a GES device and another 58 patients not implanted primarily for insurance purposes serving as controls. At latest follow-up, median 4 years, most patients implanted (135 of 156) were alive with intact devices, significantly reduced gastrointestinal symptoms, and improved health-related quality of life, with evidence of improved gastric emptying. Most patients explanted, usually for pocket infections, were later reimplanted successfully. There were no deaths directly related to the device. McCallum et al. also reported long-term outcomes in 55 gastroparetic patients receiving GES therapy beyond 3 years [13]. Of the 55 patients, ten died of nonpacemaker-related complications, six had the devices removed and two could not be reached. The remaining 37 patients had the device activated for a mean of 45 months. Total symptom score, hospitalization days and the use of medications were all significantly reduced at 1 year and were sustained beyond 3 years. The total symptom score decreased by 62.5% for the 37 patients completing 3 years of GES. At implantation, 15 of 37 patients required nutritional support but only five continued beyond 3 years. Mean HbA1c level in diabetics was significantly reduced from 9.5 to 7.9% at 3 years. These open label studies show improvement in symptoms and other measures of clinical outcome can be maintained for long term with GES in patients with refractory gastroparesis.

Hospitalizations for Gastroparesis

The course of patients with gastroparesis is variable. One grading scheme for the clinical severity of gastroparesis uses a scale originally proposed by Tack et al. and reported in the American Neurogastroenterology and Motility Society (ANMS) review on the treatment of gastroparesis [3]: grade 1 or mild gastroparesis (symptoms relatively easily controlled and able to maintain weight and nutrition on

a regular diet); grade 2 or compensated gastroparesis (moderate symptoms with only partial control with the use of daily medications, able to maintain nutrition with dietary adjustments); and grade 3 or gastroparesis with gastric failure (refractory symptoms that are not controlled as shown by the patient having ER visits, frequent doctor visits or hospitalizations and/or inability to maintain nutrition via an oral route). Thus, some patients with relatively mild symptoms can be maintained on dietary treatment (small meals, low fat, low fiber diet) and oral prokinetic and antiemetic medications, whereas other patients may need more invasive treatments with jejunostomy feeding tubes and/or the use of gastric electric stimulation.

Patients may have periodic hospitalizations for exacerbations of symptoms. The number of gastroparesis-related hospitalizations has been increasing in the USA, and the economic impact of gastroparesis-related hospitalizations is significant and may be increasing [4]. The trends, characteristics, and outcomes of gastroparesis-related hospitalizations during 1995–2004 were studied using the publicly available Healthcare Cost and Utilization Project Nationwide Inpatient Sample which comprises a nationally representative sample of 5–8 million hospitalizations per year [14]. Gastroparesis-related hospitalizations were identified using the International Classification of Diseases (ICD-9) code 536.3. Hospitalizations with gastroparesis as the primary diagnosis increased from 3,977 in 1995 to 10,252 in 2004 (+158%) and hospitalizations with gastroparesis as the secondary diagnosis increased from 56,726 to 134,146 (+136%). These compared to smaller increases in diabetes-related hospitalizations (+53%), and all hospitalizations (+130%). The increased number of gastroparesis-related hospitalizations in the USA may be related to several factors, including the increasing prevalence of diabetes, the withdrawal of pharmacologic agents (cisapride and tegaserod), the lack of currently effective pharmacologic treatment, the need for hospitalization for implantation of gastric stimulators, and possibly an increase in the prevalence and severity of gastroparesis.

To investigate precipitating factors leading to hospitalization for exacerbation of symptoms in patients with gastroparesis, a retrospective review of 103 admissions (63 patients) for gastroparesis exacerbation at one center was reported [15]. Poor glycemic control was present in 36%, infection in 19% (12 urinary tract infections and two bacteremia), and noncompliance with and intolerance of, medications in 6 and 5% of patients, respectively. In the epidemiologic study reported from Olmstead County, Minnesota, 24.8% of patients with gastroparesis required therapeutic interventions with 22% of patients needing hospitalizations for tube feeding or total parenteral nutrition [4]. Thus, poor glycemic control, infection, noncompliance with/intolerance of medications, and need for invasive treatment options were contributory factors leading to hospitalizations of gastroparetic patients.

Mortality of Gastroparesis

The causes of death in patients with gastroparesis are not well described. Mortality in patients with gastroparesis can be from gastroparesis-related complications, complications from the treatment for gastroparesis, the underlying disease causing

gastroparesis, or death from disorders that also affect the general population. Contrary to current thinking, some studies suggest that diabetic gastroparesis is not associated with a poor prognosis with similar mortality compared to diabetic patients without gastroparesis [7]. However, others suggest that there is a high mortality in patients with gastroparesis, particularly diabetic gastroparesis with severe symptoms [11]. Abell et al. have shown a higher mortality rate in severely symptomatic gastroparetic patients referred for consideration of gastric electric stimulation who do not undergo gastric electric stimulation compared to those that did [11]. Three of nine patients in the medical treatment group died primarily from intravenous access-related problems; none of the stimulator patients died.

The population data from Olmsted County in Minnesota reveals that the overall survival of patients with gastroparesis over 5 years is significantly lower than the age and sex-specific expected survival [4]. The estimated 5-year survival in patients with gastroparesis was 67% compared to an expected survival of 81%. Older age at diagnosis and male gender were associated with decreased survival. Idiopathic gastroparesis was associated with better survival than nonidiopathic gastroparesis. Causes of death were cardiovascular disease in 25%, respiratory failure in 23%, malignancy in 16%, chronic renal failure in 16%, cerebral vascular accident in 10%, and other causes in 10%. This study that suggests gastroparesis is associated with a poor outcome.

Aspects on the Natural History of Different Etiologies of Gastroparesis

Diabetic Gastroparesis

Typically, gastroparesis develops after diabetes has been present for >5 years and patients have evidence for other complications of diabetes, such as retinopathy, nephropathy, peripheral neuropathy, and often, autonomic dysfunction. The prognosis in diabetic gastroparesis has been assumed to be poor, but follow-up over at least a decade indicates that this is not necessarily the case [7, 16]. In a longitudinal study of gastric emptying and upper gastrointestinal symptoms in patients with diabetes mellitus, Jones et al. did not observe any marked changes in either gastric emptying or upper gastrointestinal symptoms during a 12-year period [6]. In this study of diabetic patients, delayed gastric emptying was not related to the mortality after adjustment of comorbidities [6]. The association between diabetic gastroparesis and mortality has also been assessed in other studies. In a cohort of 86 outpatients with diabetes followed by Kong et al., it was determined that gastroparesis was not associated with a poor prognosis [7]. Diabetes predisposes to many medical complications that influence morbidity as well as mortality. The increased mortality in patients with diabetic gastroparesis is usually related to other organ dysfunction. The median time of death after the diagnosis of gastroparesis in a patient with

diabetes was 6 years (range: 1–12) with major causes of death were cardiovascular or renal disease. In those patients who had died, the duration of diabetes and scores for autonomic neuropathy, retinopathy, and esophageal transit were greater than in the patients who were alive. The study showed that gastroparesis was not directly a determinant of mortality over a follow-up period of about 12 years, but brought up the possibility that gastroparesis was associated with a greater risk of complications and therefore indirectly with mortality.

Hyperglycemia and autonomic neuropathy are two factors that have been implicated in the pathogenesis of diabetic gastroparesis [17, 18]. The association between overall glycemic control and diabetic microvascular and macrovascular complications is well documented in both type 1 [19, 20] and type 2 diabetes [21]. Poor glycemic control is associated with increased prevalence of upper GI symptoms. In a cross-sectional questionnaire study of 8,657 subjects, Bytzer et al. found that gastrointestinal symptoms are independently associated with both diabetic complications (particularly peripheral neuropathy) and glycemic control in the general diabetic population [22]. Interestingly, psychological distress is also linked to GI symptoms in diabetes mellitus, particularly nausea and early satiety [23].

Hyett et al. report on the increased morbidity of patients with diabetic gastroparesis [24]. Diabetic patients (type 1 and type 2) with classic symptoms of gastroparesis and delayed gastric emptying had more hospitalizations, emergency room visits, and office compared to symptomatic diabetic patients with normal gastric emptying and diabetic patients without symptoms of gastroparesis. In addition, diabetic patients with symptomatic gastroparesis had more cardiovascular disease, hypertension, and retinopathy. This study suggests that delayed gastric emptying correlates with negative outcomes in diabetic patients who have symptoms of gastroparesis with delayed gastric emptying being an independent maker for morbidity. A nonsignificant increase in mortality was seen in the symptomatic diabetic gastroparesis group.

Idiopathic Gastroparesis

Much less is known about the epidemiology and natural history of idiopathic gastroparesis compared to diabetic gastroparesis. In a tertiary referral series of patients with idiopathic gastroparesis [8], several subgroups were identified: 23% had a presentation consistent with a viral etiology and a small subset (8%) had the onset of symptoms after cholecystectomy (8%). From a symptom standpoint, 48% had prominent abdominal pain; other subgroups included patients with predominant symptoms of gastroesophageal reflux disease or functional dyspepsia.

McCallum et al. report on viral induced gastroparesis as a subgroup of idiopathic gastroparesis [25]. Twelve of 52 (23%) patients with idiopathic gastroparesis were identified as consistent with a postviral etiology. The “postviral gastroparesis” patients reported gradual improvement of their symptoms, no hospitalizations during the previous 6 months, stable weight, were not disabled, and remained professionally active. In comparison, 21 nonpostviral “idiopathic” patients had an

indolent, slowly progressive clinical presentation. These authors suggest that a viral etiology should be considered in gastroparesis patients when their illness is characterized by an acute onset, initial severe illness and slow resolution toward a satisfactory quality of life. Idiopathic gastroparesis is a more slowly progressive illness, and patients remain significantly more symptomatic for a longer period of time. Infectious prodromes at the onset of gastroparetic symptoms were also reported by 17% of gastroparesis patients followed in the NIH gastroparesis registry [26]. The most common type of infectious prodrome was gastroenteritis or food poisoning. Postinfectious gastroparesis patients were younger and showed lesser gastric retention. There were greater decreases in postprandial fullness over 48 weeks in the postinfectious gastroparesis group compared to the nonpostinfectious group. Evolution of other symptoms and measures of severity were not different in relation to infectious prodromes. Longer follow-up may uncover other attributes specific for postinfectious gastroparesis.

A recent study of 165 patients with gastroparesis sought to determine if mild, moderate, and severe degrees of gastroparesis based on the scintigraphic gastric emptying test can predict treatment responses for gastroparesis [27]. In this study, gastric emptying in patients whose gastroparetic symptoms were refractory to standard medical therapy and required gastric electric stimulation was significantly slower than in gastroparetic patients whose symptoms responded to medical therapy. Stratifying gastric emptying into mild, moderate, and severe degrees of gastric retention helped correlate the need for gastric electric stimulation to control the symptoms in patients with idiopathic gastroparesis, but not in patients with diabetic gastroparesis [27].

Postsurgical Gastroparesis

Postsurgical gastroparesis is identified as a chronic form of gastric atony in the absence of mechanical obstruction. Historically, operations for ulcer disease, such as vagotomy with or without hemigastrectomy may be followed by delayed gastric emptying. Postsurgical gastroparesis develops in up to 10% of patients who undergo vagotomy (either deliberate or inadvertent) as part of their upper gastrointestinal surgery. The incidence increases to as high as 50% in those with chronic gastric outlet obstruction before vagotomy surgeries. Over the last decade, surgery for ulcer disease has decreased. Currently, the most common surgical procedure resulting in gastroparesis appears to be Nissen fundoplication.

Data on natural history of postsurgical gastroparesis is limited. Many symptoms following abdominal surgery may decrease with time. The resolution of symptoms may also be accompanied by the improvement in gastric emptying, suggesting that either the enteric nervous system may be able to adapt to loss of vagal input or that vagal reinnervation or regeneration of nerve fiber may occur, as shown for afferent (but not efferent) fibers in experimental models.

Symptomatic management of postsurgical gastroparesis includes dietary manipulation and the combination of prokinetic and antiemetic agents. Without an

antrum, medical therapies are less successful, and medications might not be reliably absorbed because of bezoar formation. In severe cases, patients might be placed on a liquid caloric diet. Medical therapy is tried with avoidance of repeat surgery. However, after a year or more has passed since the putative injury, the likelihood of spontaneous improvement begins to decline. Management of patients with postsurgical gastroparesis can be particularly challenging at this point. Their illness has generally been longstanding, and their symptoms have remained despite a variety of medical and surgical interventions (with each new procedure often directed at "revising" the one preceding it). Chronic abdominal pain and associated psychosocial behavioral patterns are common in such patients, as is narcotic dependency. A multidisciplinary approach is important for patient care, with careful counseling and input from psychologists, nutritionists, pain specialists, and surgeons specializing in the care of such patients. For patients who fail these therapies, surgical interventions are often contemplated. These include tube gastrostomy for gastric decompression and jejunostomy for enteral feedings and gastric electric stimulation therapy. Total gastrectomy is preferred to Enterra therapy when there is less than 50% of stomach remaining after a Billroth I or II with or without a Roux-en-Y reconstruction [28].

Conclusions

The course of gastroparesis for an individual patient is difficult to determine. Gastroparesis is often a chronic disorder. Some patients slowly improve, particularly idiopathic gastroparesis with an abrupt onset of symptoms suggesting an infectious prodrome. In contrast, diabetic gastroparetic patients often have prolonged duration of symptoms. In diabetic patients, symptoms may improve, in part, with improvement in glucose control. In diabetic patients, gastroparesis appears to be another diabetic complication along with nephropathy, neuropathy, and retinopathy; thus, gastroparesis may be another marker of the severity of the diabetic disorder. Many patients have exacerbations of their symptoms leading to intermittent hospitalizations, primarily due to poor glycemic control, infection, noncompliance with/intolerance of medications, and need for invasive treatment options. Studies on the treatment for gastroparesis are generally short term over several months. Few long-term treatment studies over a year or more have been reported. Those long-term (1–3 years) studies reported appear to be favorable for treatment improving symptoms and helping to improve the natural history for a given patient.

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Chapter 9
Gastric Emptying Scintigraphy

Alan H. Maurer

Keywords Gastric emptying • Scintigraphy • Radiolabeled solid meal • Radiolabeled liquid meal

Introduction

Dyspeptic symptoms are characterized by early satiety, postprandial fullness, nausea, vomiting, abdominal distention, and bloating. The term functional dyspepsia, used in the absence of obstruction or ulcers, is estimated to affect 20% of the population of the USA [1]. In spite of the development of many new scintigraphic and nonscintigraphic methods for evaluating gastrointestinal (GI) motility, the gastric emptying scintigraphy (GES) study has remained the most recommended study for evaluating patients with dyspepsia for suspected GI dysmotility [2]. This is in spite of the fact that delayed GE is documented in only 30–60% of patients with dyspepsia and the severity of delayed GE does not correlate well with symptoms. Other GI motor abnormalities, altered visceral sensation and psychosocial factors have been shown to be important factors which should also be considered in evaluating patients with functional dyspepsia [3].

A GES study is indicated for patients with dyspepsia after an anatomic cause has been excluded. A GES study may also be indicated for patients with severe gastroesophageal reflux disease not responding to acid suppressants, evaluating a diabetic with poor glycemic control or as a part of whole-gut transit scintigraphy for identification of a "pan motility" GI disorder [4]. Most often, the goal of identifying delayed GE is to identify which patients will benefit from a prokinetic drug to alleviate symptoms [5].

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The use of a radiolabeled meal remains the gold standard for measuring GE. Once the solid or liquid phase of a meal is combined with a radioisotope (radiolabeled), the radioactive counts detected by the nuclear medicine camera are directly proportional to the volume of the meal remaining independent of any geometric assumptions typically needed for estimating volume with other imaging modalities.

While a conventional single-head nuclear medicine gamma camera can be used for imaging, one with a large field of view is preferred. Dual-head (two detector) SPECT cameras are now in common use and permit simultaneous anterior–posterior imaging required for depth and attenuation correction. The two most commonly used radioisotopes for labeling solid and liquid meals are ^{99m}Tc and ^{111}In. To image solids and liquids simultaneously, the camera and collimator must be capable of separating the lower (140 keV) signal of ^{99m}Tc from the higher signal energy (273 keV) of ^{111}In.

Which radiopharmaceutical is used to label the meal depends on the study to be performed. For solid-phase GE studies, ^{99m}Tc sulfur colloid (^{99m}Tc-SC) labeled egg is used. ^{99m}Tc-SC has a short radioactive decay (half life = 6 h) which limits radiation exposure and when cooked is tightly bound to egg protein so that no radioactive material is absorbed from the GI tract. This further reduces radiation exposure. For a 0.5 mCi dose of ^{99m}Tc-SC, the estimated total effective dose received by the patient is 0.03 mSv [6]. ^{111}In-diethylenetriaminepentaacetic acid (DTPA) is usually given with water as the liquid component of the meal. It is also nonabsorbable. Because oral ^{111}In is not approved for routine clinical use in the USA, a special (broad scope) radiopharmaceutical license may be required for its use. For a 0.15 mCi dose of ^{111}In-DTPA, the estimated total effective dose received by the patient is 0.3 mSv [6].

Patient Preparation

The study should be performed the morning after an overnight fast. Patients are instructed to take regular medications with a small quantity of water before coming for the test. In general, the referring physician should determine if the patient is to be studied on or off any medications that may affect gastric emptying. Any medication directions should be directly communicated to the patient. Typical prokinetic agents, such as metoclopramide (Reglan), tegaserod (Zelnorm), erythromycin, and domperidone (Motilium), are stopped two days prior to the test. Opiate analgesics, such as demerol, codeine, morphine, oxycontin, percodan, and percocet, which delay gastric emptying, should be stopped two days before the test. Anticholinergic agents, such as bentyl, donnatal, levsin, and robinul, are also stopped for two days prior to the test. The physician interpreting the gastric emptying study should be informed if the patient is taking such medications.

Menstruating females are preferably studied during the first 10 days of their menstrual cycle. Diabetic patients should self test and measure their blood glucose

prior to beginning the study. For insulin-dependent patients or those with a history of poor glycemic control, the imaging center should measure the blood glucose. Marked hyperglycemia (glucose >275 mg/dl) is a relative contraindication as it may slow gastric emptying. Insulin-dependent diabetics are usually instructed to take one-half their normal insulin dose just prior to the test meal and to supplement any needed insulin immediately after completion of imaging.

Subjects should be informed that they will be in the imaging facility for at least 4 h and advised to bring a book, a music player, or other material to occupy them for the 4 h of the study. Patients should refrain from smoking the morning of the test and throughout the time of imaging.

The Test Meal

Normal values must be established not only for the meal, but also for the method used for image acquisition and processing. GE is dependent on body position, smoking, gender, phase of the menstrual cycle, and on the time of day the test is performed [7–9]. Normal values for a variety of meals, including meat, porridge, pancakes, and eggs, have been reported. For any test meal, the stability of the radioisotope bound to the solid phase must be established to ensure that the radioisotope does not dissociate in acidic gastric juice. When ^{99m}Tc-SC is injected into a live chicken, it is phagocytosed by the Kupffer cells of the liver resulting in an intracellularly bound radiolabeled food. This meal has been the gold standard to which all other radiolabeled solid foods have been compared.

Because of the ease of preparation, high stability and large normative database solid-phase, GE studies are now performed with ^{99m}Tc-SC labeled egg white. A recent consensus report has recommended the use of a standardized, solid meal consisting of 0.5 mCi of ^{99m}Tc-SC, 120 g of liquid egg white (EggBeaters™ or other generic egg white), 2 slices of white wheat bread, 30 g of strawberry jam, and 120 ml of water (255 kcal, 24% protein, 2% fat, 72% carbohydrate, 2% fiber) [10]. The normal values for this meal are based on the largest number of normals included in a multicenter study. The 1-, 2-, and 4-h values for the percentage of the meal retained are very similar to another popular meal consisting of two large natural eggs, two pieces of white toast, and 300 ml of water (282 kcal, 22% fat, 32% protein, 46% carbohydrate) [11]. With the currently consensus recommended egg-white meal, GE is abnormal if greater that 60% of the meal is retained at 2 h or greater than 10% at 4 h.

To prepare the meal, the liquid egg is poured into a container and mixed with the ^{99m}Tc-SC. The egg can be cooked either scrambled on a nonstick frying pan or microwaved in an appropriately shielded container. The egg mixture should be stirred once or twice during cooking and is cooked until it has the consistency of an omelet (3–5 min). The bread is toasted. Jelly is spread on the bread. Usually, a sandwich is made of the jellied bread and cooked egg; however, the egg and bread can be served separately with the water.

A prolonged time (>15 min) for meal ingestion can affect the quantification of gastric emptying. The patient is encouraged to consume the entire test meal within 5–10 min. For quality control, the nuclear medicine technologist should record how long it takes the subject to consume the meal and how much was consumed. If less than the entire standard meal is ingested, the study is technically nondiagnostic since a smaller meal will empty faster than the entire standard meal.

Imaging Protocol and Image Analysis

Immediately after eating the meal, the patient is positioned standing in front of the nuclear medicine camera. Upright imaging is preferred since supine positioning can slow gastric emptying of solids (20% emptying at 1 h in a supine position versus 50% in an upright position) [12]. Frequent image acquisition is needed to quantify a lag phase and to accurately quantify a rate of emptying. These are probably unnecessary for clinical purposes, and a simplified standard method for screening for abnormal GE is desired by the gastroenterologists.

As solids move from the posterior located fundus to the anterior antrum, there is an increase in measured counts as the depth of the meal moves closer to a camera positioned in front of the patient. Depth attenuation correction is therefore needed. Correction using the geometric mean $(\text{anterior counts} \times \text{posterior counts})^{1/2}$ is most commonly used. This correction results in only a 3–4% variation in counts for the depths typically encountered. For patients who cannot stand, a single left anterior oblique view may be used [13]. Between images, patients are permitted normal daily activities (sitting, standing, or walking) in the nuclear medicine waiting area usually in close proximity to the imaging room.

The images are acquired using a 140 keV ^{99m}Tc photopeak with a 20% window. Either a low energy all purpose (LEAP) collimator or a low energy high resolution collimator can also be used. Computerized digital images are required for quantification. These are acquired in a 128×128 word-mode matrix.

Computer regions of interest corresponding to the stomach are defined to obtain the total gastric counts. Manual regions of interest are drawn on the anterior and posterior images for all acquisition times using an irregular ROI tool to outline the stomach (Fig. 9.1). The total gastric ROI should include the fundus and antrum with particular attention to avoid any loops of small bowel in close proximity to the stomach. An exception would be if the patient has small bowel activity on the first image or there is retained esophageal activity. Then, the entire field of view should be used so that time $t = 0$ min (immediately postmeal ingestion) includes all activity ingested. The geometric mean corrected counts for each time point is calculated and corrected for ^{99m}Tc decay. The gastric counts remaining at each time are then graphed and the percentages of activity remaining in the stomach are normalized based on 100% taken as the initial maximal gastric counts (Fig. 9.1).

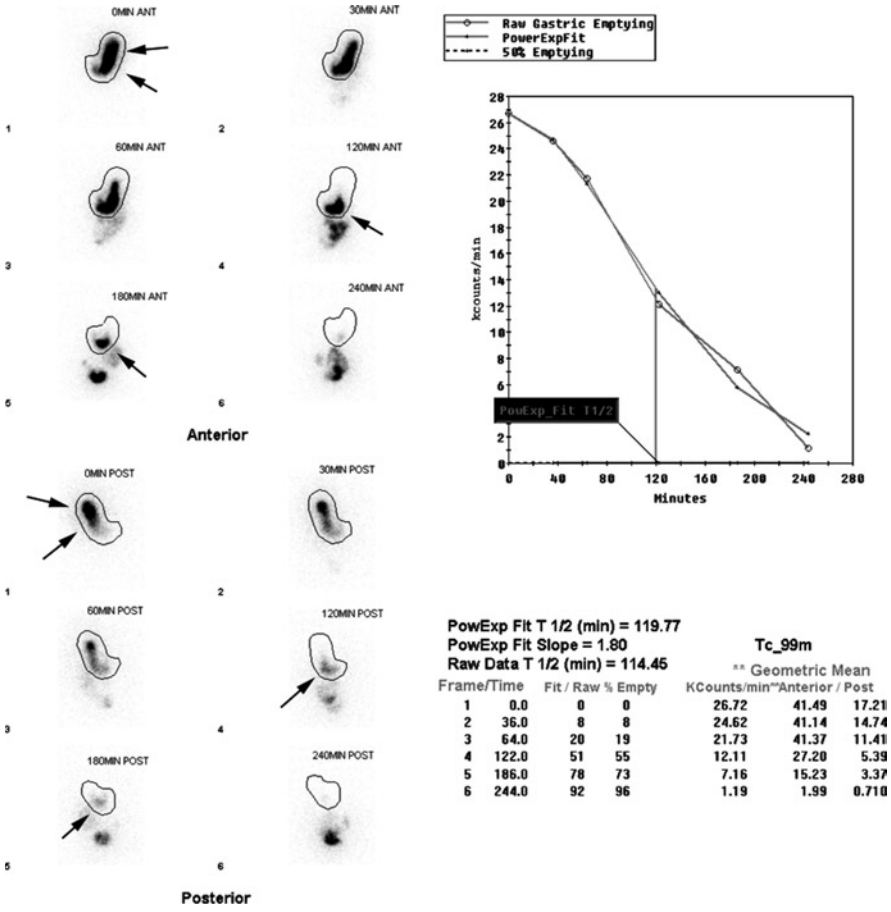

Fig. 9.1 Normal solid-phase images and analysis. Gastric emptying software should permit analysis of all anterior and posterior ^{99m}Tc gastric images (*left upper* and *lower panels*) to calculate the geometric mean and decay corrected counts at fixed time intervals after meal ingestion. The raw counts are plotted (*open circles*) as a function of time. The lower tables indicate both the total corrected gastric counts (*right lower table*) and the derived percentage emptied (*left lower table*) for each time interval. The percent retained is 100% minus the percent emptied. The solid gastric emptying curve is sigmoidal in shape due to the early lag phase for solids. Many software programs will also perform a computerized curve fit (*solid dots*) to the data to calculate a $T_{1/2}$ emptying value. In addition to the quantitative analysis the images should be reviewed to look for the normal progression of solids from the fundus (*double arrows*) to the antrum (*single arrow*). Solids should initially localize primarily in the fundus reflecting normal fundal accommodation. With time, the solids move distally into the antrum, where they are triturated and then emptied

Test Interpretation and Reporting Results

Understanding the different roles of the fundus and antrum has become increasingly important for analyzing GE studies. Normally, solids are temporarily stored in the fundus until slow, sustained contractions transfer solids to the antrum. The normal early segregation of solids in the fundus is usually apparent in initial images of a GE study (Fig. 9.1). A persistent transverse band separating the fundus and antrum is commonly observed. Solids then move from the posteriorly located fundus to the more anteriorly located antrum. After the solids are in the antrum, peristaltic contractions work by a process called trituration, in which the solids are mixed with gastric digestive juices and are ground into particles of 1–2 mm, which are then able to pass through the pylorus. The contractile activity of the antrum is controlled by a pacemaker located high on the greater curvature, at the boundary between the fundus and the antrum. The time required to complete trituration so that solid particles can then begin to empty from the stomach is referred to as the lag phase.

Emptying of liquids is controlled by a sustained pressure gradient generated by the fundus. Liquids require no trituration and are distributed rapidly after ingestion throughout the stomach and emptying monoexponentially (Fig. 9.2). Liquid GE can be adequately described by a simple half-time ($T_{1/2}$) or the time to 50% emptying. Until recently, liquid GE studies have been considered of little clinical value as liquid emptying was believed not to be abnormal until gastroparesis was advanced [14]. Recent studies, however, have created renewed interest in liquid gastric emptying showing that liquid emptying may be abnormal when solids are normal in up to 20% patients [15].

Radiolabeled water may be administered simultaneously with radiolabeled solids during GE scintigraphy for evaluation, not only of liquid gastric emptying, but also as part of the measurement of small bowel transit and/or whole gut transit. Whole gut transit studies have been shown to be beneficial in the clinical evaluation of patients who present with both upper or lower gastrointestinal symptoms [4]. Occasionally, a liquid only study is useful if a patient is unable to tolerate a solid meal.

The simplest approach to analyze GE data has been to report either the time to 50% emptying of the meal ($T_{1/2}$) or to use the percent of emptying measured at fixed times after meal ingestion (Figs. 9.1 and 9.2). Until recently, GES studies were commonly performed up to 2 h after meal ingestion. Recent studies, however, have shown that the percent retained at 4 h is more reproducible [16] and detects more patients with abnormal GE [11]. It remains important, however, to measure both early phase (1–2 h) gastric retention as well as late phase (3–4 h) retention as it is not uncommon to find abnormal retention at 2 h but normal retention at 4 h (Fig. 9.3) or normal at 2 h but abnormal at 4 h (Fig. 9.4).

The study report should also include mention of the presence of delayed esophageal emptying which may be observed when food is seen in the distal esophagus especially in the initial images immediately postmeal ingestion or the presence of any gastroesophageal reflux that may be observed during the course of the study (Fig. 9.5).

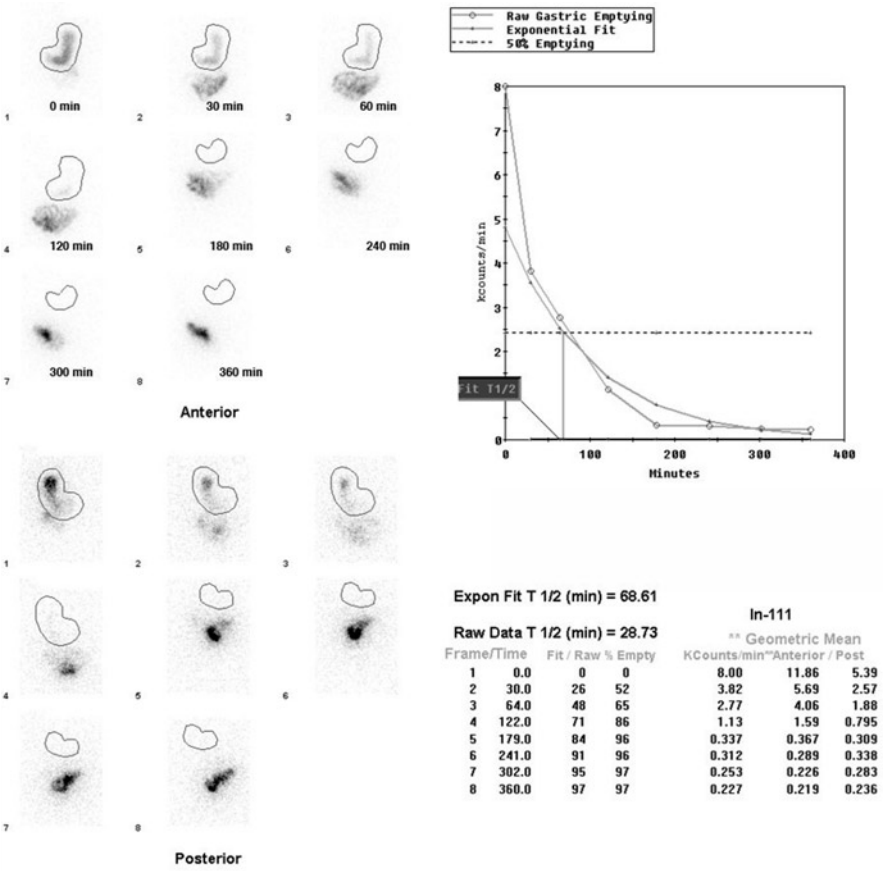

Fig. 9.2 Normal liquid phase images and analysis. As for solids, the anterior and posterior ^{111}In liquid gastric images are analyzed to obtain geometric mean, decay corrected counts. The liquid emptying curve is monoexponential since there is no lag phase for the onset of liquid emptying. Liquids should demonstrate early diffuse distribution of liquids throughout the stomach with no fundal accommodation

Numerous studies have confirmed the occurrence of a lag phase followed by emptying, during which the stomach expels solids at a characteristic rate [17–19]. To more completely characterize all phases of GE, one can fit the data to a mathematic function, such as a modified power exponential [20] which is given by:

$$y(t) = 1 - [1 - \exp(-kt)]^{\mathrm{B}}$$

where $y(t)$ is the percentage of gastric activity remaining at time t; k is the slope of the exponential portion of the curve; and $\beta(\beta\varepsilon\tau\alpha)$ is the y intercept (Fig. 9.1).

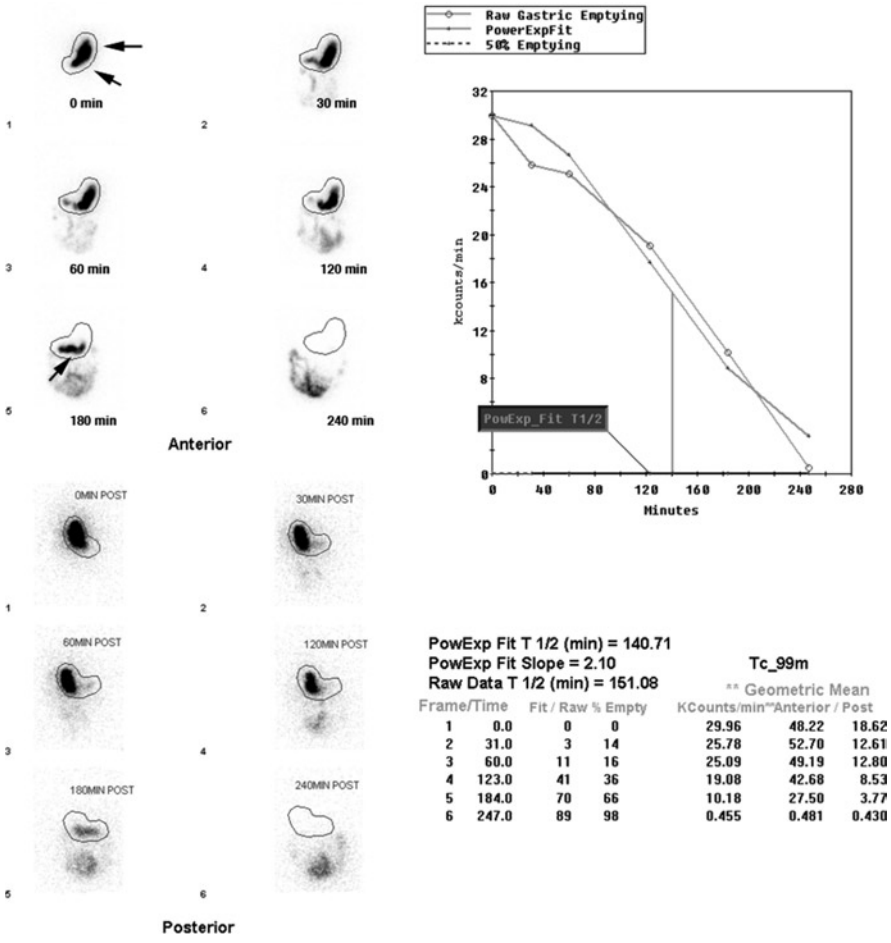

Fig. 9.3 Abnormal early solid emptying and fundal dysmotility. The images (0–120 min) show normal fundal accommodation with a delay in emptying from the fundus. There is approximately 65% retained (35% emptied) at 120 min. Visually, there is retention of the labeled meal in the fundus (*double arrows*). Once the meal has progressed to the antrum (*single arrow*) it empties normally with less than 5% retained at 240 min. This is consistent with a primary motility disorder of the fundus. It is helpful if this can be correlated with early postprandial symptoms of bloating, fullness, nausea, and abdominal pain

The lag phase ($\ln(\beta(\beta\varepsilon\tau\alpha)/k)$) corresponds to the time of peak activity in the antrum which physically corresponds to maximal filling of the antrum just before the triturated and suspended solids and liquids begin to empty at a uniform rate (k). Definition of the lag phase has been controversial. Recent data suggest measurement of the lag phase has no additional clinical value over simple reporting of the percentage of gastric retention at 2 and 4 h [21].

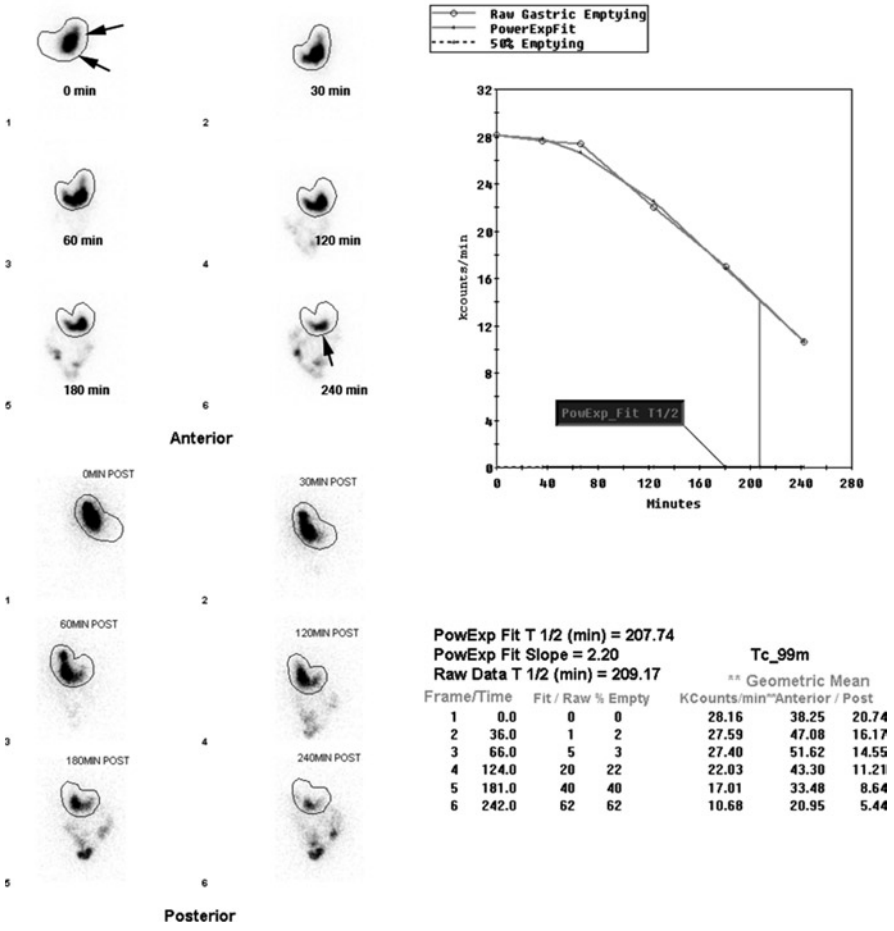

Fig. 9.4 Abnormal late solid emptying and primary antral dysmotility. The immediate postmeal image ($t=0$ min) shows normal fundal accommodation (*double arrows*). There is approximately 80% retained at 120 min and 40% at 240 min. Visually, the meal moves normally from the fundus to the antrum, where it is retained (*single arrow*) consistent with a primary motility disorder of the antrum

Other Specialized Tests of Gastric Function

Delayed GE is found in a significant number (30–70%) but not all patients with diabetes or functional dyspepsia [3]. It is increasingly recognized that other special studies are needed to more completely evaluate the stomach including: separate fundal and antral motor function, fundic relaxation, visceral hypersensitivity, asynchronous antroduodenal coordination, and gastric dysrhythmias [22–24].

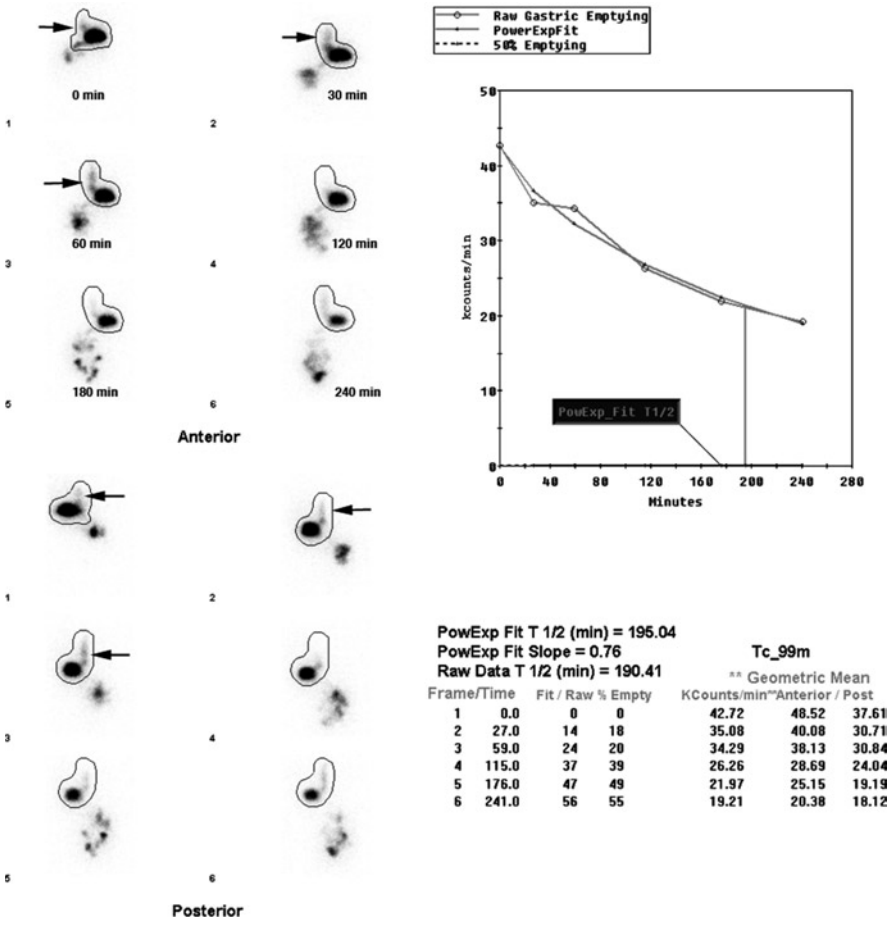

Fig. 9.5 Gastroesophageal reflux and delayed gastric emptying. Gastroesophageal reflux may be visualized during a GE study (*single arrows*). Visualized activity in the esophagus may be due either to esophageal retention from esophageal dysmotility or reflux. In such cases, a barium swallow may help differentiate these two possibilities. This patient, however, shows intermittent episodes of reflux associated with a marked delay in GE (45% retained at 240 min)

Bicompartmental (Fundal and Antral) Gastric Emptying

Since scintigraphy easily permits analysis of the intragastric distribution of the test meal between the fundus and antrum it is ideal for measuring both regional and global GE. Studies have shown an association between symptoms of nausea, early satiety, abdominal distention, and acid reflux with proximal gastric retention and vomiting is associated more with delayed distal GE. Inspection of fundal and antral gastric emptying in the images and quantification of regional emptying can be helpful

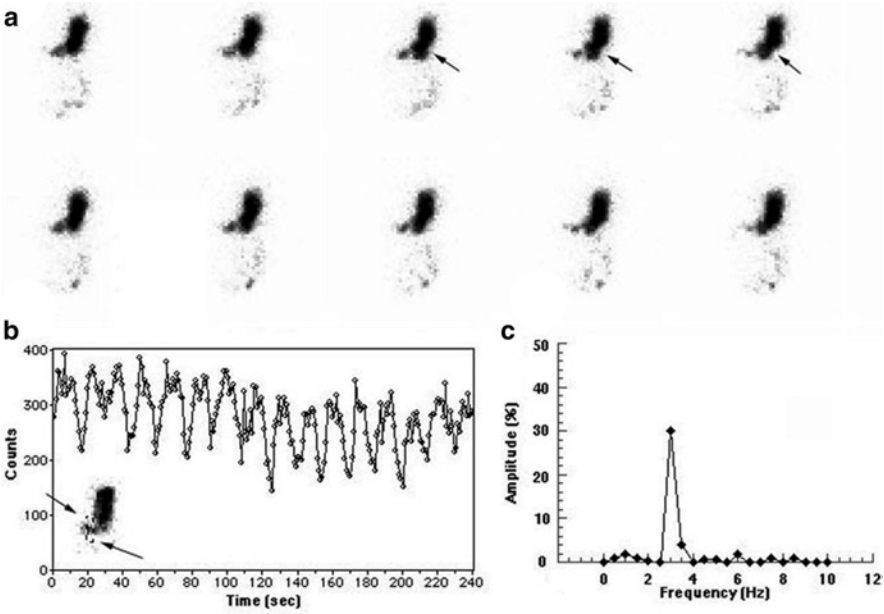

Fig. 9.6 Antral contraction study. In order to measure the amplitude and frequency of antral contractions, images of the stomach (**a**) can be acquired rapidly (min one second per frame). By placing a region of interest over the antrum (*left arrows*) (**b**) the resulting activity curve characterizes antral contractions. These data are then analyzed by Fourier analysis (**c**) to measure both the amplitude and dominant frequency of antral contractions (3 Hz)

for explaining dyspeptic symptoms especially when global GE values are normal [25, 26]. Regional analysis of GE can be qualitatively assessed and should be included as a part of the interpretation of GE studies (Figs. 9.3 and 9.4).

Antral Contraction Scintigraphy

Methods for analyzing GE data have been developed which permit analysis of the frequency and amplitude of antral contractions. Normal antral contractions occur at a rate of three per minute (Fig. 9.6). In diabetic gastroparesis, GE is delayed due not only to retention of food in the fundus, but also to decreased strength of antral contractions [27]. A majority of patients with gastroparesis are women with up to an 82% predominance in one large study [28]. Differences in normal male and female GES have been shown to be due to the amplitude of antral contractions and not the frequency. Using scintigraphy to measure the amplitude of antral contractions, women have been shown to have lower amplitude contractions not associated with higher progesterone during the luteal (late) phase of the menstrual cycle [29].

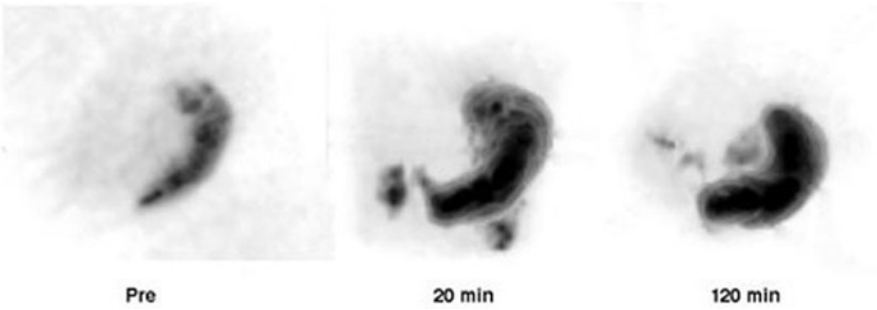

Fig. 9.7 SPECT 3D gastric accommodation study. These 3D images demonstrate the contracted state of the stomach prior to a gastric emptying meal. At 20 min, there is a marked increase in the volume of the gastric fundus (accommodation). Gastric dilatation may persist to 4 h in spite of the continual gastric emptying of the solids

Fundal Accommodation Studies

Fundal relaxation (accommodation) is a well-established physiologic response which allows the stomach to increased intragastric volume without increased intragastric pressure. The barostat is the current reference method to assess accommodation but has been criticized as invasive and nonphysiologic [30]. In addition to imaging techniques, nutrient or water loading tests have also been used to assess gastric filling capacity and sensation (visceral hypersensitivity).

Since the gastric mucosa accumulates ^{99m}Tc-pertechnetate after intravenous administration, this permits 3D SPECT volumetric imaging of the wall of the stomach. This has been validated as a noninvasive method to measure gastric volumes prior to a meal and at any time after meal ingestion [31, 32] (Fig. 9.7). It is also possible to simultaneously assess the relationship of liquid or solid meal emptying and gastric accommodation. Such studies have shown maximal gastric volume change (mean = 185%) occurs immediately after mean ingestion and persists in spite of relatively rapid emptying of the meal [33].

It is expected that methods to measure gastric accommodation will be of clinical value to study patients with dyspepsia and normal GE parameters and may help direct medical therapy.

Pediatric Gastric Emptying

Delayed GE may be suspected in infants under 2 years of age who have vomiting, abdominal pain, or early satiety. In infants, GE scintigraphy is usually performed combined with evaluation for GER with the patient's milk or formula feeding to which ^{99m}Tc-SC is added. Unfortunately, there is less consensus on how pediatric GE studies should be performed and normal values for GE for infants for various

meals have not been established. However, a range of gastric retention between 40 and 70% at 1 h has been reported and is in general use [34].

In children, the "milk scan" is used to evaluate not only GE, but also potential gastroesophageal reflux and pulmonary aspiration. Prior studies which compared scintigraphy with simultaneous pH probe monitoring reported a sensitivity and specificity of 79 and 93%, respectively. In recent studies, scintigraphy found an incidence of reflux ranging from 20 to 40% in children from less than 1 year to 6 years of age [35].

^{99m}Tc-SC is mixed with the child's usual volume of milk, formula, apple juice, or glucose water and is given at the time of routine feeding. Images are recorded after the feeding is completed. A high-sensitivity collimator is recommended to increase counting efficiency. Initial swallowing curves are recorded to evaluate esophageal transit. With the patient placed supine and directly on the camera, posterior images of the chest and abdomen are obtained for at least 60 min [36]. Visual cine review of computer-enhanced images increases sensitivity for detecting small volumes of reflux. Time-activity curves are helpful to document the frequency of reflux, delayed esophageal clearance, and to improve reproducibility in the readings [37]. Rapid imaging (10–20 s/image) is important because transient reflux can rapidly dissipate. Delayed images at 1, 2, and 24 h can be acquired to detect pulmonary aspiration. Pulmonary aspiration is documented with this method in 35–55% of children with severe pulmonary disease [38].

Conclusion

New standards for performing radioisotope, solid phase gastric emptying studies in adults have been established which now permit more reproducible and comparable results between imaging centers. There is increasing recognition, however, that the measurement of gastric retention from a solid-meal gastric emptying study may not be sufficient to explain all patients' symptoms. There is increasing evidence that separate analysis of fundal and antral function as well as the measurement of liquid gastric emptying may improve our ability to detect gastric motor dysfunction in symptomatic patients. Pediatric gastric emptying studies remain less well standardized. There are no well-defined standards, and their interpretation is still usually based on locally established criteria.

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Chapter 10
Wireless Motility Capsule in Gastroparesis

Rita Brun and Braden Kuo

Keywords Capsule technology • Gastrointestinal tract • Gastrointestinal transit • Electronic radiotelemetry capsule

Introduction

Capsule technology has opened up a new era in the evaluation of the gastrointestinal tract, being an alternative to more invasive conventional methods. The intricate activity of gastrointestinal transit is coordinated by the motor function of the stomach, small intestine, and colon. The concept of a swallowable electronic radiotelemetry capsule dates back to the 1950s [1, 2]. The Heidelberg capsule had been used to measure pH inside the gastrointestinal tract and the GI transit times in the late 1980s [3, 4]. However, the Heidelberg capsule was not widely clinically available. Recently, there has been a reemergence of capsule technology, devices able to provide internal physiologic parameters as video, pressure, pH, and temperature. Assessment of GI transit times by wireless motility capsule (WMC) is one of the first important clinical applications of this new technology.

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Wireless Motility Capsule Procedure Description

Wireless Motility Capsule

The WMC (SmartPill, The SmartPill Corporation, Buffalo, NY, USA) is a wireless device able to evaluate whole gut and regional gut transit and motility. The capsule houses sensors for pH, temperature, and pressure and transmits the data to a receiver worn by the subject during ambulatory monitoring. The WMC is 13 mm across and ·26 mm long. The capsule and receiver have battery lives rated for 5 days. pH is accurate to within 0.5 pH units and pressure is accurate to ±5 mmHg. After completion of the test, data is downloaded to a computer from the data receiver through a docking station and analyzed using pressure analysis software (GIMS 1.8; The Smart Pill Corporation) Fig. 10.1.

Wireless Motility Capsule Test

After overnight fasting, the patient ingests a standard eggbeaters sandwich meal with a total caloric value of (255 kcal, 72% carbohydrate, 24% protein, 2% fat, and 2% fiber) or granola bar [SmartBar] (260 kcal, 62% carbohydrate, 18% protein, 2.2% fat, 3 g fiber), followed by the patient swallowing the WMC with 50 cc of water. Patients do not eat or drink for the next 6 h. Six hours after capsule ingestion, patients consume 250 ml Ensure and water ad libitum. After the second meal, patients may resume their diet routine. At 120 h postingestion, patient returns with the data receiver and diary.

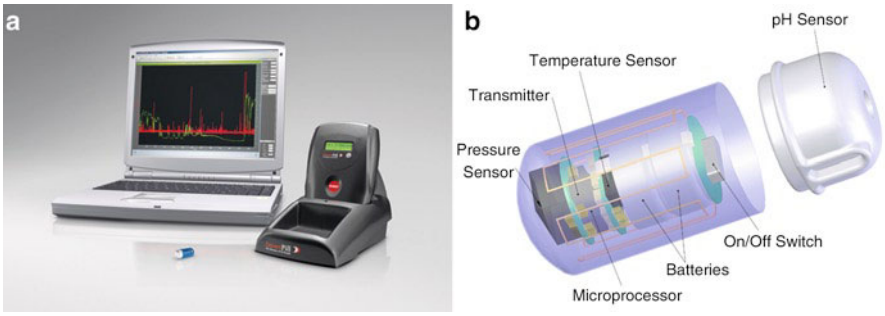

Fig. 10.1 SmartPill System (**a**) and SmartPill Capsule (**b**)

Indications for Use

The SmartPill system is FDA approved for the following indications:

1. Evaluation of gastric emptying time (GET) in patients with suspected gastroparesis or delayed gastric emptying and those with idiopathic and diabetic gastroparesis and functional nonulcer dyspepsia.
2. Evaluation of colonic and WGTT or combined small- and large bowel transit time in chronic constipation and differentiate slow versus normal transit.

Interpretation of the Results

Gastric Emptying Time. The GET is the time difference between capsule ingestion and an abrupt rise of pH to >4 or at least a rise in 3 pH units above baseline. Patients are advised to stop proton pump inhibitors (PPIs) for 7 days prior to the test and histamine type 2 antagonists for 3 days prior to the test. For patients treated with PPIs and have difficulty stopping these medications, modified GET criteria may be considered based on the study of subjects treated with 40 mg of esomeprazole twice daily. Using the sudden sustained pH increase of >0.6 pH-units, the pattern for GET with WMC was identifiable in all patients taking PPIs [16]. However, if possible, it is better to be off acid suppression medications during the test to prevent confusion because the pH transition is much less pronounced between the stomach and small bowel.

Small Bowel Transit Time (SBTT). SBTT is defined as the time interval between the pH rise in the proximal duodenum to a more than 1 unit pH drop in the cecum that lasted for at least 5 min. Normal subjects had a mean GET of 4.7 ± 4.5 h, mean small bowel and large bowel transit time of 25 ± 14 h and mean WGTT of 29.4 ± 14.3 h [5].

Colonic Transit Time (CTT) and Whole Gut Transit Time (WGTT). The CTT is defined as the time interval between capsule entry into the cecum and the temperature drop from 98°C as well as signal loss representing exit of capsule from the body, and the WGTT as the time interval between capsule ingestion and capsule exit from the body.

Physiologic Basis of Definition of GET by WMC

After overnight fast and ingestion of the standard meal, the patients swallow the capsule. This order of actions resets the gastric motility pattern by starting the postprandial pattern and thus ensuring the functional recalibration of the GI tract.

Ingesting the WMC after the meal allows standardization of the emptying times measured by device. The gastric emptying occurs in the following order: first the fluid empties, then the solid meal empties, and finally emptying of indigestible objects, such as WMC mediated by high amplitude contractions or MMC [6, 7]. As a result of this phenomena, 5 h cut off for normal gastric emptying measured by WMC as an indigestible particle is used, compared with 4 h cut off for radioactive meals [8]. Meal ingestion before capsule ingestion ensures that capsule stays in the stomach during the initial part of the study to measure the gastric emptying of a meal and helps to prevent its premature emptying from an MMC during the fasting state.

Attempts to measure the GI transit times using the capsule video endoscopy are reported [9]. The test is performed in fasting state; otherwise, the food will obscure the landmarks. During fasting, MMC cycle is activated in GI tract every approximately 90 min [10]. If the capsule is ingested during the fasting state which is the typical protocol for wireless video capsules, capsule emptying from the stomach into the small intestine occurs randomly depending on the timing of the ingestion relative to the MMC cycle. This unpredictability disrupts any standardization of gastric emptying time. Severe cases of gastroparesis probably will be captured by capsule endoscopy. However, this method does not allow having quantitative information.

Diagnosis of Gastroparesis with WMC

The use of WMC for diagnosis of gastroparesis was evaluated in the study on 87 healthy and 61 gastroparetic subjects (based on clinical symptoms and previous GES documenting delayed gastric emptying). The subjects underwent simultaneous WMC monitoring and gastric emptying scintigraphy. In fasted state, they ingested capsule and [99mTc]-SC radio-labeled meal. Scintigraphic images were obtained every 30 min for 6 h; GET and percentage of meal remaining at 2 and 4 h were determined for each subject. As can be seen by Fig. 10.2a, b, the scintigraphic meal empties almost completely before the emptying of the capsule. Correlation between GET and GES-4 h was 0.73 and GES-2 h was 0.63. The 300-min (5 h) cut-off time for GET had sensitivity of 0.65 and specificity of 0.87 for the diagnosis of gastroparesis. The corresponding sensitivity/specificity for 2 and 4 h standard GES measures were 0.34/0.93 and 0.44/0.93, respectively. This study demonstrated that WMC is able to discriminate between normal gastric transit time and gastroparesis, and it is a reliable test with good specificity/sensitivity ratio with the 5 h cut off time, increasing specificity of diagnosis [8] Table 10.1, Fig. 10.2a, b.

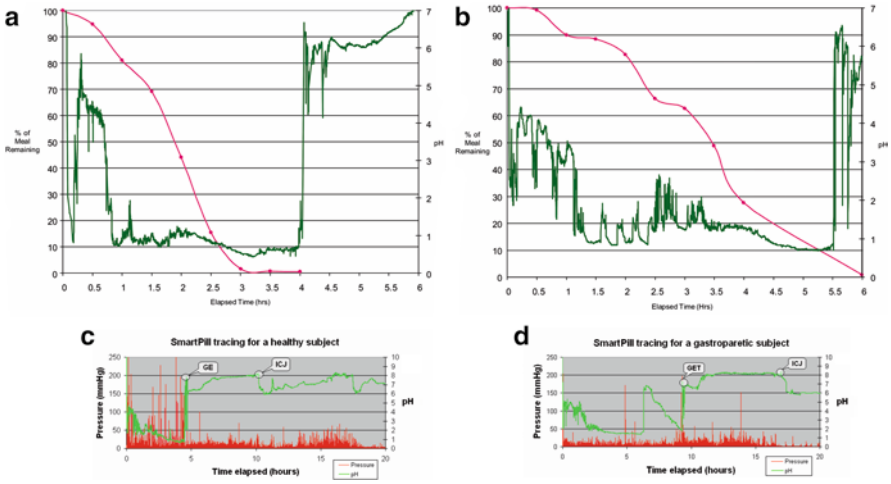

Fig. 10.2 (**a, b**) Relationship between scintigraphic emptying of a meal (gastric emptying scintigraphy) and gastric emptying time of the capsule. The magenta tracing and axis on the left show the percent meal remaining over time. The green tracing and axis on the right show pH as measured by the capsule. The pH tracing shows the pH changes induced by the meal in the first hour followed by reacidification of gastric pH. (**a**) Healthy subject. The emptying of the meal occurs almost completely by 3 h. Emptying of the capsule occurs at about 4 h (normal limit <5 h) when the pH rapidly changes more than 3 pH units from the acidic gastric pH to the alkaline duodenum pH. (**b**) Gastroparetic subject shows more than 10% of the meal remaining at 4 h with the emptying of the capsule at 5.5 h. [8]. (**c**) WMC tracing in a healthy subject (GET <5 h). (**d**) WMC tracing in a gastroparetic patient (GET >5 h). Notice the low amplitude antral contractions

Table 10.1 Correlation of GES 2h and GES 4 h with gastric emptying time (GET) by WMC along with sensitivity and specificity values [8]

Gastric emptying parameter	WMC-GET correlation	Sensitivity	Specificity
GES 2 h	0.63	0.34	0.93
GES 4 h	0.73	0.44	0.93
GET	n/a[a]	0.65	0.87

GES gastric emptying scintigraphy, *GET* gastric emptying time, *WMC* wireless motility capsule
[a]Not applicable

WMC Data About Other Physiologic Parameters in Gastroparesis

In addition to the assessment of gastric emptying time, WMC data provides other interesting insights into gastroparesis pathophysiology, by measuring various physiologic parameters as whole GI transit times, contractile activity during fasting and

Table 10.2 Median values of motility parameters for healthy vs. gastroparetic subjects [11]

	Stomach		Small bowel	
	Ct/h	MI	Ct/h	MI
Normal	72	11.83	145	12.78
Gastroparesis	47	11.12	93	12.12
	$p=0.01$	$p=0.02$	$p=0.02$	$p=0.04$

Ct frequency of contractions, *MI* motility index

fed state, and pH profiles. Further characterization of dysmotility in gastroparetic patients could help in understanding of underlining pathophysiology and developing appropriate treatments.

Contractions Patterns and Intraluminal Pressure in Health and Gastroparesis

The phasic pressure profiles of the stomach and small intestine were compared in 71 healthy and 42 gastroparetic subjects. Significant differences were observed between healthy and gastroparetic subjects for frequency of contractions (Ct) and motility index (MI) ($P<0.05$). Median values of the motility parameters in gastric window were Ct = 72, MI = 11.83 for healthy and Ct = 47, MI = 11.12 for gastroparetics. In the small bowel, median values were Ct = 144.5, MI = 12.78 for healthy and Ct = 93, MI = 12.12 for gastroparetics. The 5th percentile of normals was 29/h for Ct and 9.82 for MI.

The correlation between GET and frequency was only partial: from gastroparetic patients who had a GET > 5 h, 52% had abnormal low gastric contractility, suggesting that contractile and transit abnormalities can occur independently. On the other hand, 73% of the severe gastroparetics with prolonged (>12 h GET) had gastric frequencies below the 5% of normal.

Diabetic subjects with gastroparesis showed significantly lower Ct and MI compared with healthy subjects in both gastric and small bowel windows while idiopathic gastroparetic subjects did not show significant differences.

The WMC was able to differentiate between healthy and gastroparetic subjects based on gastric and small bowel motility profiles [11]. Interestingly, studies of antral motility using imaging modalities as the US and MRI have also showed decreased antral motility in gastroparesis [12, 13]. These findings suggest that the emptying time is important in the understanding of pathophysiology of gastroparesis, however other factors, as altered pressure characteristics contribute further to the diverse clinical picture of gastroparesis. Table 10.2, Fig. 10.2c, d.

Regional GI Tract Transit Times

The regional gut transit times in healthy controls and patients with gastroparesis were investigated using wireless motility technology. A total of 66 healthy controls

and 34 patients with GP (15 diabetic and 19 idiopathic) swallowed WMC together with standardized meal [13]. GET, colon transit time (CTT), and WGTT but not SBTT were significantly longer in GP than in controls. Median WGTT in healthy was 27.7 (25th percentile = 22.9 h, 75th percentile = 34.3 h). Median WGTT in gastroparetics was 45.9 h (25th percentile = 30.0 h, 75th percentile = 59.0 h), $p = 0.0001$.

Median SBTT in healthy was 4.6 h (25th percentile = 4.0 h, 75th percentile = 5.9 h). Median SBTT in gastroparetics was 4.5 h (25th percentile = 3.6 h, 75th percentile = 5.5 h), $p = 0.615$. Eighteen percent of gastroparetic patients had delayed WGTT. Both diabetic and idiopathic etiologies of gastroparetics had significantly slower WGTT ($P < 0.0001$) in addition to significantly slower GET than healthy controls.

Diabetic gastroparetics additionally had significantly slower CTT than healthy controls ($P = 0.0054$). The prolongation of CTT and WGTT indicates that dysmotility beyond the stomach in is present in gastroparesis, and it could contribute to symptoms presentation [14].

pH Profiles

Gastric pH profiles were found to be different in gastroparesis of different etiologies and varying degrees of gastric stasis compare to healthy stomach in the study by Hasler et al. Sixty-four healthy control subjects and 44 gastroparesis patients (20 diabetic, 24 idiopathic) underwent simultaneous WMC and gastric scintigraphy off any acid suppression treatment. Basal pH was higher in diabetic (3.64 ± 0.41) vs. control subjects (1.90 ± 0.18) and idiopathic subjects (2.41 ± 0.42; $P = 0.05$). Meals evoked initial pH increases that were greater in diabetic (4.98 ± 0.32) than idiopathic patients (3.89 ± 0.39; $P = 0.03$) but not control subjects (4.48 ± 0.14). pH nadirs prior to gastric capsule evacuation were higher in diabetic patients (1.50 ± 0.23) than control subjects (0.58 ± 0.11; $P = 0.003$). Compared with control subjects, those with moderate–severe stasis (>20% retention at 4 h) had higher basal (3.91 ± 0.55) and nadir pH (2.2 ± 0.42) values ($P = 0.05$). Both diabetic and idiopathic patients with moderate–severe gastroparesis exhibited increased pH parameters vs. those with mild gastroparesis.

Diabetic patients with gastroparesis exhibit reduced gastric acid, an effect more pronounced in those with severely delayed gastric emptying. Idiopathic gastroparetic subjects exhibit nearly normal acid profiles, although those with severely delayed emptying show reduced acid vs. those with mild delays. Thus, both etiology and degree of gastric stasis determine gastric acidity in gastroparesis [15].

Another study compared small bowel pH in gastroparetic and healthy subjects. GP had significantly higher mean gastric pH before GET ($p < 0.01$) and also significantly more alkaline pH ($p < 0.04$) throughout the entire small bowel [16]. The increased small bowel pH of gastroparetic patients may imply that the rate at which acid is delivered from the stomach into the duodenum is slower than in healthy population. Although the SBTT is not affected, the change in SB pH may impact the absorption of nutrients, drug metabolism and might be predisposing to bacterial overgrowth; those factors may further impair GI motility in gastroparetic patients.

Clinical Use and Implications of WMC Testing

The information obtained by WMC contributes to our understanding of gastroparesis and can pave the way for more rational therapeutic choices to optimize clinical management.

Documentation of extremely prolonged capsule retention in the stomach (e.g., more than 24 h) helps to recognize the most severe cases which fall far beyond traditional 4 h assessment available by scintigraphy. At the same manner, lack or very low contractile activity of the stomach may help to evaluate the degree of gastric motor function impairment.

Measurement of gastric and small bowel pressures are not easily available with conventional techniques, such as gastroduodenal manometry, and this new modality can noninvasively collect such measurements in the stomach and small bowel.

The new data obtained by WMC as very prolonged stomach capsule retention and very low contractility may help to identify the most severe cases which imply early aggressive management of those selected patients with J tube feeding or gastric pacing.

The discordance between gastric emptying scintigraphy (GES) and WMC assessment of gastric motility is another interesting issue. Some patients might have normal gastric emptying by GES and abnormal gastric emptying by WMC, and vice versa. Each modality assesses different physiologic functions of the stomach-GES measures the emptying of the meal, and WMC measures the emptying of indigestible particles. The WMC test also indirectly measures the meal emptying because capsule empties only after the meal was emptied. Scintigraphy alone cannot assess the emptying of indigestible particles and recognize this phenomenon. Various upper GI physiologic parameters can be measured noninvasively in gastroparetic patients and not all the patients may have the same defects contributing to their symptoms. Different pathophysiologies may explain why correlation of symptoms with a single parameter may be poor [17].

Another advantage is that the information about whole GI and regional transit times can be defined with the single test, which could be especially relevant in gastroparetic patients. Coexistent constipation is not uncommon in this patients' group and quantitative data about small bowel and colonic motility is helpful while choosing appropriate treatment and nutritional access [14].

Summary

WMC has good sensitivity and specificity diagnosing gastroparesis and could serve an alternative to GES in appropriate cases, providing standardized, ambulatory, noninvasive, nonradiation, and convenient way to assess gastric and small bowel motility. Additional data that provided by this multisensor device gives us important new insights into the pathophysiology of gastroparesis and potentially can make clinical management of these patients more efficient.

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Chapter 11
Breath Tests for Assessment of Gastric Emptying

Henry P. Parkman and Lawrence A. Szarka

Keywords Gastroparesis • Gastric emptying • Scintigraphy • Radiation exposure • Nonradioactive isotope breath testing

Introduction

Patients are often evaluated for gastric motility disorders, such as gastroparesis by measuring gastric emptying. For nearly 30 years, scintigraphy has been considered the main test for measuring gastric emptying and documenting delayed gastric emptying. There are a variety of ways to measure gastric emptying with scintigraphy with marked variations in the type of meal and duration of imaging. Clinically, it is best to measure the emptying of solids because liquid emptying can often be normal when solid emptying is markedly delayed [1]. Recently, it has become apparent that prolonging the GES for 4 h may improve the diagnostic utility of the test [2, 3]. However, institutions perform the test in different ways with regards to meal content, imaging intervals, and length of test. These differences in performance of gastric emptying scintigraphy at different institutions have made this test less helpful in clinical settings. Scintigraphy is also limited by several drawbacks, including radiation exposure, expensive equipment, and the limited availability of facilities. Thus, there has been great interest in developing alternatives for effective measurement of gastric emptying in a standardized fashion. One such alternative is nonradioactive isotope breath testing.

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Breath Tests for Gastric Emptying

Stable nonradioactive isotope breath tests for gastric emptying represent a promising way to evaluate gastric emptying noninvasively. These breath tests, although initially developed with radioactive ^{14}C, now use nonradioactive ^{13}C-labeled substances [4, 5]. Breath testing is an indirect measure of gastric emptying; the profile of $^{13}CO_2$ excretion is used to estimate the half-life of gastric emptying [6] since gastric emptying is the rate limiting step in the pulmonary excretion of ingested ^{13}C-substances. A patient's gastric emptying can be calculated by measuring the expiration of labeled carbon dioxide in breath samples which results from the breakdown of the ^{13}C-labeled substrate. The presence of $^{13}CO_2$ in the breath arises from the digestion and absorption of the ^{13}C-labeled substrate in the gut lumen and finally its metabolism in the body. The $^{13}CO_2$ is the end product of metabolism and is exhaled. The optimal methods used by laboratories to mathematically model the gastric emptying process continue to be refined since the original, pioneering work of Ghoos et al. [4].

Many studies have shown that this test is comparable to gastric emptying scintigraphy. ^{13}C-breath tests can be used to test patients in a gastroenterology practice, the community, or even at a patient's bedside, areas where gamma camera facilities are not readily available. Breath samples can be preserved and shipped to a central laboratory for analysis.

Most gastric emptying breath testing (GEBT) is performed for clinical research and pharmaceutical studies, since it is not yet FDA approved for clinical use. The indication for the GEBT is the evaluation of gastric emptying in a patient suspected of having a gastric motility disorder after upper endoscopy and/or a radiographic upper gastrointestinal series have excluded gastric outlet obstruction.

Types of Breath Tests for Gastric Emptying

There are several ^{13}C-labeled substrates used to measure gastric emptying, including octanoic acid, glycine, acetic acid, and most recently *Spirulina platensis*. The choice of substrate depends on whether the physician is measuring the gastric emptying of solids or liquids. ^{13}C-glycine and ^{13}C-acetic acid are best used for measuring the liquid phase of gastric emptying [7, 8], whereas ^{13}C-octanoic acid and ^{13}C-*S. platensis* are preferred to assess gastric emptying of solids [9, 10]. For the determination of gastroparesis, measuring the gastric emptying of solids is more sensitive because liquid emptying may remain normal even in patients with advanced disease.

There are several types of breath tests available for clinical research. Presently, these tests are not FDA approved for clinical evaluation of patients. In general, there are two types of breath tests available in the USA: (1) the standard, classic ^{13}C-labeled octanoate, a medium-chain triglyceride, is bound into a solid meal, such as a muffin [4, 10, 11]; and (2) ^{13}C bound to edible algae (*S. platensis*) administered as part of an egg meal [12]. For each test, patients should discontinue medications that may affect gastric emptying for 48 h before the test, and fast overnight for 8 h, and refrain from smoking during the test.

Octanoate Breath Test

^{13}C-labeled octanoate, a medium-chain triglyceride, is bound into a solid meal, such as an egg meal or a muffin. After ingestion and stomach emptying, ^{13}C-octanoate is absorbed in the small intestine and metabolized to $^{13}CO_2$, which is then expelled from the lungs during respiration. The rate-limiting step for excretion of ^{13}C is usually gastric emptying and not postgastric emptying processing [4]. Thus, by measuring the amount of ^{13}C in breath samples, gastric emptying is indirectly determined. The octanoate breath test (OBT) has been shown to be reproducible and correlate with GES in normal subjects, as well as patients [6–8]. It also appears useful for intraindividual treatment comparisons [13]. The half-emptying time of solids using the OBT significantly accelerates in both patients and controls with the administration of prokinetic agents [14].

The gastric motility breath test (GMBT), available through Metabolic Solutions, Inc, uses an easy to prepare, low fat muffin meal (350 calories) which is labeled with ^{13}C-octanoate [11, 15]. The breath samples are collected every 15 min over 4 h. These breath samples are analyzed using a gas isotope ratio mass spectrometer to analyze the ratio of $^{13}CO_2/^{12}CO_2$. The ^{13}C enrichment is expressed as the delta per milliliter difference between the $^{13}CO_2/^{12}CO_2$ ratio of the sample and the standard. To calculate the quantity of ^{13}C appearing in breath per unit time, delta over baseline (DOB) is used [16]. The percent dose recovered per hour and the cumulative percent dose curves are modeled according to the original, nonlinear regression method of Ghoos et al. [4]. Normal values for T-1/2 are 82–193 min.

Spirulina Gastric Emptying Breath Test

^{13}C can be incorporated into the edible blue-green algae *S. platensis* by special cultivation techniques. *S. platensis* is nontoxic, and it is used as a food source and nutritional supplement in many parts of the world [17]. The ^{13}C labeled *S. platensis* is usually administered as part of an egg meal giving reproducible $^{13}CO_2$-kinetics in breath reflecting gastric emptying.

A standardized ^{13}C-*S. platensis* GEBT that is easy to prepare in a microwave oven is available through Advanced Breath Diagnostics, Llc and consists of 100 mg ^{13}C-*S. platensis*, 27 g freeze-dried egg mix, 6 saltine crackers, and 180 mL of water. After ingestion, breath samples are be collected at just a few fixed time points (45, 150, 180 min). The samples can be mailed to a reference laboratory for mass spectrometry to determine the $^{13}CO_2/^{12}CO_2$ ratio in the samples. The currently preferred GEBT metric is the percent dose (abbreviated PCD) excreted at time *t* after consumption of the test meal.

There are different mathematical analyses used to derive gastric breath test emptying parameters [18]. The analysis proposed by Ghoos et al. requires a steady state in the $^{13}CO_2$ excretion to have been achieved by the end of the breath collection; otherwise, this needs to be estimated. In many instances, particularly in patients

with severely delayed gastric emptying, this can be overestimated leading to erratic performance of the mathematic modeling for GEBT [18]. Multiple mathematical analysis methods have been proposed for the interpretation of the breath test metrics [4, 19–21], but the linear regression method had the highest concordance correlation coefficient with scintigraphic $T_{1/2}$ [18].

Performance Characteristics of Breath Tests

Intra- and interindividual variations of measurements of GE with the ^{13}C-octanoic acid GEBT were not significantly different from the variations observed with scintigraphy [9].

The intraindividual variations for scintigraphy and the ^{13}C-*Spirulina* GEBT were highly comparable (within 3–4% different) at all time points from 45 to 180 min in healthy subjects. Interindividual variations at each time for the GEBT and scintigraphy were typically about 1–2% higher than intrasubject COVs [12]. As compared with detailed scintigraphy over a period of 4 h, the ^{13}C-*Spirulina* GEBT utilizing 3 time points at 45, 150, and 180 min has a sensitivity of 89% and specificity of 80% for detecting delayed gastric emptying, and a sensitivity of 93% and specificity of 80% for detecting accelerated gastric emptying [12].

Several studies utilizing the ^{13}C-octanoic acid and the ^{13}C –*S. platensis*-based breath tests have documented the effect of pharmacological agents on the gastric emptying parameters in health and diseases, such as diabetes mellitus [20, 22].

Pitfalls and Common Artifacts in Breath Testing

The ^{13}C-containing *S. platensis* undergoes intraluminal digestion before mucosal absorption, hepatic metabolism, and pulmonary excretion. Breath tests assume gastric emptying is the rate limiting step in a body's handling of the ingested ^{13}C-substrate; however, in some disease states it is possible, that other steps may become rate limiting. In the validation studies of the standardized ^{13}C-*S. platensis* GEBT, subjects who had a history of malabsorption due to mucosal disease, pancreatic disease, or liver dysfunction were excluded. Octanoic acid has the advantage that it is absorbed directly from the intestinal lumen without undergoing digestion and postgastric emptying processing of ^{13}C-octanoic acid does not seem to be affected by liver, kidney, or lung disease [23, 24]. Artifacts that may affect both the ^{13}C-octanoic and the ^{13}C-*Spirulina* breath tests include factors that alter the endogenous carbon dioxide production and excretion, such as exercise, thyroid disease, and fever.

When interpreting any gastric emptying study, it is important to be aware that many medications, as well as hyperglycemia which can delay gastric emptying and lead to improper diagnosis.

The best time intervals for breath sampling and the ideal length of the test are not clear. More frequent breath sampling over a prolonged duration (6 h) may increase

the sensitivity and specificity of the test in detecting gastroparesis; however, this often inconveniences the patient, physician, and ancillary staff that has to perform the test. Studies by Camilleri et al. [10] have reduced the number of breath samples needed to assess gastric emptying, but these results are specific to the standardized ^{13}C-*S. platensis* GEBT.

Use of Results in Patient Management

Both the ^{13}C-*S. platensis* and ^{13}C-octanoic acid breath tests are promising as noninvasive, accessible tests that could emerge as widely available and acceptable screening tests for gastric motility disorders.

Gastric emptying rate does not correlate well with symptoms and is poorly predictive of therapeutic responses to prokinetic agents [25, 26]. An abnormal gastric emptying test suggests, but does not prove, that the symptoms are caused by gastroparesis or accelerated gastric emptying.

Stable isotope breath testing has several advantages over gamma scintigraphy, the gold standard method for measuring gastric emptying, including the absence of radiation exposure. Additionally, only limited training is required to administer the breath test; results are not operator independent. The breath test can also be administered in virtually any location, facilitating assessment at the bedside, in the clinic in underserved areas, or at different sites in multicenter research studies. The major disadvantage of the GEBT with ^{13}C-*S. platensis* is the need for normal small intestinal digestion. However, the multiple advantages of stable isotope breath testing make it very appealing for the incorporation into clinical practice.

Conclusions

^{13}C-GEBT are simple, safe, radiation free, and validated test for assessing GE. They are presently used primarily for clinical research in Europe and the USA. They are used clinically in some centers in Europe, but are not presently available for clinical use in the USA.

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Chapter 12
Ultrasonography for Evaluation of Patients with Suspected Gastroparesis

Karen L. Jones, Diana Gentilcore, Trygve Hausken, and Odd Helge Gilja

Keywords Gastroparesis • Ultrasonography • Gastric emptying • Gastric motor function

Introduction

Ultrasonography represents a relatively simple, non-invasive, inexpensive and readily available technique for the assessment of gastrointestinal motor function which has the capacity to assess structural and functional abnormalities. While scintigraphy remains the "gold standard" for the measurement of gastric emptying, it is associated with a radiation burden and requires expensive equipment. Two dimensional (2D) ultrasonography is now used clinically to quantify gastric emptying. Arguably of greater significance is that the use of ultrasonography has also provided fundamental insights into the pathophysiology of disordered gastric motor function – it has been used to evaluate gastric distension/accommodation [1–4], antral contractility [5–7], mechanical deformation (strain) [8–13], transpyloric flow [6, 7, 14], intragastric distribution as well as gastric emptying [14–21]. In this section, the role of ultrasonography in the measurement of gastric emptying, distal and proximal stomach area (accommodation), transpyloric flow and gastric motility, is discussed.

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Gastric Emptying

The 2D measurement of gastric emptying is widely used clinically, particularly in Europe, and has several advantages over other methods. The technique was established in the early 1980s [22] and is relatively easily acquired by instruction from an individual experienced in the technique. It is an indirect measurement of gastric emptying which is determined by quantifying changes in antral area (discussed below) over time [15, 16, 22] following ingestion of a meal [19]. Several test meals have been used, e.g. low nutrient beef soup, beans, pasta, orange juice and dextrose, although in the majority of studies test meals have been liquid or semi-solid [15–19, 22]. The 2D ultrasonography technique has been validated against scintigraphy [16, 19]. It is intriguing that changes in antral area can be used to evaluate gastric emptying from the total stomach, particularly as scintigraphic studies have shown a relationship between total stomach with proximal stomach, but not distal stomach content [23]. In 1986, Holt et al. [16] reported a correlation in measurements of the time for 50% of a low nutrient beef soup to empty from the stomach (T50) between ultrasonography and scintigraphy. Studies by Hveem et al. [19] further validated the technique against scintigraphy in healthy subjects by quantifying emptying of a low nutrient beef soup and high nutrient (75 g dextrose) drink and determining strong correlations between the gastric emptying T50s for ultrasonography and scintigraphy, and modest limits of agreement. In patients with functional dyspepsia, 2D ultrasonography has primarily been used for research purposes to demonstrate overall delayed gastric emptying and occasionally, more rapid "early" emptying [24], while in longstanding diabetes, gastric emptying has been reported to be delayed in ~50% of patients. A limitation of 2D measurements of gastric emptying is that the technique relies on assumptions about the geometry of the stomach based on a single, sagittal, antral image [19] and imaging may be challenging in the obese.

Three dimensional (3D) ultrasonography, described in the mid 1990s, and pioneered by the group in Bergen, Norway, offers significant advantages over 2D, particularly the ability to assess intragastric meal distribution which is often disordered in functional dyspepsia and diabetic gastroparesis [25]. Measurements of gastric emptying by 3D ultrasonography also show greater accuracy, and less variability, than 2D [26]. The use of 3D ultrasonography necessitates scanning in a continuous sweeping movement, commencing proximally at the left subcostal margin with the transducer tilted cranially, and moving distally towards the pylorus [20, 26]. The transducer is fitted with a snap-on sensor to detect information emitted from a positioning and orientation measurement (POM) transmitter that produces a magnetic field, placed next to the subject/patient. Dedicated reconstruction software (EchoPAC-3D) [27] is used to convert images of transverse sections of the entire stomach to volumes (Fig. 12.1), which can then be divided into distal and/or proximal stomach volumes [26].

The use of the 3D ultrasonography technique for the measurement of gastric emptying, was validated initially in vitro in a porcine model, which showed an excellent correlation between true and estimated volumes [26], and subsequently, in humans using a gastric barostat [28]. More recently, the technique has been validated against scintigraphy in both healthy subjects [20] and patients with diabetic gastroparesis [21]. While 3D ultrasonography offers a number of advantages over 2D ultrasonography, currently it is not used extensively for either clinical or research purposes.

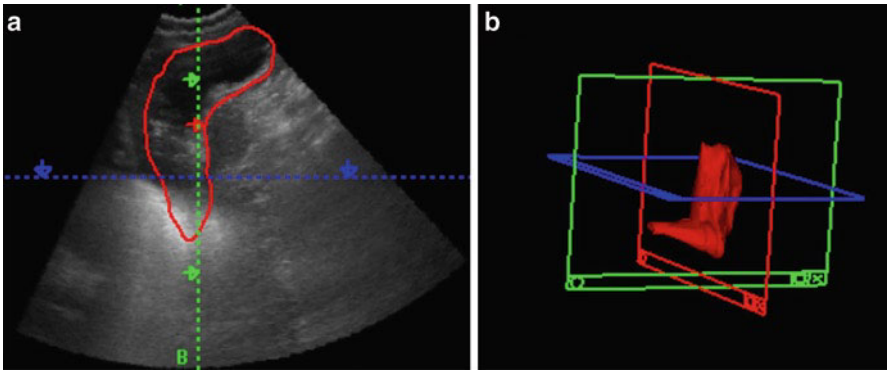

Fig. 12.1 Ultrasonographic image of the stomach, following 3D reconstruction, demonstrating (**a**) region-of-interest and (**b**) 3D reconstructed volumetric image of the stomach

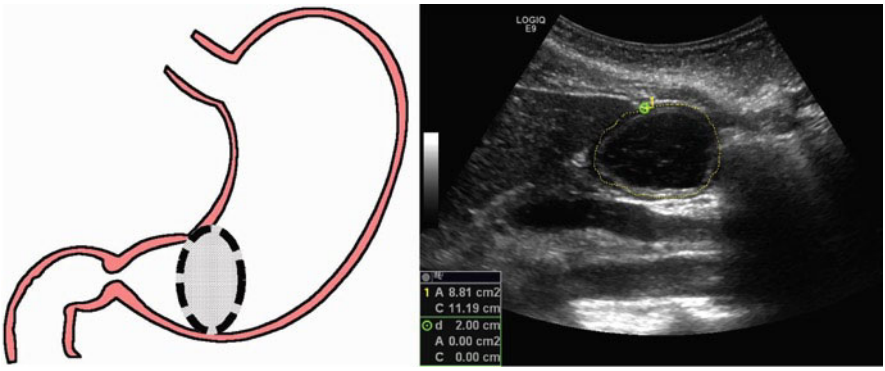

Fig. 12.2 2D sagittal ultrasound image of the antrum

Antral Area

2D ultrasonography has been used to image the distal stomach, thereby providing information relating to antral distension. A probe (3.5–5.0 MHz) is placed over the abdomen and a sagittal image of the antrum, in the region of the aorta and superior mesenteric vein, is obtained (Fig. 12.2) [15, 19]. Studies using 2D ultrasonography have demonstrated that functional dyspepsia is frequently associated with an increase in antral area (both fasting and postprandially) [29], which can be reduced with cisapride [29]. In patients with diabetes, both fasting and postprandial antral area are also frequently increased [30]. Perceptions of fullness and subsequent energy intake have been shown to correlate directly with postprandial antral area in both healthy subjects [31] and the elderly [32], suggesting that antral "distension" is a significant determinant of appetite [31, 32]. The relative simplicity and noninvasiveness of ultrasound is particularly appealing in such studies.

Proximal Stomach (Accommodation)

Both 2D and 3D ultrasonography have been used to evaluate proximal stomach function/accommodation [1, 26, 33, 34]. With the 2D technique, proximal stomach area can be calculated from a sagittal image by drawing a region-of-interest from the top margin down 7 cm along the long axis (Fig. 12.3a) of the stomach [33]. An additional measurement, representing the diameter of the fundus, is derived using an oblique frontal section maintained within 7 cm of the long axis (Fig. 12.3b) of the proximal stomach [33]. 3D volume reconstructions of the stomach can be divided into proximal and distal stomach portions, thereby providing information relating to intragastric meal distribution [26]. Studies using ultrasonography have demonstrated the frequent occurrence of impaired proximal stomach relaxation in both patients with functional dyspepsia [1] and diabetes [35]. In patients with functional dyspepsia both symptoms and proximal stomach accommodation, induced by a meal, improved by administration of sublingual glyceryl trinitrate [36], but not in patients with diabetes [37]. Gastric accommodation using ultrasonography, as assessed by changes in the ratio of the total/proximal gastric volume, is decreased in functional dyspepsia [3, 38] and increased in GERD patients [38]. The "gold standard" for the assessment of proximal stomach accommodation is the gastric barostat but this has significant disadvantages, such as the invasive nature of the procedure and the inability to calculate gastric volume. It should, however, be acknowledged that imaging methods, such as ultrasonography, provide only an indirect measure of gastric relaxation, therefore providing slightly different information about the accommodation process when compared to the barostat; the barostat adjusts volume in response to gastric muscle tone, whereas ultrasonography directly visualises gastric size and volume. Assessment of proximal gastric volumes by 3D ultrasonography has been shown to correlate closely with measurements made with the gastric barostat [3]. In a cohort of 15 patients with functional dyspepsia, as assessed by the barostat, 7 (46%) had abnormal accommodation, compared to 10 (67%) with 3D ultrasonography – 6 patients had

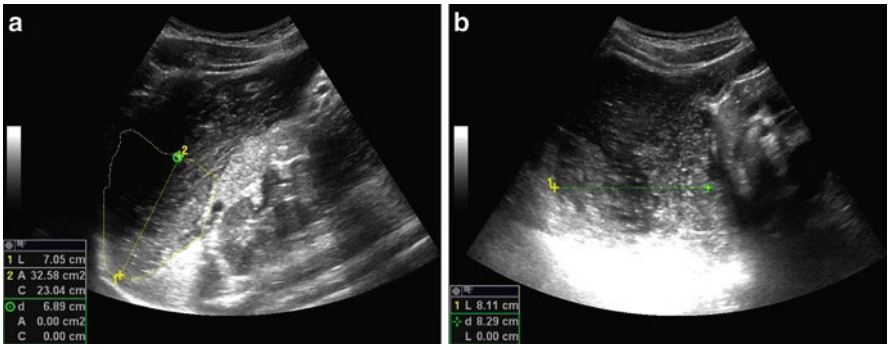

Fig. 12.3 2D ultrasound images of the proximal stomach in (**a**) sagittal section and (**b**) oblique frontal section

evidence of disordered accommodation using both techniques [2, 3]. In both patients with functional dyspepsia and healthy subjects, sensations of fullness are related to distal, but not total, or proximal, gastric volume [3], consistent with observations using 2D ultrasonography [31, 35].

Antropyloroduodenal Motility

Gastric contractions can be divided broadly into two categories – lumen- and non-lumen-occlusive. Manometry is frequently used to assess gastric motility by measuring luminal pressure, but requires invasive intubation of an antropyloroduodenal catheter and is limited to the assessment of only occlusive events. In contrast, ultrasonography has the capacity to assess the frequency and magnitude of both lumen- and non-lumen occlusive events. In healthy subjects who had concurrent antropyloroduodenal manometry and ultrasonography measurements following a low nutrient soup, only ~55% [5, 39] of ultrasonographic contractions were shown to be associated with corresponding gastric manometric pressures, indicating that ultrasonography has the capacity to provide more comprehensive information relating to patterns of antral motility than manometry.

Transpyloric Flow

It was traditionally believed that the stomach emptied at a continuous rate; however, methods to assess gastric emptying were limited in temporal resolution. Studies in dogs [40] and humans [6] have subsequently demonstrated that "gastric" emptying is in fact predominantly pulsatile so that emptying occurs in a series of gushes that may vary on a second-by-second basis. Duplex ultrasound (incorporating both Doppler and B-mode imaging) can be used to measure the direction and velocity of transpyloric flow [6, 41, 42]. Hausken et al. [14] have developed a 3D Doppler technique to determine "stroke volumes" of transpyloric flow episodes. While several techniques have been used to assess transpyloric flow in humans, ultrasonography has the advantage of being able to also provide information relating to gastric emptying and motility within the one examination. While its use is largely restricted to the research setting, considerably more information relating to gastric physiology can be provided by these measurements at low cost.

Gastric Strain Rate Imaging

Gastric strain rate imaging (SRI) is a relatively recent ultrasonography technique, based on tissue velocity imaging, providing quantitative information relating to gastric wall deformation [8–13]. The accuracy of SRI has been validated in vitro in

a porcine model [9]. SRI has the capacity to evaluate the contractile activity of both longitudinal and circular muscle layers and in healthy subjects studies using both SRI and gastric balloon distension demonstrate an inverse correlation between pressure and radial strain [10]. In patients with functional dyspepsia, divided into subgroups of "epigastric pain syndrome" (EPS) and "postprandial distress syndrome" (PDS), antral strain was shown to be higher in EPS patients when compared to both normal subjects and PDS patients during both the fasting state and postprandially [43]. This non-invasive technique is currently limited to the research setting.

Conclusions

Transabdominal ultrasonography offers a number of advantages over other techniques to evaluate gastric motor function in humans. It is non-invasive, readily available, inexpensive, does not involve a radiation burden, can be performed at the bedside and has the capacity to assess gastric emptying, transpyloric flow and antropyloroduodenal motility concurrently. While 3D ultrasonography provides more information about gastric pathophysiology than 2D ultrasonography, it is a more time consuming technique that requires the skill of an experienced operator and relatively expensive equipment. For these reasons 3D ultrasonography should, at the moment, be regarded as an excellent research tool. 2D ultrasonography provides a simple and straightforward assessment of gastric emptying and is currently more suited to the clinical setting for the diagnosis of gastroparesis.

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Chapter 13
Magnetic Resonance Imaging for Gastric Motility

Adil E. Bharucha and Roger C. Grimm

Keywords Gastroparesis • MRI • Imaging modalities • Gastric motor functions

Introduction

Driven by technological advances, the ability of magnetic resonance imaging (MRI) to assess gastric motor functions has substantially advanced since the earliest studies of gastric emptying and antral and small-bowel motility nearly two decades ago [1, 2]. Those studies used the echo-planar imaging (EPI) sequence on a home-built scanner to acquire an image plane within tens of milliseconds using a single shot sequence scheme that allows easy weighting of the sequence to the relaxation times T_1 and T_2 or diffusion and to measure these MRI parameters quantitatively [3]. However, EPI is prone to artifacts and has limited spatial resolution. Since then, imaging modalities have improved substantially, initially through spin echo sequences and more recently with development of fast spin echo and spoiled gradient echo sequences, which provide high-resolution abdominal imaging in a matter of hundreds of milliseconds, permitting GI function, including gastric volumes and contractility, to be evaluated in real time by MRI.

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Advantages and Limitations of MRI for Assessing Gastric Motor Functions

Multiplanar imaging capability, rapid imaging, excellent spatial resolution and soft tissue contrast, and lack of exposure to ionizing radiation are among the advantages of MRI. Since the signal originates from endogenous hydrogen protons, the contrast depends on their physicochemical environment, mobility, and concentration. Imaging parameters can be adjusted to highlight desired characteristics of the organ or test meal being examined and the signal from body fat can be suppressed if desired. With some rapid imaging sequences, high-resolution scans can be obtained within one breathhold to reduce motion artifact in real-time, permitting "*cine*" MRI (or "MRI fluoroscopy"). Since nonionizing radiation is used, repeated scans, e.g., to observe postprandial phenomena at multiple times on one day or for longitudinal assessments over time, are possible. Moreover, providing appropriate imaging sequences are used, MRI can simultaneously measure gastric volumes, emptying, and motility and also document extraluminal disease. Ultrasound can also measure all parameters. However, in contrast to ultrasound, gastric visualization by MRI is not limited by the presence of air in the stomach.

Despite these advantages, the use of MRI to evaluate gastric motility is almost exclusively limited to research, partly constrained by the availability of scanners, scanner time, and expense. Most scanners permit scanning in the supine position only. Studies evaluating gastric motility by MRI have included a relatively small number of healthy subjects and imaging protocols are not standardized. Performance characteristics require further study.

Overview of MR Imaging Sequences Used to Evaluate Gastric Motor Functions

Imaging of gastric motility requires high temporal resolution and lends itself to 2D imaging techniques. Typically, 2D imaging provides higher in-plane than through-plane resolution. Obtainable in-plane resolutions for gastric motility studies range from 1.56 to 3.5 mm with through-plane resolutions in the 5–10 mm range. A variety of sequences (i.e., gradient recall echo (GRE), steady-state free precession (SSFP), EPI, and half Fourier acquisition single-shot turbo spin echo (HASTE) sequences) have been used to evaluate gastric motility (Table 13.1). These sequences have been detailed elsewhere [4, 5]. GRE sequences employ RF and gradient spoiling to remove coherent signal between repetitions of the playout. This produces a robust and stable signal at the cost of spoiling the remaining signal after echo readout. By contrast, SSFP sequences attempt to refocus the entire signal at the end of each playout to increase signal. While this approach accentuates signal in homogeneous areas, imperfections in field homogeneity, as those occuring at air boundaries, which cause magnetic susceptibility interfaces, can cause bands in the resulting image that

Table 13.1 Comparison of studies evaluating gastric motility by MRI

Author, *n*, subject group	Imaging parameters	In plane resolution (mm)	Temporal resolution (s)	Comments
Borovicka, DM with delayed (8) or normal (7) gastric emptying [32]	2D GRE sequence, 2 coronal slices, 120 images over 2 min, shallow breathing	3.1×3.1	1	Cisapride improved gastric emptying and proximal but not distal gastric contractility
Kunz, 8 healthy [40]	2D GRE sequence; Coronal slice, 10 mm thick, 120 images over 2 min	3.1×3.1	1	Evaluated emptying of liquid and solid meals
Marciani, 28 healthy [41]	2D EPI sequence, 8 slices, 10 mm thick, 72 time samples over 3.6 min	3.5×2.5	3	Compared antral motility after liquid, mixed liquid/solid, or mixed viscous/solid meals
deZwart, 6 healthy [42]	2D fast GRE sequence, 1 slice, 10 mm thick, 300–900 s	1.8×3.5	1	Gastric volumes and motility were simultaneously assessed by MRI and a barostat
Ajaj, 6 healthy, [43]	2D SSFP sequence, 1 slice, 5 mm thick, 20 s during breathhold. Scanned with and without 6 mm tag lines	2.0×1.6	1	Metoclopramide increased and scopolamine decreased motility
Ajaj, 10 each healthy, gastroparesis, and pylorospasm, [33]	2D SSFP sequence, 1 slice, 5 mm thick, 20 s during breathhold. Scanned with and without tag lines	2.0×1.6	1	Motility was reduced in gastroparesis and increased in pylorospasm
Kwiatek, 9 healthy, [44]	SSFP with SENSE, 3 slices; 8 mm thick, 120 images over 167 s	1.56×1.95	1.4	Assessment of gastric volumes and motility after 10% glucose
Trier, 10 healthy [15]	SSFP with SENSE, 3 slices, 10 mm thick, interleaved acquisition, 155 s	Not available	1.3	Sequence characteristics refer to assessments performed in right position. Different sequences used to assess gastric motility in seated position
deZwart, 14 healthy [22]	2D fast GRE, 1 slice, 10 mm thick, 300 s	1.8×3.5	1	Compared volumes and motility with MRI with or without a barostat
Bharucha, 20 healthy, 17 dyspepsia [34]	2D SSFP, 3 slices, 10 mm thick, 60 s for each slice	1.6×1.6	0.8	Gastric contractility, which was analyzed by a semiautomated technique, was increased in idiopathic rapid gastric emptying

DM diabetes mellitus, *GRE* gradient recalled echo, *SSFP* steady-state free precession, *EPI* echo planar imaging

increase with distance from the isocenter of the magnet. The EPI sequence samples multiple lines of data with each RF excitation pulse. While this is efficient in time, T_2 decay along the sampling window produces blurring in the phase encoding direction of the image. Additionally, areas of magnetic susceptibility, particularly at tissue–air interfaces, can cause signal voids and signal pileup. Geometric distortions in EPI scans caused by gradient imperfection can also be an issue if care is not taken in pulse sequence design and calibration. The HASTE sequence acquires all image data lines during a single acquisition. It differs from the EPI sequence in that the acquisition of individual lines is separated with RF refocusing pulses. The added refocusing pulses eliminate geometric distortions and susceptibility artifacts found in EPI scans while adding RF energy deposition can cause tissue heating or decreased slice throughput at higher magnet field strengths. Like EPI, HASTE scans will suffer from blurring in the phase encoding direction. Parallel imaging can be used with any of these imaging sequences in a tradeoff of signal for increased temporal or spatial resolution [6]. The sensitivity encoding (SENSE) technique exploits spatial information which can be obtained with a calibration scan of the multiple receiver coils used in a MRI exam. In dynamic exams, such as gastric motility, coil sensitivities would also be dynamic, and a parallel imaging method, such as generalized autocalibrating partially parallel acquisitions (GRAPPA), which employs an embedded dynamic calibration scan, is preferred.

Volumetric scans can be performed with multiplanar versions of any of the previously mentioned 2D sequences or higher through-plane resolution can be obtained with a 3D GRE sequence. One technique is the liver acquisition with volume acceleration (LAVA) sequence, which uses fat suppression along with SENSE parallel imaging.

Assessment of Gastric Volumes

The stomach relaxes or accommodates after a meal, providing room for food to be broken down into smaller particles. This process, referred to as accommodation, can be measured by a barostat or by less invasive techniques [i.e., single photon emission computed tomography (SPECT), ultrasound, or MRI]. Studies with a barostat and separately with ultrasound suggest that impaired accommodation may explain early satiety in functional dyspepsia [7–9].

Most studies evaluating gastric volumes and emptying by MRI labeled the nutrient meal with gadolinium, which appears bright on T_2-weighted sequences allowing the meal to be discriminated from air within the lumen [10–20]. These imaging sequences probably also suffice for measuring total gastric volume under fasting conditions. However, intragastric fluid and air appear dark, and it is challenging to demarcate the boundary between the inner stomach wall and gastric contents or to distinguish between gastric fluid and air with these sequences. Therefore, if it is necessary to discriminate between intragastric air and fluid under fasting and postprandial

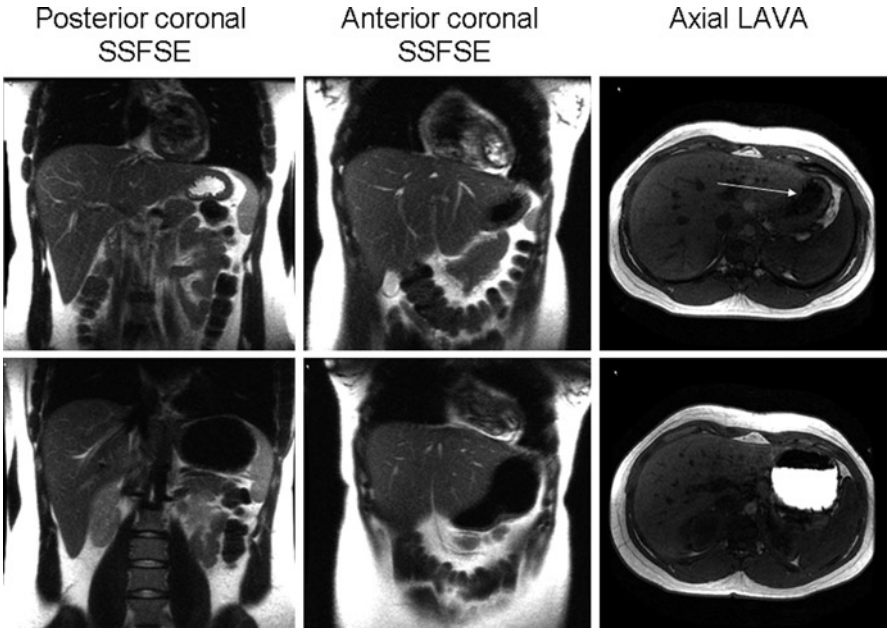

Fig. 13.1 Fasting (*upper panel*) and postprandial (*lower panel*) images acquired by MRI. In the fasting half-Fourier acquisition single-shot turbo spin echo (HASTE) images, the distinction between high signal intensity fluid, which is layered posteriorly (i.e., in the dependent position) and low signal intensity air, which is anterior, is obvious. In the LAVA images, the air–fluid interface is subtle (*arrow*). Postprandially, air and fluid have low signal intensity in HASTE images but easily distinguishable on LAVA sequence (i.e., nutrient labeled with gadolinium appears bright, while air is dark). Reproduced with permission from Fidler JL, Bharucha AE, Camilleri M, Camp J, Burton D, Grimm R, Riederer SJ, Robb R, and Zinsmeister AR. Application of Magnetic Resonance Imaging to Measure Fasting and Postprandial Volumes in Humans. Neurogastroenterol Motil 2009;21(1):42–51

conditions, images should be acquired by two sequences (e.g., two-dimensional T_2-weighted (HASTE) and a three-dimensional LAVA sequences) (Fig. 13.1) [21]. There is excellent agreement between volumes measured by both sequences. The 3D LAVA sequence, which acquires 4-mm slices with 2-mm overlap, images the entire stomach in a single breathhold, while the HASTE sequence images the entire stomach in 28 s. In the largest study to measure gastric volumes [21], comprising 20 subjects, the postprandial change in excess of the ingested meal (300 mL Ensure) was 106 ± 12 mL (Mean ± SEM), which is comparable to the average increase (79 mL) after dextrose (500 mL, 400 kcal) in another study [17]. Together, these observations suggest that postprandial gastric expansion measured by MRI exceeds the volume of the ingested nutrient. However, another study observed that the postprandial gastric volume did not exceed the fasting volume plus volume of ingested nutrient, arguing against the concept of accommodation [22].

The intraindividual, day-to-day reproducibility for gastric volumes measured by MRI was better for postprandial than fasting volumes and better for HASTE than LAVA sequences [21]. Thus, for postprandial volumes and volume changes measured by the HASTE sequence, the within subject coefficient of variation was generally less than 30% and often 15% or lower, which is comparable to the intrasubject coefficient of variation of gastric emptying half-time measured by scintigraphy [23].

The postprandial change in gastric volume is larger when assessed by a barostat than by noninvasive techniques (e.g., ultrasound or MRI), perhaps because an intragastric balloon distends the stomach and displaces food toward the antrum [22, 24]. In the only head-to-head comparison of gastric volumes measured by noninvasive techniques, volumes measured by MRI and SPECT were not correlated, perhaps because the 2 techniques use different approaches to visualize the stomach [21].

In addition to gastric relaxation, swallowed air, gastric emptying, and gastric secretion contribute to the postprandial increase in gastric volume [17, 22, 25], which is also influenced by the ingested meal volume and caloric intake. The postprandial "excess" volume measured by MRI mainly comprises air, which increased by approximately 60 mL in 2 studies [17, 21]. Presumably, some of the postprandial increase in gastric air content represents air displaced from the hypopharynx; indeed, healthy subjects swallow an average of 17.7 mL of air with a single bolus of 10 mL [26]. However, the postprandial increase in gastric air was not significantly different when volunteers were asked to drink the same nutrient liquid volume in 2 or 10 sips, suggesting that the mode of drinking did not significantly affect the postprandial increase in gastric air measured by MRI [21]. However, the number of swallows necessary to swallow a 150 mL aliquot was not counted. When nutrients are infused into the stomach by a nasogastric tube, the volume of gastric air, averaging 188 mL, is stable during gastric filling [27]. Together, these observations suggest that the postprandial increase in gastric air volume probably reflects swallowed air. Conceivably, the recumbent position might limit belching of air trapped in the fundus above the gastroesophageal junction in the recumbent position. However, a comparison of gastric MRI in the seated and recumbent positions revealed significant differences in intragastric air only during the late (i.e., 30–90 min) and not during the early postprandial period (0–30 min) [15].

Using a variety of techniques (i.e., scanning frequently [e.g., every 5 min for 90 min postprandially], administering pentagastrin, comparing effects of smaller and larger meals, measuring gastric pressures during MRI and T_1 mapping), the Zurich group have partially deconvoluted the contribution of gastric secretion and emptying to postprandial gastric volume changes and also evaluated the effects of caloric composition on postprandial gastric volumes [17, 20, 27]. T_1 mapping utilizes the in vitro relationship between the concentration of the contrast agent and the T_1 relaxation time to estimate the dilution of gastric contents in vivo. The key inferences from these studies are as follows. First, gastric volume responses after nutrient delivery can be characterized by a filling phase, during which gastric volume generally increases, followed by an emptying phase, during which gastric volume declines. When nutrients are delivered by a nasogastric tube, which avoids swallowing of air,

the volume of gastric contents increases if the rate of secretion exceeds the rate of gastric emptying [18]. Second, after nasogastric delivery of nutrients, postprandial changes in gastric pressure are remarkably small, averaging <3 mmHg even for a 400 kcal (800 mL) meal. Subsequently, emptying of nutrients into the duodenum triggers gastrointestinal neurohormonal responses, which influence postprandial gastric volumes. Third, with respect to macronutrient composition, the postprandial increase in gastric volume was higher after isovolumic and nearly isocaloric glucose meals than after lipid or protein meals delivered via a nasogastric tube [17]. However, these findings are difficult to interpret since the osmolality of glucose meals used in this study (1,110 mosmol/l) was higher than that of the fat or protein (308 msmol/l) meals. Moreover, while emptying of all 3 nutrients was comparable for the first 45 min, fats emptied at a faster rate thereafter. These observations contrast with other studies suggesting that among isocaloric meals, lipids delay gastric emptying. Perhaps, these differences are also partly explained by the tendency for lipids to flocculate and layer above gastric nonlipid content, which in turn may affect gastric emptying [28].

Assessment of Gastric Emptying

Gastric emptying can be measured from a time series of gastric volumes. However, since a liquid meal is generally used, and because volumes are also influenced by gastric secretion, frequent scans are necessary, particularly early after the meal is given. In the first study to evaluate gastric emptying by MRI from 1992, Schwizer et al. observed comparable gastric emptying profiles of a liquid meal (500 mL glucose [10%]) mixed with Gd-DOTA (gadolinium tetraazacyclododecane tetraacetic acid), when measured by MRI and scintigraphy in 5 healthy subjects and 5 patients with upper gastrointestinal symptoms, of whom 3 had delayed, 1 had normal, and 1 had rapid gastric emptying [10]. Perhaps because these two-dimensional images were acquired with a weaker (0.35 or 0.5 T) magnet and long acquisition times, image quality was poor and correlation between MRI and scintigraphy was imperfect. Thereafter, Feinle compared gastric emptying of isocaloric (523 kcal) liquid (10% Intralipid, 10 g albumin, and water) and mixed solid–liquid meals (pancake with water) by MRI and scintigraphy on separate days in 8 healthy subjects [13]. This is the only study that evaluated gastric emptying of solids and also compared gastric emptying of solids by MRI and scintigraphy. While the liquid meal was labeled with Gd-DOTA, the solid meal was not; both meals were visible on postprandial MR images. The entire stomach was imaged during four 15 s breathholds, separated by an interval during which breathing was permitted, at several time points after a meal. Gastric meal volume was corrected for progressive dilution due to gastric secretion using in vitro data examining the signal characteristics of meals mixed with different concentrations of 0.01 M hydrochloric acid. Consistent with the relatively high caloric content, the average gastric emptying half-times were relatively long, higher for

solids (MRI 129 ± 9 min, Mean ± SEM; scintigraphy 123 ± 11 min) than liquids (MRI 100 ± 7 min, scintigraphy 110 ± 8 min), and comparable for MRI and scintigraphy. However, individual values for subjects were not provided. Moreover, for this study, and for another study which used echo planar imaging, more scanner time was required because the gastric emptying half-time was long, limiting clinical utility [29]. Lauenstein measured gastric volumes and emptying by a time-resolved 3D gradient echo (GRE) sequence whereby 64 contiguous 3-mm thick slices were acquired during an end inspiratory breathhold lasting for 21 s [30].

While most studies have been limited to healthy subjects, delayed emptying of caloric liquids has been demonstrated in diabetic autonomic neuropathy (15 patients), [31] diabetic gastroparesis [32], and functional dyspepsia [30].

Assessment of Gastric Motility

Assessment of gastric contractions requires faster imaging sequences than those used to measure gastric volumes or emptying. These studies have employed a variety of 2D MR sequences, mostly imaging the stomach at one or more slices parallel to the antrum every second over a variable duration (Table 13.1). Images can be analyzed manually [33] or by an semiautomated process by measuring gastric dimensions along equidistant points along the gastric contour, typically along planes perpendicular to an axis drawn through the long axis of the stomach [34]. The contraction frequency, amplitude, and velocity can be calculated by manual or semiautomated analysis (Figs. 13.2 and 13.3). The latter entails a spectral analysis of a time-series of gastric cross-sectional diameters to identify the dominant contractile frequency. Then, the phase at this frequency is plotted against location along the long axis. In these phase shift plots, a linear change (i.e., $R^2 \geq 0.93$) in phase versus location was used to document propagated contractions. The velocity of propagation was estimated from the (inverse) slope of this line. The relative amplitude of contractions was estimated by calculating the magnitude of the Fourier coefficient at the dominant peak, which was normalized to the largest diameter at that perpendicular plane over the entire 60-s epoch. Alternatively, motility can be quantified by "tagging," wherein a reference grid is magnetically superimposed onto the image of the stomach by spatially modulating the magnetization prior to imaging. After imaging, motility is calculated with reference to the spatial grid [33].

While intraluminal manometry may affect gastroduodenal motility, MRI does not [35]. MRI is also more likely than manometry to identify non-lumen-occluding contractions, [36, 37] which is an important advantage since a significant proportion of antral contractions approaching the pylorus as shown previously and confirmed here are nonocclusive [38]. In one study, MRI was more sensitive than manometry for detecting contractions [39].

MRI has been used to document altered gastric motility due to pharmacological modulation and disease (Table 13.1). In one study, proximal and distal gastric contraction parameters were not significantly different among 8 diabetic patients

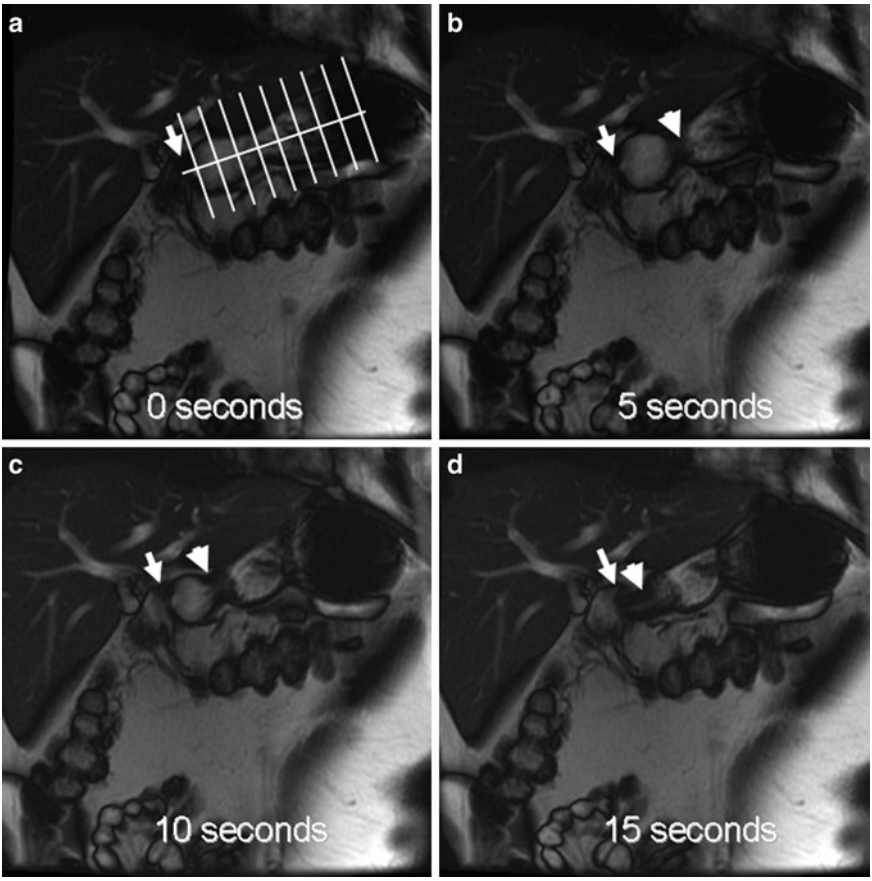

Fig. 13.2 Time sequence of 2D oblique coronal plane MR images (multiphase 2D FISP sequence) of the stomach in a patient with rapid gastric emptying. For clarity, only every fifth image (i.e., at 5-s intervals) is shown. The longitudinal axis and perpendicular planes used to measure gastric dimensions are shown in Panel (**a**). Panels (**b**) and (**c**) depict a propagating contraction (*arrowhead*), which distends the antral bulb proximal to the pylorus (*arrow*). Panel (**d**) shows a terminal antral contraction (*arrowhead*) with filling of the duodenal bulb distal to the pylorus (*arrow*), which contrasts to the typical pattern wherein the pylorus is closed ahead of a terminal antral contraction. Reproduced with permission from Bharucha AE, Manduca A, Lake DS, Fidler J, Edwards P, Grimm RC, Zinsmeister AR, Riederer SJ. Gastric Motor Disturbances In Patients With Idiopathic Rapid Gastric Emptying. Neurogastroenterol Motil 2011;23(7):617–e252

with and 6 without gastroparesis and healthy subjects [32]. However, cisapride increased the amplitude of proximal gastric contractions in diabetic gastroparesis [32]. By contrast, another study observed increased antral motility in pylorospasm and reduced antral motility in gastroparesis [33]. Compared to health, the amplitude of gastric contractions was also increased in patients with functional dyspepsia and rapid but not normal gastric emptying, demonstrating for the first time that patients

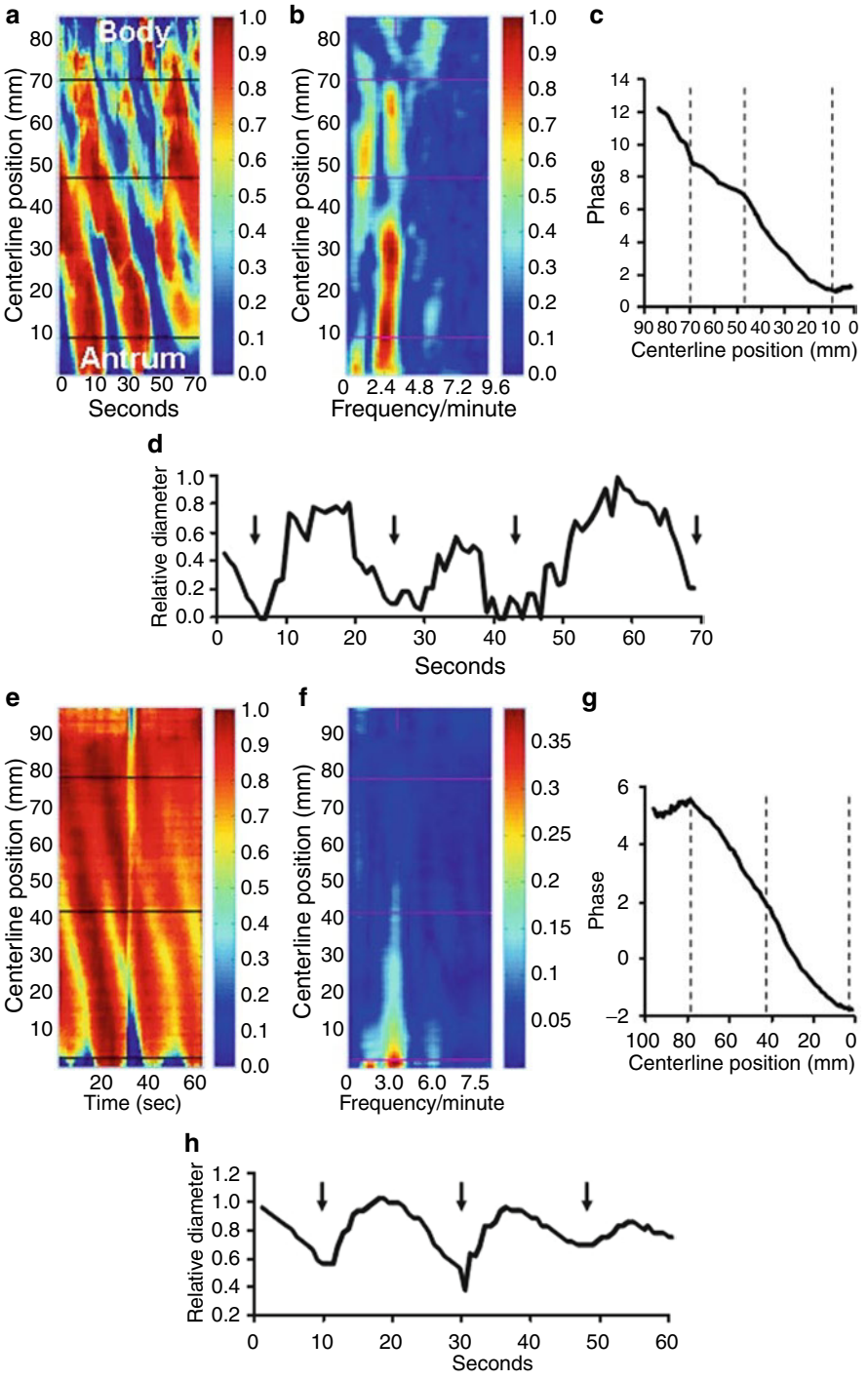

Fig. 13.3 Analysis of gastric contractions ("contractograms") from the same study shown in Fig. 13.2. Panel (**a**) is a time-sequence of gastric cross-sectional diameters at various locations along the longitudinal axis of the stomach (*y* axis). The relative diameter is colored according to the vertical scale to the right of panel (**a**). At each time point, gastric diameter is expressed relative

with idiopathic rapid gastric emptying have increased gastric motility [34]. However, fasting and postprandial gastric volumes and the postprandial gastric volume change were not significantly different between healthy people and patients with dyspepsia.

Other Applications of Gastric MRI

MRI can document to-and-fro flow of contents across the pylorus, [35] Integrated assessments of wall motion by MRI and gastric pressures by a fiber- optic recording system, which is compatible with the MRI environment, can assess the relationship between gastric volumes, wall motion, pressure changes, and emptying in detail [27]. These findings confirm that gastric wall stress (passive strain and active tone) provide the driving force for gastric emptying, but distal resistance to gastric outflow regulates further passage of nutrients.

Summary and a Look at the Future

Among non invasive techniques, MRI has the unique ability to measure gastric volumes, emptying of liquids, and motility without radiation exposure. Offsetting these advantages, most scanners permit imaging in the supine position only. Other limitations of existing studies (i.e., small sample size, predominantly healthy people) can be overcome, particularly as the availability of scanners and imaging sequences increases. While the performance characteristics of MRI for evaluating gastric volumes are excellent, further validation for assessments of gastric emptying and motility is necessary. Although it is unlikely that gastric MRI will replace scintigraphy for evaluating gastric emptying, its ability to simultaneously assess gastric contractility, volumes, and pyloric flow should facilitate our understanding of gastric motor dysfunctions.

Fig. 13.3 (continued) to the maximum diameter at that location; maximum diameter is shown in dark red and minimum in dark blue. Three narrow contractions, which are shaded in blue, propagated from the body to the pylorus (i.e., from 72 to 11 mm along the centerline). The horizontal line at 48 mm separates a proximal propagating contraction from a more slowly propagating distal contraction (see panel **c**). The spectral analysis (Panel **b**) reveals a dominant frequency of 2.4 cpm. The phase shift plot (Panel **c**) shows 2 linear contractions, i.e., from 11 to 49 and from 49 to 72 mm with differing propagation velocities. Panel (**d**) shows the relative diameter change at 59 mm along the line; the contractions, which are identified by black arrows, are not only extremely powerful and completely occlude the lumen, but also relatively prolonged, lasting 10 s or longer. Panels (**e-h**) show gastric contractions ("contractograms") derived from gastric MRI images (multiphase 2D FISP sequence) in a healthy subject. In contrast to Panels (**a-d**), the contractions are weaker. Reproduced with permission from Bharucha AE, Manduca A, Lake DS, Fidler J, Edwards P, Grimm RC, Zinsmeister AR, Riederer SJ. Gastric Motor Disturbances In Patients With Idiopathic Rapid Gastric Emptying. Neurogastroenterol Motil 2011;23(7):617–e252

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Chapter 14
Electrogastrography for Evaluation of Patients with Suspected Gastroparesis

Kenneth L. Koch

Keywords Electrogastrography • Electrogastrogram • Tachygastria • Bradygastria • Gastroparesis • Slow waves • Myoelectrical activity

Introduction

Electrogastrography refers to methods for recording gastric myoelectrical activity from electrodes placed on the abdominal surface. The gastric myoelectrical signal is termed an electrogastrogram or EGG. The EGG reflects the gastric slow wave during fasting, and in the postprandial condition, the EGG reflects the migrating slow wave linked to plateau or action potential activity occurring in the stomach [1]. In normal circumstances, the 3 cpm EGG frequency reflects the 3 cycle per minute (cpm) slow-wave frequency. Changes in the amplitude of the 3 cpm EGG signal after a noncaloric water load or a caloric meal reflect the "electrical summation" of slow wave and plateau or action potential activity [2]. On the contrary, a variety of gastric dysrhythmias have been found in clinical conditions that include nausea, vomiting, and gastroparesis [3–7]. These dysrhythmias include tachygastrias (3.5–10.0 cpm), bradygastrias (0–2.5 cpm), and nonspecific or mixed dysrhythmias, all of which are described below in the evaluation of the patient with suspected gastroparesis.

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Physiological Basis of the Electrogastrogram

The stomach has a "pacemaker region" located on the greater curvature between the fundus and the proximal corpus [8]. From this pacemaker region, spontaneous electrical events termed slow waves originate and migrate in a ring-like "electrical halo" across the corpus and antrum to the pylorus at approximately 20 s intervals. As one wave front of slow wave terminates in the antrum, another electrical wave sequence has begun to form and migrate distally from the pacemaker region. Thus, the normal slow wave frequency recorded by EGG is approximately 3 cpm (2.5–3.5 cpm) in healthy humans [8, 9].

The interstitial cells of Cajal (ICCs), located between the circular and longitudinal muscle layers (ICC-MY), are the "pacemaker cells" responsible for the slow wave frequency of 3 cpm [10]. In the postprandial period, recurrent peristaltic waves produced by circular muscle contractions triturate the ingested food and then empty the nutrient chyme into the duodenum. The electrophysiological basis of circular muscle contractions involve plateau potentials or action potentials linked to slow waves. This linkage of plateau potentials and slow waves results in the peristaltic contractions required for trituration and emptying of foods at a normal rate [9]. The normal rate of emptying also requires normal fundic motility, antral-duodenal coordination, and appropriate vagal-sympathetic neural inputs to the stomach for the type of ingested meal [11]. The ingested food itself, ranging from carbohydrate and protein to fat, also affects the gastric neuromuscular activity required for mixing and emptying. When one or more of these elements of gastric electrophysiology and/or neural-hormonal activity is abnormal, then the rate of gastric emptying may become delayed and the result is gastroparesis [11, 12].

Slow waves produced by the ICCs are crucial elements in the organization of normal gastric peristalsis in the postprandial period. ICCs are decreased in murine diabetes and gastroparesis secondary to diabetes in humans [13, 14]. Furthermore, in patients with gastric dysrhythmias and nausea who were treated with domperidone or cisapride, symptoms were reduced and normal 3 cpm EGG activity was restored [15, 16]. These observations suggest gastric dysrhythmias are a "biomarker" for the symptom of nausea and also represent a key pathophysiological mechanism for the delay in gastric emptying. The presence of gastric dysrhythmias (e.g., tachygastria) disrupts the normal 3 cpm EGG rhythm and the associated peristaltic contractions to varying degrees.

Recording EGGs in Patients with Symptoms Suspicious for Gastroparesis

Recording the EGG is relatively simple with the dedicated hardware and software now available. However, the electrodes must be applied properly and the raw EGG signal must be carefully inspected to identify quality EGG signals for analysis and movement artifacts that distort EGG signals. *Electrodes*. High-quality, fresh, disposable electrodes such as those used for EKG recording are recommended.

The electrodes should show little bias or offset potential since the EGG signal is relatively low amplitude and low frequency. *Recording Equipment*. A high-quality recording system is needed to amplify and process the 100–500 μV EGG signals. Several medical device companies produce complete EGG recording and analysis systems that include appropriate amplifiers and filters with analog-to-digital boards that digitize the EGG signal for analysis with software (e.g., 3CPM Company, Towson, MD; Alpine BioMed, Fountain Valley, CA). Visual display of the raw EGG signal is very important to select artifact-free EGG signal for visual or computer analysis. *Electrode Placement*. Electrodes are placed on the skin surface of the epigastrium over the general area of the corpus and antrum of the stomach. The first active electrode is placed approximately 2 fingerbreadths below the left anterior rib margin in the midclavicular line. The second active electrode is placed midway between the umbilicus and xiphoid on the midline of the abdomen. The reference electrode is placed two fingerbreadths below the lowest anterior rib on the right side along the midclavicular line [1].

EGG Recording Procedure

Patients fast after midnight and then ingest a 200-kcal breakfast of two pieces of toast and 4 oz of apple juice 2 h prior to the EGG test to standardize the baseline EGG recording. By controlling the pretest meal, a consistent baseline EGG is obtained prior to provocative water load or caloric test meal [3]. Before placement of the EGG electrodes, the patient's skin must be prepared by shaving excess hair and cleaning the area with alcohol to lower electrical resistance and achieve an optimal electrode–skin interface. This is a very important part of the EGG recording procedure. If the electrical resistance between the electrode and skin is high, then the EGG signal amplitude will be decreased and artifacts may increase in the signal. The best EGG recordings are obtained if the patient reclines 30–45° in a comfortable chair. The patient should be instructed to minimize talking and movement during EGG recording to prevent movement artifacts. If possible, the patient should be in a quiet room separated by some distance from the person doing the testing. Loud noises, crying children, and other stimuli that might startle the patient should be avoided. Movement of limbs or body may physically disturb the electrode–skin interface and create movement artifacts in the EGG signal.

Analysis of EGG Recordings

The EGG signal is channeled from the amplifier to an analog to digital (A/D) converter. The signal is digitized into a series of numerical values representing discrete voltage levels of the raw EGG signal. A/D conversion units typically allow a wide range of sampling rates, such as 4.267 Hz to prevent alias. Alias refers to the process whereby unwanted high-frequency components, such as the EKG, appear under the alias of the desired low-frequency signal, in this case the EGG [17].

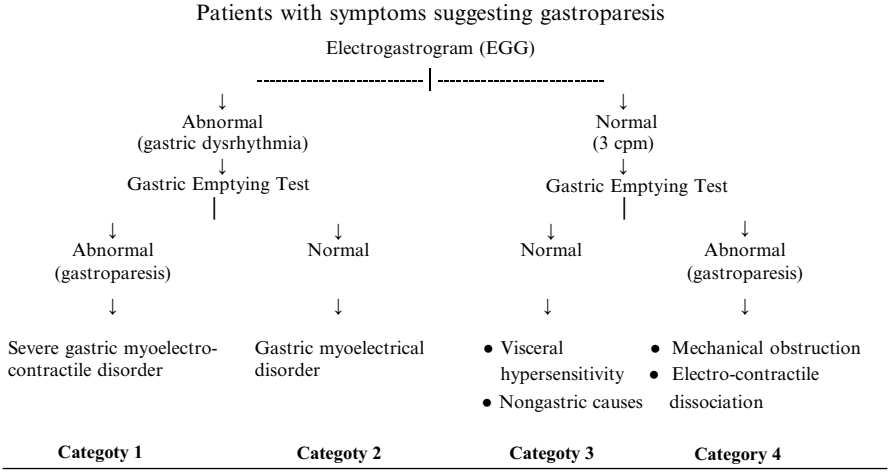
Once the entire EGG recording has been digitized, the data must be preprocessed to meet the assumptions of FFT analysis; therefore, analysis of at least 4 min of EGG data is recommended [17].

Evaluation of Patients with Suspected Gastroparesis

The possibility of a gastric neuromuscular disorder such as a gastric dysrhythmia or gastroparesis should be considered in patients who have unexplained nausea, vomiting of undigested food, early satiety, prolonged fullness, and vague epigastric discomfort, and in whom upper endoscopy is normal. The EGG recording is a part of the neuromuscular evaluation of the stomach which includes assessment of solid-phase gastric emptying [3, 12]. Several techniques for measuring solid or liquid food emptying are described in other sections. However, the standard gastric emptying tests do not reveal the *mechanism* of the gastroparesis. The EGG test is a diagnostic test to determine the status of gastric myoelectrical activity at baseline and after a provocative test such as the noncaloric water load test [3] or a nutrient-based satiety test [18]. The combination of a gastric emptying study and an EGG with provocative test is analogous to the study of cardiac neuromuscular function during which cardiac output (by echocardiography) and the electrical rhythm (by EKG) during the exercise stress test are measured in patients being evaluated for palpitations or chest discomfort. Similarly, "gastric output" is measured with the solid-phase gastric emptying study and the electrical activity of the stomach is measured with the EGG. Thus, the EGG recording results are important in interpreting the cause of the gastric emptying results and the upper gastrointestinal symptoms. Table 14.1 outlines the four pathophysiological categories that are defined when EGG and gastric emptying tests are combined.

As shown in Table 14.1, the EGG results indicate the presence of gastric dysrhythmias or normal 3 cpm EGG activity. In patients with gastroparesis and gastric

Table 14.1 Combined electrogastrogram and gastric emptying test results in patients with suspected gastroparesis



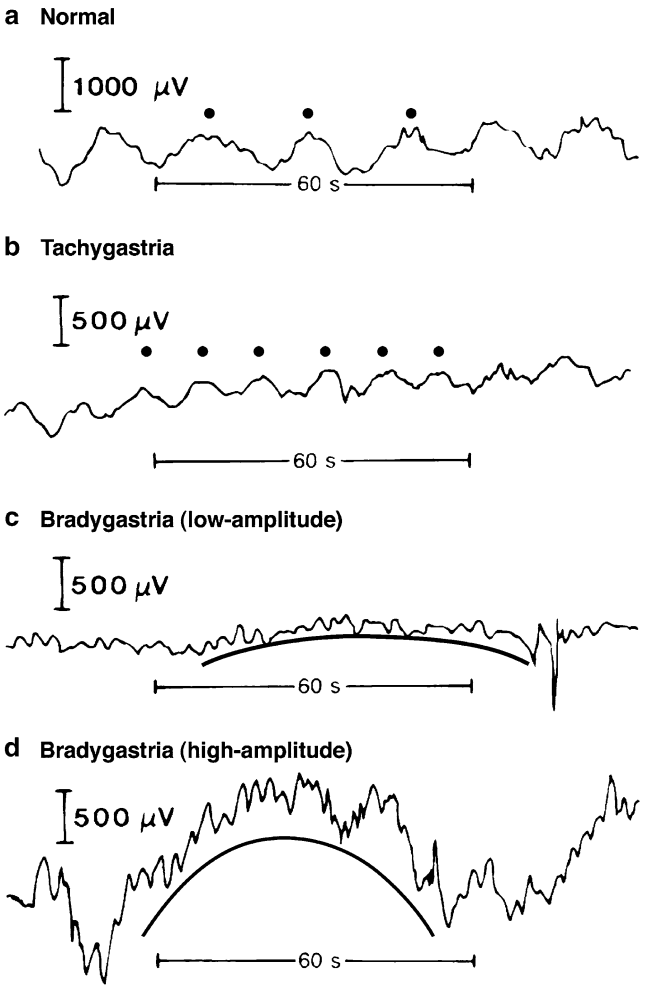


Fig. 14.1 Normal 3 cpm, tachygastria, and bradygastria signals recorded with EGG methods

dysrhythmias, electrical and contractile abnormalities are both present (Category 1). On the contrary, a normal 3 cpm EGG in a patient with gastroparesis (Category 4) suggests mechanical or functional obstruction [7]. Electromechanical dissociation is another physiological explanation for this finding. Some symptomatic patients have a dysrhythmia only (Category 2) and other patients have normal EGG and emptying tests (Category 3). In recording the EGG before and after a provocative test meal, the EGG rhythms of greatest interest occur in the time after the test meal is completed, the time when the neuromuscular apparatus of the stomach has been challenged with a water volume or food. It is during the postingestion period that the diagnosis of normal 3 cpm rhythm, tachygastria, bradygastria, or mixed gastric dysrhythmia is made (Fig. 14.1).

EGG Test Results in Patients with Suspected Gastroparesis

An EGG diagnosis of normal 3 cpm activity is associated with a normal 2 or 4 h gastric emptying study 95% of the time [3]. However, high-amplitude 3 cpm EGG signal is unusual and discordant in the patient with documented gastroparesis (Fig. 14.2). This discordant finding of 3 cpm EGG activity and gastroparesis suggests that the interstitial cells of Cajal are normal, but the gastric smooth muscle cell contractions are unable to empty the test meal. The reasons for this discordant finding may be divided into two categories: (a) obstruction, e.g., a stenosis or "spasm" at the pylorus or postduodenal bulb region, or (b) electromechanical dissociation [7]. This finding of normal 3 cpm EGG and gastroparesis is clinically important because a mechanical obstruction at the pylorus (obstructive gastroparesis) can be relieved with pyloric dilation, stents or surgery. Other forms of obstruction such as pylorospasm with "functional" obstruction are more difficult to prove, but may be the mechanism of "obstructive gastroparesis" in some patients. Right upper quadrant postprandial discomfort in patients with gastroparesis and a normal 3 cpm EGG rhythm suggests this possibility. These patients may undergo injection of Botox 100–200 mcg into

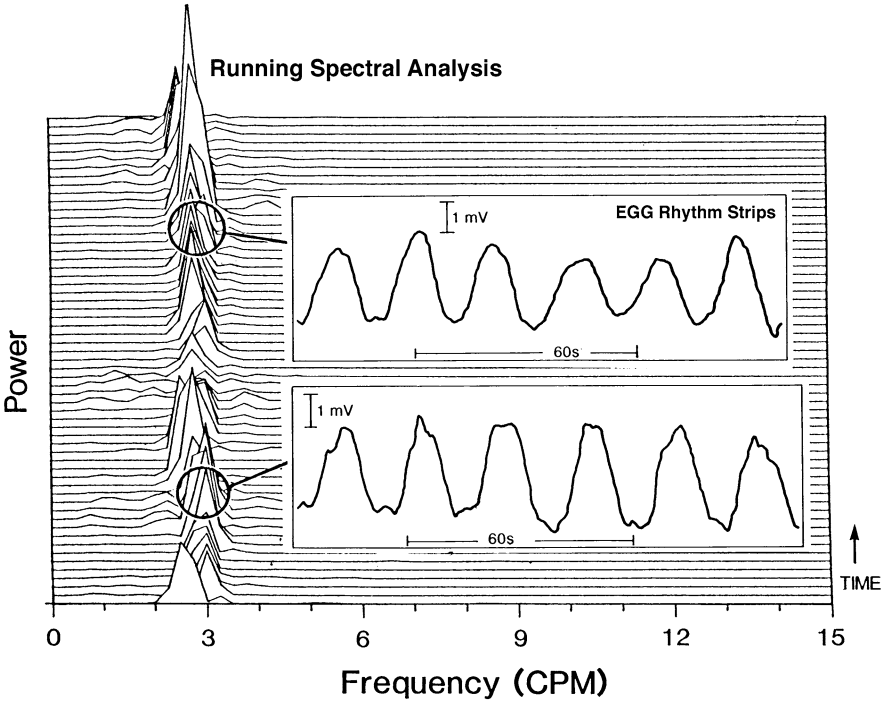


Fig. 14.2 Running spectral analysis of EGG signals recorded from a patient with obstructive gastroparesis due to pyloric channel narrowing from chronic ulcer disease. Note the extremely regular and high amplitude EGG signals in the rhythm strip. The running spectral analysis of the EGG recordings shows an extremely uniform series of peaks at 3 cpm

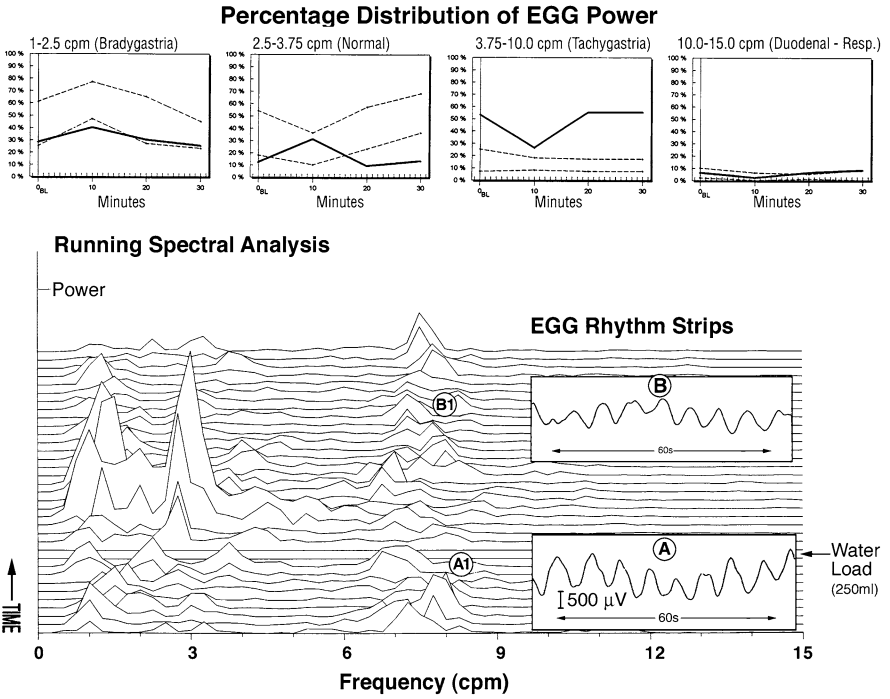


Fig. 14.3 Running spectral analysis of the EGG signal recorded before and after a water load of 250 ml in a patient with idiopathic gastroparesis. The EGG rhythm strips show a 7–8 cpm tachygastria. The running spectral analysis shows most peaks before and after the water that range from 7 to 8 cpm. There are several peaks at 3 cpm immediately after water load volume was ingested, but few peaks at 3 cpm thereafter

the pylorus to help the symptoms and improve the rate of the gastric emptying [19]. In the rare case where the EGG shows normal 3 cpm signal with normal amplitude and there is no mechanical obstruction and no pylorospasm to explain the gastroparesis, electromechanical dissociation may explain the gastroparesis.

Gastric dysrhythmias, on the other hand, are seen more frequently than the 3 cpm pattern in patients with gastroparesis [7]. These patients may have tachygastrias which range in frequency from 3.5 to 10 cpm (Fig. 14.3). These rapid electrical waves generally originate in the antrum and may be unifocal or multifocal in nature. The presence of tachygastrias and bradygastrias (0–2.5 cpm) interfere with normal 3 cpm slow wave activity and disrupt normal gastric peristalsis. The correction of these gastric dysrhythmias and restoration of 3 cpm rhythm with cisapride and domperidone is associated with improvement in nausea [15, 16]. Thus, gastric dysrhythmias also represent a peripheral pathophysiological mechanism for nausea symptoms. Correction of the dysrhythmias may not affect the rate of gastric emptying, depending on the function of the ENS and smooth muscle.

Recent studies suggest the enteric nerves and the ICCs are damaged more often than smooth muscle in patients with type 1 and type 2 diabetic and idiopathic gastroparesis [20]. The presence of 3 cpm EGG activity correlated with normal numbers of ICCs in gastric biopsies; on the contrary, the patients with poor 3 cpm activity and gastric dysrhythmias had greater loss of ICCs and a poorer response to gastric electrical stimulation [21, 22]. Thus, when the EGG test shows normal 3 cpm activity, then the response to gastric electrical stimulation is improved in patients with refractory nausea and vomiting from gastroparesis compared with patients who have diminished 3 cpm EGG activity [21, 22]. These studies indicate that the preservation of some level of ICCs and of 3 cpm EGG activity is a marker for more favorable response to electrical stimulation therapy.

Other electrocontractile abnormalities may result in abnormal EGG tests and contribute to the delay in gastric emptying: abnormal coupling of the ICC activity to the smooth muscle, abnormal enteric neuron function, and/or abnormal gastric smooth muscle. Recent histological studies of full thickness gastric tissues from patients with gastroparesis showed that 83% of the patients had abnormalities in the ICCs or neural elements of the gastric wall [20]. Furthermore, almost 40% of the patients had increased inflammatory cell infiltrates (macrophages) in the myenteric plexus, while the smooth muscle was normal in these subjects with diabetic or idiopathic gastroparesis [20]. Thus, abnormalities of ICCs and intrinsic neurons of the stomach are common in patients with gastroparesis and reflect the histological underpinnings of gastric dysrhythmias and poor smooth muscle function, abnormalities that alter the rates of gastric emptying and ultimately result in gastroparesis. The EGG recordings provide important clinical insights into the pathophysiology of gastroparesis and associated nausea, much like EKG, and cardiac output recordings provide insights into the pathophysiology of heart failure and associated vague symptoms. In most cases "idiopathic" gastroparesis is not truly idiopathic but is secondary to gastric dysrhythmia (e.g., tachygastria) and related smooth muscle dysfunction.

Conclusion

In summary, patients with gastroparesis may have gastric dysrhythmias or normal 3 cpm activity. Thus, the EGG test results provide important information with therapeutic implications about the pathophysiology of the gastroparesis in each patient. The discordant finding of a high-amplitude 3 cpm EGG rhythm and gastroparesis requires an evaluation to exclude treatable mechanical or spasm-related pyloric dysfunction. The EGG pattern may also help in the selection of patients with gastroparesis who will respond to gastric electric stimulation. Tachygastrias and bradygastrias represent the electrical abnormalities underlying delayed gastric emptying and upper GI symptoms. Thus, EGG test results complement and provide insights about gastric emptying test results. Future studies to determine the mechanisms of gastric dysrhythmias will aid development of antiarrhythmic drugs to correct the dysrhythmias and improve gastric emptying function and symptoms.

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Chapter 15
Antroduodenal Manometry for the Evaluation of Patients with Suspected Gastroparesis

William J. Snape, Jr.

Keywords Antroduodenal manometry • Gastroparesis • Migrating motor complex • Pseudoobstruction • Partial small-bowel obstruction • Dyspepsia

Introduction

The symptom pattern of patients with a documented delay in gastric emptying has been evaluated recently in a large cohort of patients entered in the Gastroparesis Registry supported by the NIH. The predominant symptoms of gastroparesis are nausea, vomiting and in a large percentage of patients, abdominal pain. Nausea is the predominant symptom in 34.5% of 319 patients and occurs in 84.3% of patients. Similar numbers of these patients have vomiting (28.9%/68.7%) and abdominal pain (19.8%/71.8%) (personal communication). Interestingly, patients with chronic nausea, vomiting or abdominal pain may have a normal gastric emptying. This chapter addresses how antroduodenal manometry can assist in managing patients with chronic nausea, vomiting and abdominal pain by measuring baseline gastric, pyloric, and small intestinal contractions and the response to a meal or drugs.

Physiology of Gastric Emptying

The stomach and the small intestine work as a coordinated unit to process and utilize ingested food, propelling the digested and triturated food distally out of the stomach and down the small intestine. In addition, coordinated aboral contractions of the

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stomach and small intestine prevent the reflux of intestinal contents back into the stomach. Disturbance of this coordinated pattern alters the orderly aboral propulsion of luminal contents through the stomach and intestines leading to different clinical conditions such as gastroparesis, functional dyspepsia, or intestinal pseudoobstruction, all of which can be associated with delayed gastric emptying. At this time, it is unclear if these different clinical syndromes are associated as part of a spectrum of disease.

The stomach has multiple functions including accommodation to ingested food, trituration or grinding of the food, and controlled emptying into the small intestine. Accommodation is a neural reflex that initiates an active relaxation of the fundus and the proximal body of the stomach, allowing the stomach to serve as a reservoir for food as it is eaten. This function is evaluated best with the barostat, which measures changes in tone in the stomach. Powerful antral contractions then grind the food and propel the food into the small intestine. The coordinated propulsion of the food into the duodenum is dependent on peristaltic contractions in the antrum, relaxation of the pylorus, and contractions in the duodenum coordinated with the stomach and pylorus. High-pressure or uncoordinated contractions in the duodenum can decrease the rate of gastric emptying [1]. These motor functions of the distal stomach and small intestine are best measured with antroduodenal manometry. Pyloric sphincter pressure can be measured by discrete manometric ports, although a perfused sleeve manometer may provide more accurate measurements.

Phasic contractions in the stomach are a result of the rapid depolarization of the smooth muscle membrane initiating the release of calcium from the intracellular stores. The frequency and rhythm of the contractions is determined by the gastric pacemaker on the greater curvature of the proximal body of the stomach. Interstitial cells of Cajal (ICC) are present throughout the human stomach and small intestine within muscularis propria and myenteric plexus, forming both the gastric/intestinal pacemaker and conduction system relaying the rhythm throughout the gastrointestinal wall [2]. The ICC in the myenteric plexus are spontaneously active and set the pace of the stomach or intestine. The intramuscular ICC form nexuses between both myenteric nerves and smooth muscle cells and integrate the control of smooth muscle contractions [3]. A distinct small intestinal pacemaker is present approximately 10 cm distal to the pylorus in the feline small intestine [4]. The decreasing frequency gradient in the distal small intestine appears due to slow-wave drop out from the electrical refractory period of the smooth muscle. The ICC also paces intestinal motility in humans, generating a plateau of slow-wave frequency at approximately 11 cycles/min that extends into the proximal jejunum with a decreasing slow-wave frequency gradient distally in the small intestine [5].

The frequency of contractions differs between the stomach which is 3 cycles/min and the duodenum at 11 cycles/min. It is surprising that muscles that are spatially close have such differing slow-wave frequencies. Evidence in mice and rats suggests that the ICC and slow-wave activity are absent in the pylorus [6]. However, ICC may be present in the pylorus in humans [7]. In healthy controls, pyloric contractions are a mixture of antral-type and duodenal-type contractions with or without tonic elevations in the basal pressure. Tonic and phasic pyloric contractions increase

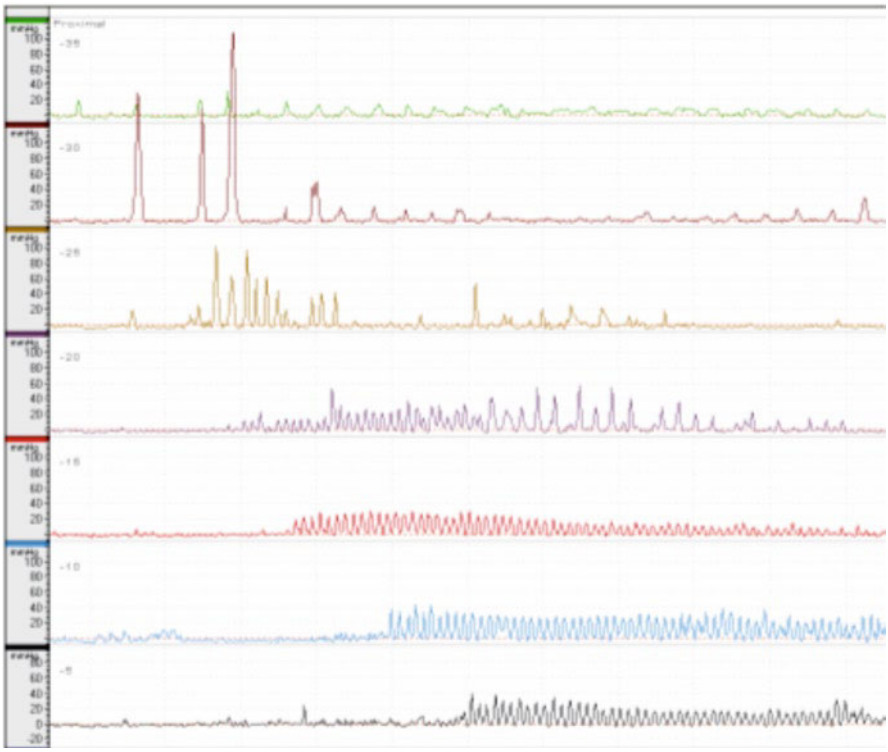

Fig. 15.1 Fasting antroduodenal manometric tracing from the stomach (*top* 2 ports) and duodenum (*bottom* 6 ports). The normal phase 3 of the migrating motor complex propagates from the antrum into the proximal jejunum

resistance across the antroduodenal junction, giving rise to gastric retention of solid particles [8].

Different patterns of gastric and intestinal contractions occur depending on whether the patient is fasting or has recently eaten food [9]. Normally during fasting, there is a well-defined pattern of contractions (Fig. 15.1) ranging from quiescence (phase 1) through intermittent contractions (phase 2) and continuous contractions at the inherent frequency of the stomach or small intestine (phase 3). This pattern cycles approximately every 90 min in humans and is responsible for the aboral flow of gastrointestinal contents during fasting. The Phase 3 of the migrating complex is important for transporting nondigestible objects from the stomach and reducing the bacterial flora in the small intestine by periodically transporting the luminal contents distally.

Eating switches the pattern to a fed pattern which initiates increased contractions in the stomach and small intestine. The length of time that the patient's gastrointestinal tract remains in the fed state is determined by the volume and the fat content of the meal. In the stomach, the contractions grind solid food into particles 2–3 mm in size

that can be emptied through the pylorus at a rate of 2 kcal/min. Liquids empty through a different mechanism controlled by pressure in the proximal stomach. The postprandial small intestinal contractions mix the intestinal contents with the digestive enzymes and move it along the small intestine at a rate optimal for absorption.

Locally released neurotransmitters or circulating gut hormones are also important in the control of the migrating complex [10]. The gut hormone, motilin, stimulates the gastric component of the migrating complex through receptors on the smooth muscle cells or on the presynaptic neurons in the enteric plexus [11, 12]. In humans, motilin stimulation initiates a migrating complex only in the antrum and generally does not stimulate phasic increases in pyloric or small intestinal contractions [11]. Ghrelin, a newly described hormonal agent, has been implicated in the possibly physiologic control of gastric motility [13]. This compound may work through a receptor on the smooth muscle, which is similar to the motilin receptor, or through cholinergic nerves [14, 15]. In the small intestine, the migrating complex is initiated by opiates [16] and somatostatin agonists.

Pathophysiology of Gastroparesis

Different patterns of altered antroduodenal motility are associated with upper abdominal symptoms. Electrogastrography and antroduodenal motility were abnormal in many patients with functional dyspepsia [17]. However, the abnormalities do not necessarily correlate with each other. Antral hypomotility may delay gastric emptying and cause abdominal pain, nausea and vomiting [18, 19]. Antral hypomotility may be associated with a long lag phase, which will prolong the time necessary for the stomach to empty a solid meal [20]. The lag phase is a variable time period used to grind the meal into small particles that empty in a linear emptying pattern. In addition to antral hypomotility, diabetic patients with recurrent nausea and vomiting have a prolonged duration of pyloric activity during fasting and after feeding. Pylorospasm, defined as the prolonged (>3 min) elevation of the basal pyloric pressure >10 mmHg, occurs in approximately 60% of patients with gastroparesis, particularly diabetic gastroparesis [8].

Pathophysiologic alterations of the smooth muscle (myopathic) or neurons (neuropathic) will cause an abnormal manometric appearance, which disrupts the orderly movement of content out of the stomach and through the small intestine [21–23]. Myopathy is reflected by low-amplitude contractions that are under normal neural control. Lack of smoothelin-A, which binds to actin, decreases smooth muscle contraction in mice [24]. In neuropathy the contractions have normal or increased amplitude, but the contractions are uncoordinated because altered neural control. The presence of abnormal neural control of the antroduodenal manometry is generally identified by the absence of a phase 3 of the MMC, or retrograde uncoordinated migration of the phase 3 of the MMC. The migrating motor complex is associated with the emptying of indigestible materials from the stomach and cleansing

of the small intestine [25]. If the complex is disrupted in the stomach, the patient has an increased likelihood of developing bezoars or if disrupted in the small intestine they may have small-bowel bacterial overgrowth [26, 27].

Techniques for Recording Antroduodenal Manometry

Water-perfused or solid-state catheters are typically used to record antroduodenal manometry tracings. Recently, an ingestible capsule has been developed to record pressure from the stomach and small intestine [28, 29]. Magnetic resonance and ultrasonography are used in some centers to measure antroduodenal motility.

Water-perfused catheters have side holes, which measure intraluminal pressure by a constant flow of water. Contractions of bowel segments occlude the side holes and alter the resistance to the flow of water. Water-perfused manometry requires a low compliance, pneumohydraulic perfusion system linked to a multilumen catheter and external stain gauge transducers [30].

Solid-state manometers respond more quickly to the pressure event giving a higher fidelity response. The solid-state catheter may record a higher percentage of pressure events. The cost of these catheters has decreased and they can be easily repaired. A recent report describes the use of high-resolution manometric technique for recording gastric and small intestinal motility [31].

The number and spacing of manometry sensors can be variable depending on the desired information from the study. Sensors can be placed 1–2 cm apart if localized segments or sphincters are being studied. Sphincter pressure also can be accurately measured using a water perfused or electronic sleeve, which records the highest pressure over a short segment. If the study of longer segments is desired, sensors can be placed 5–15 cm apart. To evaluate adequate propagation of a migrating motor complex, the length of small bowel measured should be >20 cm.

The antroduodenal manometric test is of variable length. Most of the literature reports motility over a relatively short period of time (5 h). The use of perfused catheters for antroduodenal manometry restricts the recording of antroduodenal manometry to short periods of time [27]. However, studies using solid-state catheters can run for 24 h. The longer studies allow evaluation of the effect of sleep and different meals on antroduodenal motility. The shorter studies should be longer than 3 h to have a reasonable chance of observing the phase 3 of the migrating complex. The motility tracing is analyzed for the presence of a migrating complex during the fasting period and the conversion to a fed pattern after a meal. Although there is generally a migrating complex every 90 min, a 3–6 h fasting period is necessary to define the migrating complex, since some normal subjects may have a longer time interval between the migrating complexes. The fed response should be recorded for at least 1 h after eating. The response is irregular and frequent contractions throughout the stomach and small intestine. The contractions may not begin for up to 20 min after the meal. There may be a prolonged delay if gastric emptying is

slowed. The majority of the studies examine the effect of fasting and eating a meal on the gastric and the small intestinal contractions in normal subjects and patients with different clinical conditions [19, 21, 27, 32, 33]. Using this technique, clinicians are able to determine if the patient has abnormalities of the fasting or meal-related activity.

Since opiates and prokinetic drugs can alter the antroduodenal motility pattern, these should be stopped at least 12 h before the study. Hyperglycemia delays gastric emptying and also decreases the antral contractions. Therefore, the patient should be euglycemic for the study.

Parenteral administration of pharmaceutical agents also can demonstrate normal or abnormal responses of the stomach or small intestine [34, 35]. Drugs that stimulate specifically the stomach or the small intestine are used to define an abnormality in the antroduodenal region. Erythromycin binds to the motilin receptor and initiates a prolonged period of phasic gastric contractions that mimics the migrating complex in the stomach [36]. Erythromycin usually does not stimulate increase in contractions of the pylorus or the small intestine [37]. Octreotide stimulates a similar prolonged increase of small intestinal phasic contractions, with inhibition of stomach contractility [26, 34, 38]. Octreotide blocks the fed response in the stomach and initiates a phase 3 in the small intestine possible by neural inhibition mediated in the enteric plexus [39, 40].

The use of solid-state catheters placed through the nose allows antroduodenal manometry to be performed for longer periods of time, say up to 24 h. Solid-state catheters also allow high-resolution manometry of the stomach and small bowel. High-resolution manometric recordings from the upper gastrointestinal tract show multiple pacemakers and retrograde contractions in the antrum and small intestine [31].

A wireless motility capsule (SmartPill) containing a pressure, pH, and temperature sensor can be used to measure simultaneously gastric emptying and pressure in the stomach and small intestine [28]. The movement through different regions of the gastrointestinal tract can be measured by changes in pH (stomach – acidic, small intestine – alkaline, and the cecum – acidic) and temperature, as the capsule exits the body. The emptying of the capsule from the stomach correlated closely with radionuclide gastric emptying and was associated with a burst of high-amplitude gastric contractions. Small-bowel contractions and transit changes can also be measured using the wireless motility capsule [41].

Interpretation of Antroduodenal Manometry

Antroduodenal manometric recordings are recorded during fasting and after stimulation with either a meal or pharmaceuticals. The tracing is evaluated for the presence and pattern of the phase III MMC during fasting, and the types of contractions after meals or stimulating drugs such as erythromycin, octreotide, or neostigmine. Additionally, the amplitude of contractions is measured in the stomach, pylorus, and

small intestine during the studies. Thus, these studies provide information on altered neural control of small intestinal contractions and the integrity of the smooth muscle response.

During fasting, the phase 3 of the migrating complex in the antrum and duodenum is defined as contractile activity at the maximum frequency for 1 min in the antrum (2–3 cycles/min) and 2 min in the duodenum (10–12 cycles/min). A phase 3 is abnormal when it is retrograde, simultaneous, or is interrupted for more than 2 min on one of the intestinal segments. Eating abolishes the fasting pattern of the migrating complex and replaces it with an increased and more irregular pattern of contractions. This is a neural response that is dependent on the caloric and fat content of the meal. Phase 3-like contractions can be also monitored in the stomach after administration of intravenous erythromycin and in the small intestine after subcutaneous octreotide. A normal response to erythromycin is 3 cycle/min gastric contractions that last for greater than 1 min and to octreotide 11 cycle/min small intestinal contractions that last for greater than 1 min.

Antral hypomotility is defined as absence of the gastric phase 3, low-amplitude gastric contractions (<30 mmHg), and no response to erythromycin. It can be secondary to either altered neural control or smooth muscle function. Findings in functional dyspepsia include retrograde or cluster contractions with a normal amplitude (>15 mmHg) in the small intestine [42, 43]. Neuropathic pseudoobstruction is defined by disorganized high-amplitude small intestinal contractions. Myopathic pseudoobstruction has normally coordinated contractions with low-amplitude antral (<30 mmHg) and duodenal (<15 mmHg) contractions. A stationary cluster contraction compatible with partial small-bowel obstruction is a prolonged (>5 min) nonmigrating burst of contractions [32].

Indications for Antroduodenal Manometry

Antroduodenal manometry can be used to evaluate gastric and small-bowel motor function in patients with chronic symptoms of unexplained nausea, vomiting, and/or abdominal pain (Table 15.1). Patients with undiagnosed symptoms and no anatomic disease may or may not have delayed gastric emptying. Antroduodenal manometry may help define conditions such as antral hypomotility, nonulcer dyspepsia, chronic intestinal pseudoobstruction or a partial mechanical obstruction. Each of these conditions may present with nausea, vomiting, and/or abdominal pain. Pyloric manometry also can be performed depending on the patients' clinical presentation.

A normal antroduodenal manometry, showing normal-amplitude gastric and duodenal contraction and normal control of contractions, focuses therapy on the visceral afferent contribution to symptoms. Approximately 19% of children and 20% of adults with symptoms severe enough to impact daily activities had a normal study. Thus, the results of antroduodenal manometry studies can minimize unnecessary surgeries in patients with dysmotility or redirect therapy in patients with normal studies [42].

Table 15.1 Indications for antroduodenal manometry

1. Evaluate patients with unexplained nausea and vomiting [44]
   (a) Identify patients with normal smooth muscle and neural function
2. Identify gastroduodenal motility abnormality in patients with delayed gastric emptying
   (a) Differentiate antral hypomotility from duodenal dysmotility
3. Identifying patients with subacute mechanical obstruction of the small bowel [32, 49, 57]
4. Diagnose patients with chronic intestinal pseudoobstruction [57, 58]
   (a) Differentiate between gastrointestinal neuropathy or myopathy
5. Determine the extent of dysmotility
   (a) Patients with slow-transit constipation being considered for colectomy [59]

In patients with gastroparesis, antroduodenal manometry may identify the gastroduodenal motility disturbance causing the delay in gastric emptying allowing more targeted therapy. Antroduodenal manometry can identify normal contractions or a motility pattern consistent with myopathy or neuropathy in the stomach or small bowel. The response to different stimulating drugs determined during antroduodenal manometry can direct therapy depending on the observed contractile pattern.

Antroduodenal manometry can also identify a partial small-bowel obstruction that has been missed by small-bowel X-ray or CT scan of the abdomen [32]. The presence of the characteristic long-duration contractions supports repeated imaging or exploratory laparoscopy [32]. Differentiation between pseudoobstruction and mechanical obstruction by antroduodenal manometry can prevent unnecessary surgery in the pseudoobstruction group and support surgery in the patient who is obstructed. Once the diagnosis of pseudoobstruction is made, antroduodenal manometry allows for characterization of smooth muscle and/or neural function. Prognosis and therapy often can be improved by this information.

Antroduodenal manometry can identify the presence or absence of generalized pseudoobstruction in patients who have colonic inertia (pseudoobstruction) prior to abdominal colectomy. Total gut involvement with pseudoobstruction may influence the timing of surgery as well as the surgical procedure to be performed.

Use of Antroduodenal Manometry Findings in Treatment Plans

Previous studies showed that 72% of patients with nausea and vomiting had an abnormal antroduodenal motility which resulted in a new diagnosis or treatment in 10–15% of these patients [44]. Fasting and fed patterns of small intestinal motility over 24 h showed abnormalities in 40% of patients and suggested a change in therapy in 20% [45]. One third of the patients with functional symptoms have autonomic dysfunction which correlates with an altered upper bowel motility [46]. The functional disorder, functional dyspepsia with symptoms of nausea, vomiting, and abdominal pain, may have disturbed neural control of the gastrointestinal tract and may be a component of the same clinical spectrum as with neuropathic pseudoobstruction [47].

Both adults and children can have severe nonulcer dyspepsia, which may present as a surgically treatable lesion [42, 44]. Antroduodenal manometry may make an important contribution to the patients' care, since 18% of children and 51% of adults with manometric evidence for nonulcer dyspepsia had no improvement in their symptoms after surgery [42].

Evaluation of data on 105 consecutive patients referred for nausea, vomiting and abdominal pain at our institution shows that a change in diagnosis was suggested by short duration antroduodenal motility in 69% and a change in therapy in 35% of patients. The impact of a change in therapy most affected the postsurgical group, since antroduodenal manometry helped guide the need for further operations. Treatment was altered by antroduodenal manometry in 29% of non surgical patients and 54% of postsurgical patients. Antroduodenal manometry was normal in one-quarter both groups of patients, allowing the avoidance of prokinetic drugs or surgery. Antroduodenal manometry switched the diagnosis in 50% of these patients from presumed partial small-bowel obstruction to pseudoobstruction also avoiding unnecessary and potentially deleterious surgery.

Patients with symptoms related to a partial bowel obstruction may have normal radiographic studies with no change in bowel caliber, but have a disturbance of upper intestinal motility [32, 48, 49]. Imaging studies showing dilated bowel can cause confusion between ileus, pseudoobstruction or obstruction in this group of patients [49]. Thus antroduodenal manometry allows the characterization of the gastric and small intestinal contractions as either obstruction or pseudoobstruction. The definition of the altered motility patterns can suggest specific pharmacotherapeutic solutions. Gastric contraction can be stimulated by erythromycin [36] and small intestinal contractions can be stimulated by octreotide [34, 50]. The response of the stomach and the small intestine to the diagnostic administration of erythromycin and octreotide determines if these drugs will be therapeutically effective.

Erythromycin stimulates continuous contractions in the gastric antrum and also more proximally in the corpus of the stomach [51, 52]. Erythromycin has been reported to stimulate contractions in patients with previous antrectomy [51]. In contrast to children who did not respond to stimulation if the fasting gastric phase 3 was absent, erythromycin stimulated continuous gastric contractions in adults without a gastric phase 3 [53].

Octreotide can stimulate phase-3-like continuous small intestinal contractions in patients an abnormal intestinal phase 3 consistent with neuropathic pseudoobstruction, potentially decreasing small-bowel bacterial overgrowth [54]. Octreotide stimulated phasic contractions in most patients, but some patients were unresponsive [54]. Octreotide may be useful in patients with myopathic pseudoobstruction [26, 55]. Since patients with neuropathic pseudoobstruction may have variable response [38, 54], octreotide may be useful only in patients with neuropathic pseudoobstruction in whom stimulation occurs at the time of antroduodenal motility testing. This hypothesis still needs to be assessed in a prospective manner.

The presence of a normal study in patients presenting with nausea, vomiting and abdominal pain suggests a disturbance of the afferent sensory system rather than a

defect of the efferent nerves, altered smooth muscle contraction or bowel obstruction. Previous studies in patients with a normal manometry have not demonstrated an occult small-bowel obstruction [48, 49]. Patients with a normal antroduodenal manometry were given a trial of a low dose of a tricyclic antidepressant to decrease the visceral hypersensitivity [56] and patients with pseudoobstruction were treated with prokinetics. A meta-analysis showed effective reduction of functional abdominal pain following low-dose tricyclic therapy [56]. It appears to be ineffective to refer postsurgical patients with a normal antroduodenal manometry for exploratory laparoscopic surgery.

The high association of delayed gastric emptying with altered antroduodenal manometry suggests that many of the patients have a more generalized disturbance in upper gut motility. Gastric emptying was delayed in patients with normal antral contraction. Since gastric emptying can be delayed not only because of poor gastric propulsion but also because of uncoordinated duodenal contractions, the sequential use of erythromycin and octreotide may be useful for the treatment of these patients [35]. Therefore, both gastric emptying and antroduodenal manometry seem necessary to fully define the patient's condition.

Patients with colonic inertia who have signs of pseudoobstruction in the small intestine should be carefully counseled prior to subtotal colectomy. The patient may have generalized pseudoobstruction. Their bowel problem may recur after the colectomy.

Conclusion

Antroduodenal manometry can provide important information concerning the pathophysiology leading to gastroparesis. In turn, this information provides a course for initiating effective therapy. Recent improvements in technology and enhancement of our knowledge about the underlying pathogenesis of gastroparesis will hopefully be turned into more effective therapy for this difficult disease state.

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Chapter 16
Diabetic Gastroparesis

Christopher K. Rayner, Karen L. Jones, and Michael Horowitz

Keywords Diabetes mellitus • Interstitial cells of Cajal • Nitric oxide • Heme oxygenase 1 • Incretin • Glucagon-like peptide 1 • Insulin • Blood glucose concentration

Introduction

Diabetes mellitus has been recognized to be associated with disordered gastric emptying at least since Kassander coined the term "gastroparesis diabeticorum" over 50 years ago [1]. Interestingly, studies employing novel methodologies have, in recent years, proven a number of concepts related to diabetic gastroparesis to be incorrect. Diabetes is the most common known cause of chronic gastroparesis, accounting for around 30% of patients in most tertiary referral series [2]. The global concomitant increases in both prevalence of type 1 and type 2 diabetes and life expectancy suggest that diabetic gastroparesis will be an increasingly important source of morbidity in the coming decades. This chapter focuses on aspects of the presentation and management that are specific to diabetes, and in particular, the interrelationships between disordered gastric emptying and glycemic control; it is now recognized that the latter has fundamental implications for the management of patients with this condition.

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Prevalence of Disordered Gastric Emptying in Diabetes

Diabetic gastroparesis was once considered to be rare, with an invariably poor prognosis. However, when patients with long-standing type 1 and type 2 diabetes attending a tertiary referral center were studied on an otherwise unselected basis, gastric emptying of solid and/or liquid was found to be abnormally delayed in 30–50% [3]. The prevalence of delayed emptying appears comparable between type 1 and type 2, and the magnitude of delay is relatively modest in many cases, but correlates weakly with the presence of symptoms, while women are more likely to have slow gastric emptying than men [4]. A weakness of most studies in this area is that blood glucose concentrations at the time of the gastric emptying test have not been strictly controlled and in many cases are not documented. A subset of "early" type 2 patients has been reported to have abnormally rapid gastric emptying [5], although the prevalence of this phenomenon is controversial [6]. A minority of type 1 diabetic patients have rapid emptying for solids [7], and it has been suggested that this can result in "dumping" symptoms [8]. Patients with exocrine pancreatic insufficiency, such as those with cystic fibrosis, represent a distinct subset where fat maldigestion is associated with accelerated gastric emptying, impaired secretion of gut peptides including the incretins, and exaggerated postprandial glycemia [9].

While the prevalence of diabetic gastroparesis in the community has not been adequately defined, gastrointestinal symptoms appear to be commonly associated with diabetes in large surveys [10]. However, it should be noted that the relationship between symptoms and delayed gastric emptying is relatively weak, with only bloating and postprandial fullness being significantly related to the rate of emptying [2, 4, 11–13].

Limited data suggest that the long-term outcomes in diabetic patients with slow gastric emptying appear relatively good; delayed emptying is not associated with increased mortality [14], and both the rate of emptying and the prevalence of upper gastrointestinal symptoms appeared stable in a small cohort followed for around 12 years, although individuals within the group gained or lost symptoms in equivalent numbers over time [15]. However, it is yet to be established whether patients with more grossly delayed gastric emptying have a similarly favorable outlook.

Pathogenesis

Normal gastric emptying requires integration between the proximal and distal stomach, pylorus, and duodenum, under control of the gastric electrical rhythm generated by the interstitial cells of Cajal (ICC) within the myenteric plexus. The proximal stomach relaxes to accommodate a meal, while the antrum grinds solids and pumps chyme into the duodenum in a pulsatile fashion, depending on the state of pyloric contraction, so that nutrients empty to the small intestine at an overall rate of around 1–4 kcal per minute [16]. The process is regulated by neural and hormonal feedback generated primarily by the interaction of nutrients with the small intestine,

with the gut peptides glucagon-like peptide-1 (GLP-1), cholecystokinin, and peptide YY among the mediators of this process. Emptying of liquids occurs in preference to solids and is rapid and monoexponential for non- or low-nutrient liquids, becoming more linear as the caloric content increases, while solids empty in a linear manner after an initial lag phase, during which particles are ground to 1–2 mm in size.

Documented motor abnormalities in patients with diabetic gastroparesis include diminished fundic tone with retention of meal content in the proximal stomach [17], but also impaired accommodation, diminished frequency and amplitude of antral contractions, and increased phasic and tonic pressures localized to the pylorus. While it had been widely assumed that diabetic gastroparesis was uniformly attributable to the presence of irreversible autonomic neuropathy, based on similar abnormalities of gastric emptying in vagotomized patients [18], indices of cardiac autonomic dysfunction (a surrogate marker for the presence of gastrointestinal autonomic neuropathy) correlate poorly with delayed gastric emptying [4]. Nor do the presence of peripheral neuropathy or retinopathy, or the duration of diabetes, relate to the presence or magnitude of delayed gastric emptying in type 1 or type 2 diabetes [18–20]. Recent studies indicate that the underlying pathological processes are heterogeneous in both animal models and in the limited number of diabetic patients from whom full thickness gastric biopsies have been obtained, and include interrelated changes in extrinsic autonomic nerves, ICCs, the myenteric plexus, and smooth muscle [21]. Knowledge in this area is likely to improve with the establishment of the Gastroparesis Clinical Research Consortium in the USA, which is facilitating the collection of full thickness biopsies from a subset of patients [22].

Loss or dysfunction of ICCs is one of the most consistent findings, perhaps as a result of reduced levels of heme-oxygenase-1, an enzyme that protects against oxidative stress [23]. Induction of HO-1 activity, or stimulation of downstream pathways such as by inhalation of carbon monoxide, can reverse gastroparesis in a rodent model [24]. Loss of neuronal nitric oxide synthase (NOS) expression is also prominent in rodent models [25], and it has been suggested that gender differences in neuronal NOS dimerization account for the greater prevalence of diabetic gastroparesis among women than men [26]. However, whether NOS deficiency plays a major role in the pathogenesis of gastroparesis in humans remains unclear, and NO donors, such as sildenafil, appear to be unhelpful in accelerating gastric emptying in diabetic gastroparesis [27]. In regard to the abnormalities demonstrated in animal models of diabetic gastroparesis, it is often unclear whether these are primary, or secondary to hyperglycemia, insulin deficiency, or other metabolic disturbances [21].

It is now clear that acute variations in the blood glucose concentration are associated with reversible changes in gastric motor function so that gastric emptying is slower during marked hyperglycemia (blood glucose 16–20 mmol/L) than euglycemia (4–8 mmol/L) [28] and is accelerated during insulin-induced hypoglycemia, even in the presence of cardiac autonomic neuropathy [29]. Even small elevations in blood glucose, within the physiological postprandial range (8 mmol/L versus 4 mmol/L), affect the rate of emptying [30]. Hyperglycemia is associated with diminished proximal gastric tone [31], impaired antral contractions [32], and increased pyloric pressures [33], and induces abnormalities of the gastric electrical

slow wave, suggesting ICC dysfunction [34]. Hyperglycemia may also exacerbate gastrointestinal symptoms; sensitivity to gastric distension is increased during hyperglycemia in healthy volunteers [35], while in type 1 diabetic patients, postprandial fullness is related to the blood glucose concentration [36].

It remains to be clarified how the effects of acute hyperglycemia are mediated. We recently showed that NOS blockade reverses the slowing of gastric emptying induced by hyperglycemia in healthy humans [37], which seems paradoxical in light of the proposed NOS deficiency in gastroparesis. There is also evidence for glucose-responsive neurons in both the enteric and central nervous systems [38], while nutrient detection mechanisms in the small intestine are modulated by acute changes in glycemia [39]. The effects of chronically elevated blood glucose concentrations, as opposed to acute effects, remain to be established, and it should be noted that no studies have evaluated the prevalence of abnormal gastric emptying in patients with diabetes when the blood glucose has been maintained in the strict euglycemic range, when compared with their "usual" blood glucose concentration. In our experience, blood glucose tends to be at least moderately elevated when patients attend the hospital for a gastric emptying study.

Gastrointestinal Regulation of Postprandial Blood Glucose

The impact of normal and disordered gastric emptying on glycemic control has received inappropriately little attention because the "chicken and egg" relationship between the two has generally not been sufficiently considered [21].

It is now well established that good glycemic control is fundamental to reducing the incidence and progression of microvascular, and probably macrovascular, complications of diabetes. In modern society, where a high-carbohydrate and high-fat diet is consumed on a regular basis, and each meal empties from the stomach at 1–4 kcal/min, the majority of each day will be spent in the postprandial or post-absorptive phase, with only a brief period of true "fasting" for a few hours before breakfast [40]. In this regard, the traditional focus in diabetes management on the control of "fasting" blood glucose is inappropriate, and for most patients with diabetes, postprandial blood glucose excursions are likely to be more important in determining overall glycemic control [41, 42].

Determinants of postprandial blood glucose concentrations include the preprandial glucose level, the carbohydrate content of the meal and its rate of absorption, insulin and glucagon secretion, and hepatic and peripheral glucose metabolism. The relative contribution of these factors has, in general, been poorly defined, and will vary over time after a meal, but it has clearly been established that the rate of gastric emptying is a major determinant of the initial postprandial rise in blood glucose in both health [43] and type 1 and 2 diabetes [6].

It has only recently been recognized that the rate of entry of carbohydrate into the small intestine influences blood glucose concentrations in a nonlinear fashion; in health, an increase in the glucose load delivered to the duodenum from 1 to 2 kcal/min

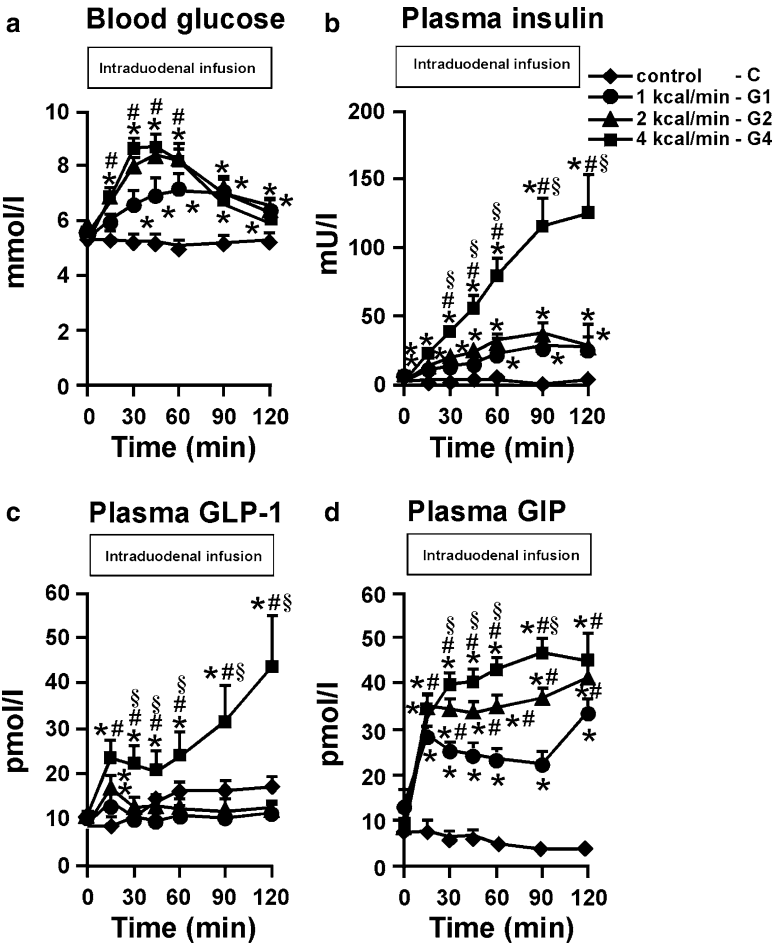

Fig. 16.1 Blood glucose (**a**), plasma insulin (**b**), GLP-1 (**c**) and GIP (**d**) in response to intraduodenal glucose (25%, 1,390 mOsmol/L) infused over 120 min at rates of 1 ("G1"), 2 ("G2"), or 4 ("G4") kcal/min, or saline (4.2%, 1,390 mOsmol/L) control ("C"), in 10 healthy males. (**a**) * vs. control: $P < 0.05$, # vs. G1: $P < 0.05$, § vs. G2: $P < 0.05$. (**b**) * vs. control: $P < 0.05$, # vs. G1: $P < 0.05$, § vs. G2: $P < 0.05$. (**c**) * vs. control: $P < 0.05$, # vs. G1: $P < 0.05$, § vs. G2: $P < 0.05$. (**d**) * vs. control: $P < 0.01$, # vs. G1: $P < 0.05$. (**e**) * vs. control: $P < 0.05$, # vs. G1: $P < 0.01$, § vs. G2: $P < 0.01$. Data are means ± SEM. Reproduced from Pilichiewicz AN, et al. Am J Physiol Endocrinol Metab 2007;293(3):E743-53, with permission from The American Physiological Society

results in a large increment in the blood glucose response, while a further increase from 2 to 4 kcal/min results in a smaller increase in glycemia, because of a proportionally greater rise in the secretion of the incretin hormone GLP-1 and insulin, as well as a more linear increase in GIP [44] (Fig. 16.1). These phenomena appear to be relatively preserved in well controlled type 2 diabetic patients [45], although in the latter the compensatory responses are less effective at limiting the incremental

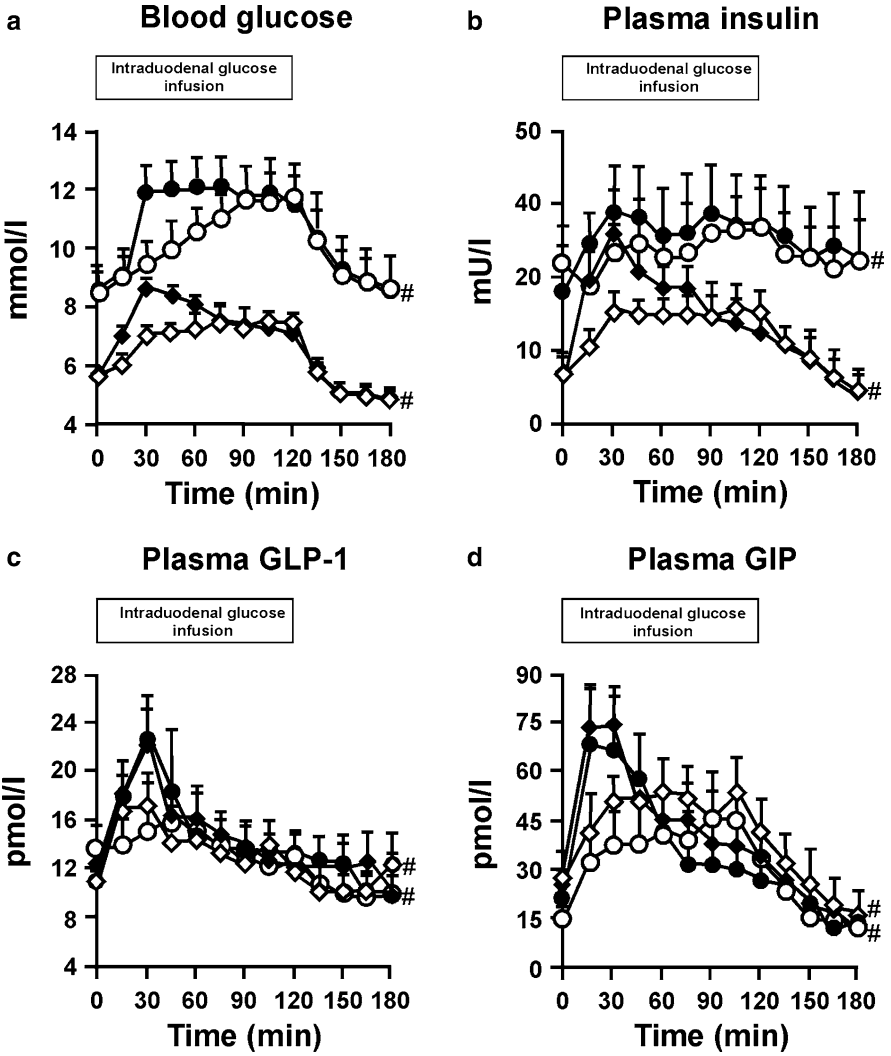

Fig. 16.2 Effect of initially more rapid intraduodenal glucose infusion (3 kcal/min between $t=0$ and 15 min and 0.71 kcal/min between $t=15$ and 120 min) (*closed symbols*) compared to constant infusion (1 kcal/min between $t=0$ and 120 min) (*open symbols*) in healthy subjects (*squares*) and patients with type 2 diabetes (*circles*) on blood glucose, plasma insulin, plasma GLP-1, and plasma GIP. Each pair of curves differs between 0 and 30 min for variable vs. constant intraduodenal infusion ($P<0.05$). Reproduced with permission from O'Donovan DG, et al. J Clin Endocrinol Metab 2004;89(7):3431–5. Copyright 2004, The Endocrine Society

rise in blood glucose. Accordingly, it appears that the most appropriate strategy in type 2 patients who are not treated with exogenous insulin is to limit the entry of carbohydrate to the duodenum to a rate of about 1 kcal/min [46] (Fig. 16.2). Indeed, it has been suggested that individuals with relatively slower gastric emptying are less prone to developing type 2 diabetes [47]. Conversely, acceleration of gastric

emptying, such as with the prokinetic drug erythromycin, results in a greater postprandial blood glucose excursion [48]. The therapeutic implications of these concepts are discussed below.

Clinical Significance of Disordered Gastric Emptying in Diabetes

Diabetic gastroparesis usually comes to attention because of symptoms such as nausea, vomiting, early satiation, postprandial fullness, or bloating, and these are associated with impaired quality of life [49]. Abdominal pain is another frequent, but often overlooked, symptom, in both diabetic and idiopathic gastroparesis [50, 51]. A small retrospective study reported that a large proportion of diabetic patients experience symptoms of nausea and vomiting in a cyclical pattern, with relatively symptom-free intervals [52]; this aspect needs further clarification in future studies, with a particular focus on determining precipitants of symptom episodes.

Both upper and lower gastrointestinal symptoms occur more frequently in people with diabetes than in the general population [53], and these impact adversely on quality of life; for example, up to 20% of patients report chronic nausea and vomiting. Adequacy of glycemic control, but not duration of diabetes, appears to be a determinant of symptom expression [10]. A Diabetes Bowel Symptom Questionnaire has been validated as a tool specifically to allow standardized evaluation of gut symptoms in patients with diabetes [54].

The presence of upper gastrointestinal symptoms is not specific for delayed gastric emptying; in a group of over 100 diabetic patients, only bloating and fullness had a relationship with delayed emptying [4]. This suggests that the etiology of symptoms is multifactorial; for example, hypersensitivity to gastric distension has been documented in patients with type 1 diabetes and gastroparesis [55]. The implication is that therapy which focuses only on accelerating emptying may not achieve the goal of symptom relief. Moreover, up to 50% of those with markedly delayed gastric emptying have few or no gastrointestinal symptoms [14]. While these patients would not fit easily into a definition of gastroparesis based solely on symptoms, their disordered stomach emptying can still result in important clinical problems, including disturbances in glycemic control and impaired absorption of orally administered drugs.

The approach to optimizing glycemic control potentially differs between patients: in type 1 and insulin-treated type 2 patients, the priority is to match delivery of nutrients to the small intestine with the action of exogenous insulin. In this group, prokinetics may have a role in accelerating gastric emptying, even in the absence of gastrointestinal symptoms, so as to make the rate of small intestinal nutrient delivery more predictable [56]. Conversely, in type 2 patients not treated with exogenous insulin, relative slowing of gastric emptying is likely to be advantageous for postprandial glycemia, so long as symptoms are not induced. Indeed, slowing of gastric emptying represents a major action of GLP-1 and its analogs [57], such as exenatide,

and of the amylin analog, pramlintide [58], in lowering postprandial blood glucose. This raises the question whether drugs such as GLP-1 analogs should be used in patients who already have abnormally slow gastric emptying. The evidence suggests that this is a reasonable strategy, as long as symptoms are not induced, because the effect on gastric emptying is probably minimal in patients with slow emptying at baseline [59], in whom the insulinotropic and glucagonostatic effects of GLP-1 potentially make a greater contribution to glucose lowering.

It has recently been recognized that delayed gastric emptying can present as otherwise unexplained episodes of hypoglycemia [60], especially those that occur early in the postprandial period, so-called "gastric" hypoglycemia [61]. This is predictable given that type 1 patients with delayed gastric emptying have lower insulin requirements in the first 2 h after a meal [62].

Gastroparesis also creates a risk of impaired nutrition, although many patients with diabetic gastroparesis are overweight [63]. Absorption of orally administered drugs can also be affected, especially medications with a short half-life, or those where rapid onset of action is required. In particular, absorption of oral hypoglycemic agents can be impaired when gastric emptying is slowed [64], and potential effects on the absorption of orally administered prokinetic drugs should be borne in mind.

The rate of gastric emptying also potentially influences postprandial blood pressure control [65]. Postprandial hypotension, defined as a fall in blood pressure of ≥20 mmHg within 2 h of a meal, represents a common and under-appreciated source of morbidity and mortality in those with type 1 and 2 diabetes complicated by autonomic neuropathy, as well as the elderly [66, 67]. More rapid delivery of nutrients to the small intestine is associated with a greater fall in postprandial blood pressure, while gastric distension is protective, so that interventions that slow gastric emptying or delay absorption of carbohydrate, such as the alpha-glucosidase inhibitor, acarbose, are potentially advantageous in the management of this syndrome.

The potential for abnormal gastric emptying to impact glycemic control and nutrition adversely, even in the absence of gastrointestinal symptoms, indicates that grading the severity of gastroparesis based on symptoms alone, such as by the Gastroparesis Cardinal Symptom Index [68], is inappropriate in diabetes. The authors have proposed an alternative classification, which has not been validated, but is provided to stimulate discussion [69] (Table 16.1).

Investigation of Diabetic Gastroparesis

As indicated above, diabetic patients managed with insulin who have unexplained hypo- or hyperglycemia should be referred for evaluation of their rate of gastric emptying, as well as those with symptoms referable to the upper gastrointestinal tract. Detailed discussion about scintigraphic techniques is presented in other chapters, but in diabetic patients, gastric emptying should ideally be measured during euglycemia (blood glucose between 4 and 10 mmol/L). We believe there is a rationale for testing both nutrient liquid and solid emptying concurrently, since the rates of each

Table 16.1 Proposed classification of severity of diabetic gastroparesis

Mild to moderate

- Abnormally slow rate of gastric emptying of solids and/or nutrient liquids, as quantified by scintigraphy or breath test, in the absence of mechanical obstruction or significant hyperglycemia (blood glucose >10 mmol/L)

And at least *one* of the following:

- Persistent upper gastrointestinal symptoms (early satiation, nausea, bloating/fullness, vomiting, pain) sufficient to impact on quality of life
- In insulin-treated patients, occasional unstable glycemic control (hyperglycemia and/or hypoglycemia) attributable to inability to co-ordinate insulin delivery with nutrient absorption

Severe

- Markedly abnormal slow rate of gastric emptying of solids and/or nutrient liquids, as quantified by scintigraphy or breath test, in the absence of mechanical obstruction or significant hyperglycemia (blood glucose >10 mmol/L)

And at least *one* of the following:

- Persistent, severe upper gastrointestinal symptoms (early satiation, nausea, bloating/fullness, vomiting, pain) with significantly impaired quality of life
- Inability to maintain adequate oral intake, resulting in nutritional deficiencies and loss of body weight >10% within 6 months
- In insulin-treated patients, markedly unstable glycemic control (hyperglycemia and/or hypoglycemia) attributable to inability to co-ordinate insulin delivery with nutrient absorption

Adapted from Expert Rev. Gastroenterol. Hepatol. 3(2), 167–81 (2009) [69] with permission of Expert Reviews Ltd

are only weakly related [17], and the outcome potentially affects the dietary advice given; for example, if liquid emptying is relatively preserved, it may be logical to give a greater proportion of nutritional requirements in liquid form.

While limited validation of the stable isotope breath test has been performed in diabetes [70], and it represents a potentially useful screening test, validation in patients with extremely delayed gastric emptying is lacking.

Therapy for Diabetic Gastroparesis

The goals of therapy vary in different patients with diabetic gastroparesis. As discussed above, acceleration of gastric emptying with prokinetic drugs may not always be the most important endpoint, and in some cases could affect glycemic control adversely. In patients presenting with symptoms, antiemetic and/or pain modifying drugs (e.g., low-dose tricyclic antidepressants) may have an important place in management, even despite the anticholinergic properties of the latter.

Glycemic control is an important aspect of the management for the reasons discussed above, and may need to be monitored with capillary blood glucose measurements that are more frequent than usual (e.g., 2-h after meals). Type 2 patients may need to commence insulin if not already using this therapy. The use of insulin analogs that have a short duration of action (e.g., lispro or aspart) can allow for more

precise dosing that can be given with, or after, meal ingestion [71], while insulin pumps can also allow for flexibility of basal and bolus insulin dosing. None of these aspects have been formally evaluated in diabetic gastroparesis, however.

Dietary therapy is of fundamental importance in the management of diabetes in general where, as discussed, modulation of gastric emptying to limit the rate of small intestinal carbohydrate delivery to about 1 kcal/min is advantageous. This can be achieved by low-carbohydrate diets, dietary fiber, or guar gum ingestion, or with the use of fat [72] or protein [73] "preloads" to induce small intestinal feedback mechanisms that slow the rate of gastric emptying in advance of the main meal. Protein also stimulates endogenous insulin secretion, both via incretin release and direct stimulation of the beta cells by absorbed amino acids. These strategies may be inappropriate in patients with markedly delayed gastric emptying (the majority of whom will be insulin-treated) and/or those with severe upper gastrointestinal symptoms, in whom a low fiber, low-fat diet is typically recommended. However, it should be noted that these recommendations have not been evaluated in randomized controlled trials, although they appear to be physiologically appropriate. Another potentially useful strategy is to consume smaller, more frequent meals (e.g., 4–6 meals daily). A small study indicated that meals incorporating a small particle size, as opposed to less finely divided solids, improved the rate of emptying and reduced the postprandial glycemic "dip" in patients with type 1 diabetes [74]. Patients with exocrine pancreatic insufficiency should have their pancreatic enzyme replacement therapy optimized [9].

Detailed discussion of drug therapy is beyond the scope of this chapter. In some cases it may be appropriate to give an initial empiric trial of prokinetic therapy, e.g., for 4–6 weeks, and reserve formal evaluation of gastric emptying for those who do not improve adequately or relapse [75]. However, this strategy is more difficult in countries such as the USA, where availability of prokinetic agents other than metoclopramide is severely restricted. It should be noted that subcutaneous metoclopramide may be ideally suited to insulin-treated diabetic patients. Of relevance to diabetic gastroparesis, however, is that hyperglycemia has the capacity to impair the action of the prokinetic drugs erythromycin [76, 77] and cisapride [78]; whether this phenomenon extends to other prokinetic medications remains to be established.

Gastric electrical stimulation with the Enterra™ device remains inadequately evaluated in sham controlled trials, but open label evidence suggests that patients with diabetes are more likely to experience symptom improvement that those with idiopathic gastroparesis [79].

Limited evidence suggests that combined kidney/pancreas transplantation can improve gastroparesis in patients with long-standing diabetes complicated by renal failure [80]. Pancreatic islet cell transplantation can normalize glycemic control and possibly reverse autonomic dysfunction, but there is not yet conclusive evidence that gastrointestinal symptoms or gastric emptying are improved [81]. However, this issue is worthy of further study, since many patients with recurrent hypoglycemia – the main indication for islet cell transplant – also have delayed gastric emptying [60].

Summary and Conclusions

Recent insights relating to the role of upper gastrointestinal function in glycemic control are fundamentally important in the recognition of the spectrum of disordered gastric emptying in diabetes and in determining appropriate management. Paradoxically, dietary and pharmacological interventions that slow delivery of nutrient to the small intestine are generally beneficial in diabetes, unless they result in a mismatch between nutrient delivery and the action of exogenous insulin, or induce symptoms such as nausea and vomiting. Conversely, optimization of glycemia is a priority in patients presenting with diabetic gastroparesis. Future studies are needed to refine our understanding of the underlying pathogenesis of this disorder so that more specific therapies can be developed.

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Chapter 17
Postsurgical Gastroparesis

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Keywords Postsurgical gastroparesis • Gastroenterologists • Nutritionists • Jejunostomy tube feedings • Gastric electrical stimulation

Introduction

Postsurgical gastroparesis (PSG) is a chronic form of gastric atony in the absence of mechanical obstruction resulting from surgical disruption of the normal mechanisms that govern gastric motility and emptying. The surgeries can involve resection of part of the stomach and/or disrupting vagal pathways controlling gastric motility. PSG develops in up to 10% of patients who undergo vagotomy (either deliberate or inadvertent) as part of upper gastrointestinal surgery, such as peptic ulcer disease or gastroesophageal reflux disease (GERD). The incidence increases to as high as 50% in patients with refractory ulcer disease who had chronic gastric outlet obstruction before surgery. Typical symptoms of PSG include nausea, vomiting, early satiety, and abdominal pain, often with significant weight loss [1, 2]. An excellent review of postsurgical and obstructive gastroparesis has been published by Shafi and Pasricha [2].

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Gastric Motility and Vagal Function

Normal Gastric Motility

Controlled gastric emptying of an ingested meal is important for proper delivery of prepared digested food (chyme) into the small intestine where nutrients are absorbed [1]. Gastric contractions and subsequent gastric emptying are controlled by several mechanisms. The interstitial cells of Cajal, enteric motor neurons in the gastric myenteric plexus, and gastric smooth muscle are responsible for gastric contractions allowing trituration of food into small particles with peristalsis toward the pylorus [2]. Gastric motility is modulated by the central nervous system and transmitted to the stomach predominantly by the vagus nerve. Vagal nerve stimulation causes both fundic relaxation and antral contractions. The vagus nerve innervates the stomach via presynaptic cholinergic nerves that synapse on two types of postganglionic enteric neurons. One pathway activates inhibitory, predominately nitric oxide-containing, nerves in the fundus mediating receptive accommodation. The other pathway activates excitatory, predominantly acetylcholine-containing, myenteric neurons in the antrum regulating contractions. Sequential activation of these neurons is necessary for effective gastric emptying after meal ingestion [2].

A distinct cycle of electromechanical activity during the fasting state begins in the proximal stomach and migrates distally through the small bowel [1]. This cycle, the migratory motor complex (MMC), occurs approximately every 90 min. The MMC is composed of three phases. Phase 1 is a period of motor inactivity with only rare contractions, lasting 45–60 min. Phase 2 has intermittent peristaltic contractions that increase in frequency and amplitude over an approximately 30 min period. Phase 3 has an intense increase in peristaltic contractions, lasting 5–10 min, occurring at the pacesetter potential frequency (i.e., 3 contractions per minute in the stomach). Phase 3 of the MMC is peristaltic through the stomach and small intestine, facilitating emptying of indigestible solids out of the stomach. Meal ingestion of adequate caloric intake (>300 cal) converts the fasting MMC pattern to the digestive ("fed") pattern responsible for gastric emptying of the ingested meal. Simultaneous increase in gastric, biliary, and pancreatic secretion with the MMC promotes this sweeping "housekeeper" effect, providing a deterrent for bezoar formation in the stomach and bacterial colonization of small intestine as well as aiding the digestion of remaining chyme.

Effects of Vagotomy

Truncal vagotomy results in several effects: loss of fundic relaxation, reduced antral contractions, and loss of pyloric relaxation [2, 3]. Loss of fundic relaxation and accommodation may lead to symptoms of early satiety, fullness, and bloating, with rapid transit of the ingested food from the proximal stomach to the distal stomach.

Reduced antral contractions are associated with loss of trituration and retention of solids in the stomach. Loss of pyloric relaxation also causes gastric retention. The effect of a total vagotomy is to delay emptying of solids while accelerating gastric emptying of liquids. Truncal vagotomy also affects the fasting MMC with resultant gastric retention of larger indigestible food in the stomach and occasionally bezoar formation. A gastric drainage procedure such as a pyloroplasty or gastroenterostomy is usually performed in an attempt to offset the gastroparetic effects of vagotomy. In most patients, the net result is that vagotomy combined with a drainage procedure produces little alteration in gastric emptying.

Selective vagotomy procedures (parietal cell vagotomy, proximal gastric vagotomy, or highly selective vagotomy) are used to reduce gastric acid secretion while preserving antral innervation to preserve gastric motility and emptying [2]. A trial of 152 patients compared proximal gastric vagotomy, truncal vagotomy with drainage, and truncal vagotomy with antrectomy for the treatment of chronic duodenal ulcer [4]. The proximal gastric vagotomy operation was associated with less symptoms of dumping, epigastric fullness, and diarrhea after surgery.

Some patients after a vagal nerve injury have rapid gastric emptying (dumping syndrome), while others may have delayed gastric emptying (gastroparesis). There seems to be two main explanations for this: (1) Minor or minimal trauma/or damage to the vagus may affect the fundus and proximal stomach and not the antrum with loss of fundal relaxation or storage. This presents as rapid emptying. More severe vagal nerve damage involves the nerves of Latarjet, affecting antral innervation resulting in gastric stasis. (2) Patients with prolonged gastric outlet obstruction caused by peptic ulcer disease have a dilated, distended stomach which impairs the contractility of gastric smooth muscle even after surgical relief of the obstruction. Inhibition of motility by a vagotomy related to peptic ulcer surgery further compromises this situation and leads severe delay in gastric emptying.

The vagus nerve, although primarily thought of as an efferent motor nerve regulating GI motility, is also an afferent sensory nerve, conveying sensory information from the stomach to the brain, and, under pathologic conditions, nausea [2]. Injury of the vagus nerve may generate symptoms due to dysfunction of motor and sensory components.

Incidence, Etiology, and Mechanisms of Postsurgical Gastroparesis

The incidence of postsurgical gastroparesis is difficult to determine. Most patients reported are those referred to specialized centers from a number of smaller hospitals with the responsible surgery for the PSG performed at varying time periods before referral; these referred patients to specialized centers probably represent the most severe cases of PSG [2].

Postsurgical gastroparesis represents a minority of patients with gastroparesis. In a report from University of Virginia, PSG was present in 13% of all patients with

gastroparesis, compared with 29% of diabetic cases and 36% of idiopathic ones [5]. In another report from Temple University, out of 484 patients with delayed gastric emptying, 10.7% had PSG with a prior surgical procedure that could account for their gastroparesis [6].

PSG is often a consequence of vagotomy or vagal nerve injury during gastrointestinal surgery. Classically, operations for peptic ulcer disease such as vagotomy with or without hemigastrectomy have been those resulting in gastroparesis [7, 8]. However, surgery for ulcer disease has decreased over the last decade because of treatments with proton pump inhibitors and therapy against Helicobacter pylori for ulcer disease. Other surgeries such as Nissen fundoplication for GERD and bariatric surgery for obesity have increased. Thus, the surgeries causing PSG may also be changing as the types of gastric surgeries evolve [2]. In the classic series of postsurgical gastroparesis reported in 1990 from the Mayo Clinic [7], two thirds of the patients had prior peptic ulcer operations: 12 patients had undergone truncal vagotomy and a "drainage operation" and 48 had received a partial gastrectomy with a gastroenterostomy: Billroth I ($n=8$), Billroth II ($n=11$), Roux-en-Y ($n=29$). Interestingly, the patients had delayed gastric emptying of solids but rapid gastric emptying of liquids. By contrast, the patients currently being seen at an academic tertiary care center were recently reported [6]. Fundoplication/hiatal hernia repair accounted for 42% of the PSG patients, lung transplantation 18% of patients, whereas partial gastrectomy +/− vagotomy comprised 11.5% of the patients.

Common Operations Lead to Postsurgical Gastroparesis

Surgeries that are associated with postoperative delayed gastric emptying include: Billroth I and II antral resections, Roux-en-Y gastrojejunostomy, fundoplication, bariatric surgery involving pouches and gastrojejunostomy, esophagectomy with colonic interpositions or gastric pull-up, pylorus-preserving Whipple procedure, and lung transplantation [8]. In an analysis of 955 consecutive patients who underwent gastrojenjunostomy, 23 patients developed delayed gastric emptying [9]. Risk factors for delayed gastric emptying after gastrojejunostomy included patients >60 years old, undergone nonresective gastric bypass, undergone Roux-en-Y, and prior reoperation for postsurgical gastroparesis.

Postvagotomy Gastroparesis

PSG has been classically described as a consequence of peptic ulcer surgery, usually with concurrent performance of truncal vagotomy in addition to a Billroth I (antral resection and gastrodoudenal anastomosis) or Billroth II (a 50% or greater gastric resection with a gastrojejunostomy anastomosis) [2, 8]. Although these procedures

are less commonly practiced, vagal dysfunction remains the unifying cause for this and other forms of PSG.

Roux-en-Y anastomosis is particularly associated with gastric stasis syndromes. In addition to the vagotomy and distal gastric resection, the Roux limb may contribute to gastric stasis by generating ectopic pacemaker activity with orad (retrograde) propagation. Additionally, stasis within the Roux limb itself may be an independent cause of symptoms in this syndrome [2, 10–12].

Abdominal and Thoracic Surgery

Inadvertent vagotomy has been estimated to occur in 3–5% of open surgeries on the abdomen [2]. This complication should be suspected in patients who present with gastroparetic symptoms following abdominal surgery. The surgeries that are more likely to accidentally injure the vagus nerve include antireflux surgery, gallbladder resection, ligating gastric and duodenal bleeding vessels, and resecting gastrointestinal stromal tumor (GIST) of the stomach.

Antireflux Surgery

The most common cause of postsurgical gastroparesis currently appears to be Nissen fundoplication. The development of postoperative gastroparesis after an open or laparoscopic Nissen fundoplication may result in significant morbidity [13]. Vagal nerve injury has been reported in 4% to as many as 40% of patients undergoing laparoscopic fundoplication [13, 14].

Gastrointestinal symptoms are common in the first few weeks after antireflux procedures [2]. In a series of 615 patients who underwent laparoscopic Nissen fundoplication, all had symptoms during the first 3 postoperative months, with early satiety (88%), bloating/flatulence (64%), and dysphagia (34%) being the most common [15]. However, by 1 year these symptoms had resolved in more than 90% of patients. In a minority of patients, symptoms suggestive of gastric dysfunction can persist [2]. They can take the form of mild early satiety, the classic gas-bloat syndrome (impaired ability to belch, pain, and bloating after a meal), and rarely gastroparesis. Two explanations have been offered for these symptoms. The first invokes vagal damage [2, 15, 16], which can be assessed with a sham meal study with measurement of plasma pancreatic polypeptide [17, 18]. In a regional survey of gastroenterologists and surgeons in the northwestern USA, the incidence of intractable gas-bloat syndrome and vagal injury with either gastroparesis or diarrhea was 1.4% for each [14]. The second explanation suggests that, in some patients, fundoplication unmasks a preexisting but subclinical gastric dysmotility [14]. In a series of 81 patients with long-standing severe gastroesophageal reflux, a preexisting delay in gastric emptying of solids before the procedure was associated with postoperative bloating, pain, and early satiety [19].

The effects of fundoplication on gastric emptying are complex [2]. In the absence of vagal injury, mild acceleration of initial gastric emptying may result and has been attributed to limited fundic receptive relaxation from the mechanical effects of the wrap [20]. In some patients with reflux who have preexisting delayed gastric emptying, fundoplication by itself may normalize emptying through these mechanisms [21]. A delay in gastric emptying is not regarded as a contraindication to fundoplication. If gastric emptying is slow before antireflux surgery, some suggest that a loose wrap should be performed over a 60F bougie to improve belching and decrease gas/bloating. A pyloroplasty is another consideration. In children, combining pyloric drainage procedure (either pyloromyotomy or pyloroplasty) with fundoplication in patients with gastroesophageal reflux and delayed gastric emptying, is an acceptable approach [22]. The value of this procedure remains unclear, with some studies showing a decrease in recurrent reflux and others showing no benefit [22, 23].

Heart/Lung Transplantation

A type of recently described PSG seen predominately in academic medical centers is gastroparesis after lung transplantation or heart–lung transplantation [6]. After lung transplantation, delayed gastric emptying may predispose to gastroesophageal reflux with microaspiration and subsequent pulmonary infection, which can have deleterious effects on the transplanted lungs. Delayed gastric emptying may also decrease bioavailability of orally administered immunosuppressive agents which could lead to rejection of the transplanted lungs [24]. Symptomatic delayed gastric emptying was present in 25% of patients after single lung transplantation and in 50% of patients after combined heart and lung transplantation [25]. Another study reported delayed gastric emptying in eight of ten patients after combined heart and lung transplantation [26]. Several causes may explain gastroparesis after heart and lung transplantation: vagal nerve dysfunction, viral infection, and immunosuppressive medications. Vagal nerve dysfunction from thermal or ischemic injury or dissection of the posterior mediastinum during surgery has been suggested as the most likely cause [24–26].

Bariatric Surgery

Surgical therapy for morbid obesity has increased since the late 1990s. Several procedures are designed to restrict stomach size [27]. The most commonly performed surgical procedure is the Roux-en-Y gastric bypass. The stomach is partitioned into a small proximal fundic pouch and a bypassed distal stomach; a loop gastrojejunostomy through a small gastroenterostomy drains the proximal pouch [27]. Ingestion of large meals is prevented by early satiety resulting from the small gastric pouch. Solid emptying is slower, and liquid emptying is faster after gastric bypass surgery [28]. Less commonly performed are gastric restrictive procedures including

vertical banding gastroplasty and adjustable gastric banding [27]. Vomiting can occur in 21% of patients after vertical banding gastroplasty [29]. Another study found that emptying from the proximal pouch was normal and could not explain the early satiety [30]. Sleeve gastrectomy is gaining popularity as an additional bariatric procedure [31]. The procedure uses a restrictive component and induces favorable hormonal changes with an anorexigenic effect. Gastroenterologists are increasingly seeing complications after bariatric surgery related to partitioning the stomach to forming a gastric pouch with an accompanying gastrojejunostomy. This can be associated to vagus nerve damage [2, 32].

Evaluation of PSG

PSG should be suspected in patients with persistent dyspeptic symptoms after gastric surgery [2]. In the Mayo Clinic study, nausea was present in 50%, vomiting in 30%, abdominal pain in 30%, and weight loss were the most common symptoms experienced by the patients [7]. In the Temple University study, patients with PSG rated feeling excessively full after meals, not being able to finish a meal, and bloating significantly higher than other symptoms [6]. Compared to patients with diabetic or idiopathic gastroparesis, patients with PSG had greater symptoms of early satiety, postprandial fullness, and bloating but less nausea and upper abdominal pain.

In the evaluation of the patients, an upper endoscopy is performed to evaluate for strictures and ulcers at the anastomoses [1]. The upper endoscopy may show retained food in the remaining stomach, or even bezoar formation. Upper GI radiology can also be obtained to evaluate for obstruction at the anastomosis. A spectrum of radiologic findings have been reported for gastric bezoar, appearing as a mottled or homogeneous, mobile or immobile, mass sometimes filling the gastric pouch [33]. Gastric emptying is used to document delayed gastric emptying. Generally, gastric emptying scintigraphy is used. Gastric emptying in PSG can be particularly severe. Using the Tougas EggBeaters meal, gastric emptying for solids is considered delayed if gastric retention was >60% at 2 h and/or >10% at 4 h [34, 35]. In the Temple University study, gastric retention in PSG was severe with an average 35% gastric retention 4 h postprandially [6]. The severity of the delay was more marked in patients with partial gastrectomy +/−vagotomy (48% retention at 4 h), compared to fundoplication (27% retention at 4 h), and pyloroplasty +/−vagotomy (19% retention at 4 h). Of note, the normal values for gastric emptying scintigraphy are derived from normal, nonoperated, subjects. There are few appropriate "normal" data bases to use for patients after gastric surgical procedures. In postsurgical patients, the altered anatomy is likely to alter gastric emptying compared to normal subjects without gastric surgery [7]. In general, there is delay in the emptying of solids and accelerated emptying of liquids [7]. After Roux gastrectomy, there may be retention of solids in both gastric remnant and the Roux limb [12]. The normal gastric emptying in patients with different degrees of partial gastric resections (e.g., antrectomy) and different drainage procedures is not known. This is also relevant with surgical reconstruction of the stomach, especially postbariatric surgery of the stomach.

Gastric surgery with either partial gastric resection and/or vagotomy can affect different regions of the stomach and have delayed emptying of solids but rapid gastric emptying of liquids [7]. In some postsurgical patients, determination of both gastric emptying of solids and liquids is needed. Dual labeling of solids with ^{99m}technetium and liquids with ^{111}indium allows for assessment of gastric emptying of solids and liquids which may be useful for patients after gastric surgery to assess their differential handling by the postsurgical stomach [35].

Symptoms suggesting gastroparesis in patients after gastric and esophageal surgeries may not give a clear picture on the pathophysiologic process. In patients undergoing gastric surgery, both delayed gastric emptying and rapid gastric emptying can be seen. The NIDDK Gastroparesis Consortium has reported its experience with PSG [36]. The 23 patients with symptoms of PSG had the following surgeries: Nissen fundoplication (52%), partial gastric resection (22%), myotomy or esophagogastrectomy (9% each), and stomach stapling and vagotomy (4% each). Overall, the highest mean symptom score was for nausea and early satiety. 52% of patients had been hospitalized in the past year with nausea and abdominal pain being the indications for 78% of these admissions. Gastric emptying results separated patients with PSG symptoms into: (1) Patients with delayed gastric emptying (74%) with mean value of 43% retention at 4 h and (2) Patients without delayed gastric emptying (26%), with a mean of 5% food retention at 4 h. Two patients (33%) of these patients met the criterion for dumping syndrome with <30% retention at 1 h. Thus, in the setting of postgastric and postesophageal surgeries, symptoms associated with delayed, normal or rapid emptying of the stomach may be similar. Nissen fundoplication was the major surgery associated with PSG symptoms and could be attributed to "accidental" vagal nerve injury during surgery.

Management of PSG

The general principles for treatment of symptomatic gastroparesis are maintenance of hydration; fluid and electrolyte balance; correction of nutritional deficiencies; reversal of the cause, if possible; and alleviation of symptoms [1]. Management of PSG follows these general principles.

Many symptoms following abdominal surgery may decrease with time [2]. Thus, initial management should be conservative. Resolution of symptoms may also be accompanied by improvement in gastric emptying, suggesting that either the enteric nervous system may be able to adapt to loss of vagal input or that vagal reinnervation or regeneration of nerve fiber may occur, as shown for afferent (but not efferent) fibers in experimental models [37].

Symptomatic management of PSG includes dietary manipulation and the combination of prokinetic and antiemetic agents. Dietary management consists of small, low-fat, low-fiber meals. In severe cases, patients need to be placed on a liquid caloric diet.

Primary medical therapy is with prokinetic and antiemetic agents to help reduce symptoms. Older literature suggests some efficacy with metoclopramide, cisapride, and tegaserod [38, 39]. Metoclopramide is available as an oral tablet, liquid formulation, oral disintegrating tablet, and in intravenous formulations. Domperidone is also a dopamine type 2 receptor antagonist but with less side effects than metoclopramide due to less penetration into the CNS. Intravenous erythromycin has been shown to improve gastric emptying in patients with Roux-en-Y stasis syndrome [40]. In PSG, without an antrum, prokinetic agents are less successful [41]. In addition, medications might not be reliably absorbed because of bezoar formation. Some of the antiemetics, such as ondansetron, are available as liquid medications and as oral dissolving tablets which might be better absorped.

Other nonsurgical options follow treatments for other forms of gastroparesis. A trial of low-dose tricyclic antidepressants (e.g., nortriptyline up to 1 mg/kg as tolerated), as a symptom modulator, may be considered [1, 2]. Pyloric injection of botulinum toxin has been postulated in some studies as a therapeutic option to overcome prolonged periods of increased phasic and tonic motor activity of the pylorus termed "pylorospasm" which can occur after vagotomy. Although it has been studied is several series with variable degree of success, a recent systematic review of 15 studies including 2 randomized controlled trials showed that intrapyloric botulinum toxin injection could not significantly relieve subjective symptoms and improve objective measurement in patients with gastroparesis [42]. An open-label study of endoscopic pyloric injection of botulinum toxin A was reported specifically for treatment of 11 patients with postvagotomy gastroparesis (9 postfundoplication) [43]. There were reductions seen in symptoms at 1 and 3 months after treatment with return of symptoms after 6 months suggesting botulinum toxin may produce short-term, but not sustained, reduction of symptoms.

The likelihood of spontaneous improvement begins to decline after a year or more has passed since the putative surgical injury [2]. Management of patients with persistent refractory PSG can be particularly challenging. Their illness has generally been long-standing, and their symptoms have remained despite a variety of medical and possible subsequent surgical interventions. Chronic abdominal pain and associated psychosocial behavioral patterns are common in such patients, as is narcotic dependency. A multidisciplinary approach is, therefore, important, with input from gastroenterologists, nutritionists, surgeons, pain specialists, and psychologists specializing in the care of these patients.

For patients who fail medical therapies, surgical interventions are often contemplated [44]. These include tube gastrostomy for gastric decompression and jejunostomy for enteral feedings. Total gastrectomy is reserved for intractable vomiting and weight loss after all other options have failed. This is usually in the patient after partial gastric resection with either a Billroth I or II with or without a Roux-en-Y reconstruction [45]. Most of the literature suggests performance of a "completion" gastrectomy [2, 44]. The largest series have yielded conflicting conclusions. In one series of 81 patients with PSG who underwent "near-completion gastrectomy" (the gastric remnant is resected, leaving a 1- to 2-cm portion to anastomose with the jejunum), follow-up data were available on 52 patients over an average of nearly 5 years.

Using a relatively simple subjective score, the investigators reported that almost 80% of patients reported long-term relief of symptoms [46]. By contrast, another study led to a considerably less optimistic conclusion. This study involved 62 patients, 60 of whom were followed for a mean of 5.4 years after near-completion gastrectomy. The results of this study, which applied more robust objective and subjective criteria, suggest that only 43% of patients had favorable results [47]. Surgery was most beneficial for the relief of nausea, and vomiting, but not for relief of chronic pain. In the most recent third study, 44 patients were reported who underwent near-total or total completion gastrectomies for refractory postsurgical gastroparesis [48]. Postoperative complications occurred in 36%, most commonly bowel obstruction, anastomotic stricture, and anastomotic leak. Patients rated their improvement: 78% felt better, 17% neutral, and 6% worse. There were symptom improvements in abdominal pain, vomiting, and nausea. However, most patients had significant ongoing gastrointestinal complaints and the incidence of osteoporosis was high.

Gastric electrical stimulation (GES) is an emerging option for refractory symptoms from PSG. Although electrical pacing of the Roux limb has been applied experimentally and was shown to result in abolition of ectopic pacemakers responsible for jejunogastric reflux, it has not been established as a practical clinical approach [8]. The introduction of high-frequency GES for patients with diabetic and idiopathic gastroparesis has raised hope for patients with PSG [49]. Some technical surgical issues are present with gastric electric stimulation for PSG. First, the placement of electrodes and be difficult due to the small stomach remaining. Second, the placement of the electrodes may not be at the location of the gastric pacemaker as is done in idiopathic and diabetic gastroparetic patients with intact stomachs in whom the stimulator wires are placed 9 and 10 cm proximal to the pylorus. A recent report provides some optimism in this regard: the authors reported six patients with PSG treated with GES and followed for up to 46 months. Impressive improvements in symptomatic scores, quality of life, and solid and liquid gastric emptying were seen [50]. In another study, GES was implanted in 16 patients with postsurgical gastroparesis who failed standard medical therapy [45]. The severity and frequency of all 6 upper GI symptoms, total symptom score, quality of life scores were significantly improved after 6 months and sustained at 12 months. All patients had delayed gastric emptying at baseline. Gastric emptying was not significantly faster at 12 months, although 3 normalized. At implantation, 7 of 16 patients required nutritional support with a feeding jejunostomy tube; after GES, 4 were able to discontinue jejunal feeding. The mean number of hospitalization days was significantly reduced by a mean 25 days compared with the prior year. One patient had the device removed after 12 months because of infection around the pulse generator. These observations suggest that GES can improve upper GI symptoms, quality of life, the nutritional status, and hospitalization requirements of patients with postsurgical gastroparesis [45]. Although vagal nerve damage or disruption was part of the underlying pathophysiology, GES therapy was still effective and is a potential treatment option for the long-term management of postsurgical gastroparesis [45]. The patients that were least likely to benefit from GES were these with <50% their stomach still remaining.

Recent data on 31 patients with PSG treated with gastric stimulation showed an overall response rate (>50% symptom improvement) for PSG of 53% which was slightly less for diabetic patients (58%) but more than the idiopathic group (48%) [49].

Summary

Postsurgical gastroparesis remains an important cause of gastroparesis, although it is less common than diabetic and idiopathic etiologies. The surgical setting for PSG has changed now that surgery for peptic ulcer disease is less commonly performed. Currently, PSG is more likely to be associated with vagal nerve injury following antireflux and bariatric surgery. Management of patients with persistent refractory postsurgical gastroparesis can be challenging. A multidisciplinary approach is helpful with input from gastroenterologists, surgeons, and nutritionists.

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Chapter 18
Idiopathic Gastroparesis

Linda Nguyen

Keywords Idiopathic gastroparesis • Postinfectious gastroparesis • Functional dyspepsia • Psychological dysfunction

Introduction

Idiopathic gastroparesis is a disorder of delayed gastric emptying without an identifiable cause. Several series of patients with gastroparesis found idiopathic gastroparesis to be the most common cause of gastroparesis, comprising 36–49% of patients [1–3]. Up to 23% of patients with idiopathic gastroparesis may have a postinfectious form of gastroparesis, presenting after a viral prodrome and acute onset of symptoms [1]. Patients with postinfectious gastroparesis typically have a better prognosis compared to those with idiopathic gastroparesis [4–6]. Some patients with postinfectious gastroparesis have been reported to experience symptom improvement and even resolution of symptoms anywhere from 1 to 32 months after the onset of symptoms [5, 6].

Epidemiology

The true prevalence of idiopathic gastroparesis is not known due to lack of population-based studies. A recent study using the National Inpatient Sample Database on inpatient hospitalizations, showed that the number of gastroparesis-related hospitalizations has been increasing in the USA, and associated with significant economic

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costs and inpatient mortality [7]. Interestingly, the rise in gastroparesis was predominantly related to a rise in Caucasian women with nondiabetic gastroparesis [8]. Delayed gastric emptying is reported in 15–35% of patients with functional dyspepsia, a condition that, at least by questionnaire data, is present in about 20% of the population. By these estimates, dyspeptic symptoms with delayed gastric emptying (i.e., idiopathic gastroparesis) might be present in 5% of the general population. The Mayo Clinic group, using the Rochester Epidemiology Project, found that the age-adjusted prevalence of definite gastroparesis was much lower: 9.6 for men and 37.8 for women per 100,000 persons [2].

Women account for approximately 80% of patients with gastroparesis, with an average age of approximately 40 years [1, 2, 9]. The female predominance is present in idiopathic, diabetic, and postsurgical gastroparesis. Despite chronic gastrointestinal symptoms, the NIH gastroparesis clinical research consortium found that 26% of patients with idiopathic gastroparesis were obese (BMI > 30 kg/m^2) [9].

Psychological dysfunction, either depression or anxiety, can be present in many of these patients with idiopathic gastroparesis [1, 10]. The associated or causal relationship between symptoms of gastroparesis and psychological dysfunction is not clear. Psychological dysfunction in the form of depression and anxiety does not correlate with the degree of gastric emptying delay or etiology of gastroparesis; however, depression and anxiety correlated with physician and patient-rated gastroparesis severity [10]. A history of abuse has been reported to be present in some patients with idiopathic gastroparesis [1].

Evaluation of Patients with Suspected Idiopathic Gastroparesis

Chapter 6 contains a detailed discussion of specific tests for diagnosing gastroparesis. For patients with documented gastroparesis without a known underlying cause, additional testing should be performed to exclude other causes of delayed gastric emptying. A careful history and physical examination should be performed to evaluate for the presence of an underlying malignancy or concomitant neurologic, autoimmune, or connective tissue disorder. A thorough drug history should be obtained to evaluate for medications that may delay gastric emptying: narcotics [11], anticholinergic agents [12], tricyclic antidepressants [13], calcium channel blockers [14], dopamine agonists [15], and nicotine [16]. Opiate narcotic analgesics can delay gastric emptying and also cause symptoms of nausea and vomiting. Laboratory testing has limited value in diagnosing gastroparesis. Testing is recommended to exclude thyroid dysfunction and to evaluate for metabolic derangements, such as hypokalemia or renal insufficiency. Basic testing should include complete blood count, complete metabolic panel, magnesium, thyroid function tests, and ANA. The patient's nutritional status can be screened with assessing a prealbumin level.

Symptoms

Similar to other causes of gastroparesis, symptoms are nonspecific, including nausea, vomiting, abdominal pain, early satiety, and/or abdominal distension. Symptoms of idiopathic gastroparesis often overlap with functional dyspepsia. Up to 40% of patient's meeting Rome I or II criteria for functional dyspepsia were found to have delayed gastric emptying [17, 18]. However, the rate of gastric emptying correlates poorly with symptom severity [19–21]. Vomiting and postprandial fullness is reported to be associated with delayed gastric emptying in patients with functional dyspepsia. Although gastroparesis is classically thought of as being a disorder of predominant nausea, vomiting, and fullness; abdominal pain is present in many patients irrespective of the cause of gastroparesis [22]. Abdominal pain was present in up to 90% of patients with gastroparesis [1, 22–24]. The prevalence of upper abdominal pain was similar between diabetic and idiopathic gastroparesis; however, the severity of pain was greater in patients with idiopathic gastroparesis [22]. Abdominal pain also correlated with impairment in quality of life [22].

It has also been proposed that patients with gastroparesis be classified based on predominant symptom similarly to patients with irritable bowel syndrome: (1) vomiting predominant; (2) dyspepsia predominant; and (3) regurgitation predominant [25]. In a study of 100 patients with gastroparesis, 29% had vomiting predominant, 49% had dyspepsia predominant, and 22% regurgitation predominant. Patients with vomiting predominant gastroparesis were more likely to be younger and more likely to experience weight loss and dehydration. Patients with regurgitation predominant symptoms were more likely to be older and heavier. This is an intriguing concept as it may help guide therapy. However, further studies are required to determine if this symptom based classification correlates with pathophysiology and treatment response.

Pathophysiology

The pathophysiology of gastroparesis is discussed in detail in Chapters 4–7. Delayed gastric emptying can occur as a result of alterations in a variety of gastrointestinal motor function: impaired gastric accommodation [23], antral hypomotility [26, 27], pylorospasm [28, 29], altered antroduodenal coordination, or small bowel dysmotility [28]. In a study of 58 patients with idiopathic gastroparesis, 43% were found to have impaired gastric accommodation and 29% were found to have visceral hypersensitivity [23]. In this study, early satiety and weight loss were associated with impaired gastric accommodation while pain, early satiety, and weight loss were associated with hypersensitivity to gastric distention. In a study of 20 consecutive patients with idiopathic nausea and vomiting, 70% were found to have postprandial antral hypomotility [27]. Preliminary data revealed that approximately 57% of patients with idiopathic gastroparesis had pylorospasm [30]. In a series of 13 patients with gastroparesis, 54% of patients had the presence of intestinal dysmotility [28].

Treatment of Idiopathic Gastroparesis

Treatment of idiopathic gastroparesis is similar to other causes of gastroparesis. This involves supportive measures through dietary modifications, promotility agents, and antiemetic therapy. Detailed discussions of specific treatments of each are discussed in separate chapters. However, idiopathic gastroparesis appears to respond differently to certain therapies compared to diabetic gastroparesis. These include intrapyloric botulinum toxin injection and gastric electrical stimulation.

Intrapyloric Botulinum Toxin Injection

Open label studies of gastroparesis found intrapyloric injection of botulinum toxin effective in treating gastroparesis [31–34]. However, placebo-controlled studies failed to demonstrate a benefit of botulinum toxin over placebo [35, 36]. A retrospective analysis of a large series of patients found that female gender, younger age, and a diagnosis of idiopathic gastroparesis was associated with a positive response to intrapyloric botulinum toxin injection [37]. This study also found that a higher dose of botulinum toxin was associated with a greater response (54.2% vs. 76.7% for the 100 IU vs. 200 IU of botulinum toxin; $p = 0.02$).

Gastric Electrical Stimulation

Gastric electrical stimulation uses an implantable neurostimulator for the treatment of refractory gastroparesis. Since the HDE approval of high frequency, low energy gastric stimulation, several open label studies have demonstrated variable response rates ranging from 50 to 90% improvement in gastroparesis symptoms [38–40]. In the studies that led to the compassionate use approval of gastric electric stimulation for patients with gastroparesis, patients with diabetic gastroparesis responded better with a decrease in vomiting frequency compared to patients with idiopathic gastroparesis [41]. Two single center studies have found that patients with nausea/vomiting predominant gastroparesis and diabetic gastroparesis responded better than patients with idiopathic gastroparesis or those requiring chronic daily narcotics for pain [38, 42].

Impact

Despite the "functional" classification of idiopathic gastroparesis and overlap with functional dyspepsia, idiopathic gastroparesis is associated with significant morbidity and even increased mortality [1]. Several studies report decrease in the

quality of life and impairment in functional ability. However, there are limited population-based studies that describe the impact of idiopathic gastroparesis. In a population-based study of Olmsted County, Minnesota, the overall survival for gastroparesis was significantly less than expected in that population (67% vs. 81% 5 year survival, $p<0.01$), attesting to the seriousness of this condition [2]. Importantly, idiopathic gastroparesis was associated with significantly better survival than other causes of gastroparesis, such as diabetic gastroparesis.

Summary

Idiopathic gastroparesis is the most common cause of gastroparesis. The rate of gastroparesis hospitalizations has been increasing over the past decade. This is associated with increased health care burden and decreased survival. Nausea, vomiting, postprandial fullness, and abdominal pain are common symptoms similar to those of diabetic gastroparesis. Current treatments for idiopathic gastroparesis appear to improve upon symptoms of nausea or vomiting rather than pain. The presence of pain predominant gastroparesis correlates poorly with treatment response, particularly gastric electrical stimulation. Gastric emptying has been found to correlate poorly with symptoms of gastroparesis. Likewise, accelerating gastric emptying has correlated poorly with symptom response, which suggests that the pathophysiology of gastroparesis is more complex than purely mechanical emptying. Clinicians caring for patients with gastroparesis, in order to make the greatest impact in patient's symptoms, must take these into account. Much more needs to be learned about this disorder of idiopathic gastroparesis, both in terms of pathophysiology and treatment, since patients with this disorder have significant symptoms impacting their function and life.

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Chapter 19
Gastroparesis from Other Causes

Alia Dadabhai and Robert S. Fisher

Keywords Gastroparesis • Gastroesophageal reflux disease • Connective tissue disorders • Malignancy • Viral infections

Introduction

Gastroparesis refers to delayed stomach emptying in the absence of mechanical obstruction of the gastric outlet. It can be due to failure to generate an aboral pressure gradient within the stomach (i.e., pump failure); inadequate relaxation of the pylorus (i.e., functional obstruction); or an inappropriate pressure gradient between the antrum and the duodenum caused by antral hypomotility or duodenal spasm. The majority of patients with gastroparesis can be categorized as being related to diabetes mellitus (type 1 or type 2), vagus nerve malfunction secondary to primary injury (vagotomy) or secondary injury (antireflux or bariatric surgery, heart-lung transplantation) or as idiopathic. Before classifying gastroparesis as being idiopathic, there are a number of other putative etiologies that must be considered (Table 19.1). These other putative etiologies are the subject of this chapter.

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Table 19.1 Classification of gastroparesis

Diabetes mellitus
Postsurgery
Vagotomy
Vagal injury – Antireflux
Bariatric
Heart-lung transplant
Idiopathic
"Other" causes
Gastroesophageal reflux disease
Functional dyspepsia
Hypertrophic pyloric stenosis
Constipation – generalized dysmotility
intestinal pseudoobstruction
Connective tissue disorder
Scleroderma
Dermatomyositis
Autoimmune
Malignancy
Paraneoplastic syndrome
High-dose chemotherapy
Stem cell transplantation
Viral infection
Endocrine causes
Hypothyroidism
Medication-induced
Opioids
Anticholinergic agents
Dopaminergic agents
Neurologic disorders
Multiple sclerosis
Parkinson's disease
Hollow visceral neuropathy or myopathy
Chagas disease
Psychiatric disorders
Chronic pancreatitis
Renal failure
Total parenteral nutrition

Gastroesophageal Reflux Disease

The presence of gastroparesis in a significant number of patients with GERD was initially reported by McCallum et al. [1]. This association was initially controversial, but has now been confirmed by other investigators [2]. The pathophysiologic explanation of GERD related to gastric hypomotility is still under investigation. One theory is that gastric distension as a result of gastric stasis may increase the frequency of transient lower esophageal sphincter relaxations resulting in increased

gastroesophageal reflux. Continued bathing of the distal esophagus in acidic or bilious gastric contents can be seen during exacerbations of gastroparesis leading to reflux symptoms, such as heartburn or esophagitis [2]. Although fundoplication may be an option for symptomatic relief and healing, there are always concerns that fundoplication could exacerbate the problem by making gastroparesis worse.

Hypertrophic Pyloric Stenosis

In the pediatric population, congenital hypertrophic pyloric stenosis usually presents with vomiting within the first month of life. The primary condition is rarely seen in adults. Inability to relax the pyloric sphincter is associated with hypertrophy of the inner circular muscle layer which causes delayed gastric emptying. Interstitial cells of Cajal along with nitric oxide containing inhibitory nerves are lost [3, 4]. A surgical option for treatment is pyloromyotomy (Ramstedt procedure) which is often successful. Reversal of the dearth in interstitial cells of Cajal and an increase in free nitric oxide has been reported after surgery. However, the tonicity of the pylorus remains high with diminished pyloric pressure waves. Pasricha et al. has been able to restore nitric oxide and reverse gastroparesis in a mouse model of gastroparesis by performing stem cell transplantation [5].

Constipation-Associated Gastroparesis

Constipation-associated gastroparesis is present in 20–30% of patients with chronic idiopathic constipation or irritable bowel syndrome with predominant constipation. During antroduodenal manometry, a higher prevalence of burst activity has been reported in the antrum and duodenum in the fasting state and the presence of abnormal phase III-like activity during the postprandial phase suggesting neural dysfunction affecting the enteric nervous system or the extrinsic pathways [6]. Other potential explanations for an association between constipation and gastroparesis include unintentional and intentional delays of defecation which could cause dysregulation of hormonal gut mediators and consequent colonic distension which may inhibit the gastrocolic reflex. These associations are theoretical.

Medication-Induced Gastroparesis

Medication-induced delayed gastric emptying has been related to a number of commonly used over the counter and prescription drugs (Table 19.2). Narcotics are the most common offenders. There are three major opioid receptors in the human body: delta, kappa, and mu. These receptors overlap in their distribution and function

Table 19.2 Medications associated with impaired gastric emptying

Narcotics
Anticholinergic medications
Tricyclic antidepressants
Calcium channel blockers
Clonidine
Dopamine agonists
Lithium
Nicotine
Progesterone

throughout the central and enteric nervous systems and maintain some selectivity for endogenous opioids. Exogenous opioids preferentially activate μ-opioid receptors. In the human GI tract, the μ (mu)-opioid receptor is primarily found in the myenteric and submucosal plexi of the small and large intestines [7]. Both endogenous and exogenous opioids impair gastrointestinal transit by altering neuronal excitability and inhibiting the release of acetylcholine and other neurotransmitters. Investigators in the early 1940s administered varying doses of morphine and hydromorphone to healthy male volunteers and studied their responses. While *segmental* motor tone and contractility were increased, *longitudinal propulsive peristaltic contractions were* decreased [8].

Oral naloxone, a systemic opioid antagonist with low bioavailability owing to first-pass hepatic metabolism, has been studied for its theoretical accumulation in the bowel without systemic levels in the blood making it a candidate for the treatment of opioid-induced constipation. Unfortunately, when this hypothesis was tested, a significant number of patients reported central side effects and pain when systemic opioids were withdrawn [9]. The desire to maintain analgesia without constipation has led to the investigation of peripherally acting opioid antagonists, such as methylnaltrexone and alvimopan. These agents selectively antagonize the peripheral μ (mu)-opioid receptor without diminishing opioid effects on the central nervous system. Preliminary studies using methylnaltrexone or alvimopan to treat opioid-induced gastrointestinal side effects have been encouraging [10].

Other agents have been less well studied in relationship to delay gastric emptying. Anticholinergic medicines, whose properties are found in the many common prescriptions, do have some relationship to slowing motility. Atropine, being the classic example of an anticholinergic medicine, has almost 100% cholinergic antagonist activity, while other more common medications, such as Benadryl, have less than 55% effects anticholinergic activity. The mechanism of action behind the delay in gastric emptying is inhibition of the parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptors in nerve cells. Nervous fibers of the parasympathetic system are responsible for the involuntary movements of smooth muscles present in the gastrointestinal tract, urinary tract, and lungs, etc. Anticholinergics are divided into three categories in accordance with their specific targets in the central and/or peripheral nervous system: antimuscarinic agents, ganglionic blockers, and neuromuscular blockers, of which the anitmuscarinics

are usually related to gastrointestinal delay. For example, the therapeutic effect of metoclopramide for prokinesis is thought to be mediated by muscarinic activity, D_2 receptor antagonist activity, and 5-HT_4 receptor agonist activity [11].

Connective Tissue Disorders

The prevalence of delayed emptying in scleroderma is estimated to be 40–67%, whereas the rates in polymyositis–dermatomyositis and systemic lupus erythematosus are lower. Gastric stasis is described in smooth muscle disorders, such as myotonic dystrophy and progressive muscular dystrophy [12].

Scleroderma: Gastrointestinal scleroderma most commonly affects the esophagus producing symptoms, such as heartburn, regurgitation, and dysphagia [13]. The symptoms of scleroderma-related gastroparesis are intermittent with remissions often lasting several months. Heartburn, dysphagia, bloating, nausea, and vomiting are consequences of smooth muscle and enteric neuronal damage of the esophagus and stomach in patients with scleroderma. Clinically, evidence of systemic disease involving the skin, lungs, and/or the esophagus is usually present in patients with gastric or intestinal involvement due to scleroderma [14]. Food regurgitated from the stomach may be confused with food retained retrosternally because of esophageal dysmotility or a distal esophageal stricture. A possible pathophysiologic explanation for gastric scleroderma is autoimmune-mediated injury. In one study, high titer antibodies directed against myenteric neurons were detected in 19 of 41 patients with systemic sclerosis. Normal controls of patients with idiopathic gastrointestinal dysmotility did not demonstrate these antibodies [15]. The presence of CD4+ lymphocytes in the gastric mucosa as well as fibrosis have also been noted indicating a mutifactorial etiology [16].

Malignancy

Often cancer patients attribute nausea and vomiting to their cancer therapy; however, gastroparesis is one of the most underdiagnosed disorders related to malignancy. The gastric slowing is typically seen in patients with upper GI tract tumors, such as gastric, pancreatic, esophageal, or biliary. Breast and lung cancer have also been notably related. Whether mechanical tumor-related obstruction, infiltration of the celiac plexus or vagus nerve, postsurgical resection, viral infection, or paraneoplastic mediated causes are the etiology, treatment can be difficult in the setting of baseline nausea from the chemotherapy [17, 18]. Patients with malignancy-associated gastroparesis have difficulty with gastric emptying of solids, particularly those that are fiber-rich. A mechanical gastric outlet obstruction may occur from the subsequent bezoar formation [19]. In one study, nausea was the major complaint in 93% of these patients with gastroparesis, 89% had abdominal pain, 86% experienced early satiety, and vomiting occurred in 68% [20]. In pancreatic cancer patients, as many

as 60% of patients who have received treatment clinically manifest delayed gastric emptying [21]. Dysphagia and abnormal small bowel motility with ileus and pseudo-small bowel obstruction can also be evidenced in these cases.

High-Dose Chemotherapy and Stem Cell Transplantation

Stem cell transplantation poses a significant risk for gastric motor function disruption and has been noted in up to one-half of patients undergoing hematopoietic stem cell transplantation (HSCT), both autologous and allogeneic [22, 23]. A viral precursor, such as cytomegalovirus (CMV) or herpes simplex virus, has been thought to be the instigating factor [16]. However, there have also been reports of gastroparesis or generalized gastric myoelectric activity has been documented disruption without evidence of viral infection among patients undergoing high-dose chemotherapy with autologous HSCT [23]. Allogenic stem cell transplants can also cause generalized anorexia, nausea, and vomiting with or without gastroparesis as a form of upper gastrointestinal graft versus host disease [22].

Radiation Therapy

Gastroparesis is rarely associated with radiation therapy. Radiation enteritis can be seen causing upper GI symptoms similar to gastric motility impairment. If gastric emptying is delayed, a presumed etiology is enteric nervous system damage [24, 25]. Scant information on the topic has been published.

Dysmotility and Paraneoplastic Syndrome

Autoimmune and Paraneoplastic Gastrointestinal Dysmotility

There is likely an overlap between autoimmune mediated and paraneoplastic syndromes. Autoimmune gastrointestinal dysmotility is an autoimmune dysautonomia that can occur in the setting of an anatomically remote neoplasm, most commonly small cell lung cancer. The symptoms manifest as delayed gastric emptying sometimes accompanying delayed small intestinal transit, slow colonic transit, and pelvic floor dyssynergia. In one report, the diagnosis was established through the presence of plasma membrane cation channel autoantibodies [26, 27]. Some of these patients responded to immunotherapy.

Paraneoplastic gastroparesis has been identified primarily in small cell lung cancer. However, in rare cases, other tumors such as breast, ovarian and pancreatic cancer, carcinoid, retroperitoneal sarcoma, Hodgkin lymphoma, and cholangiocarcinoma [28–31] can be associated with a paraneoplastic gastrointestinal motility disorder. Immunofluorescence assay can detect the antineuronal nuclear (ANNA-1, anti-Hu)

Table 19.3 Paraneoplastic gastrointestinal motor dysfunction

Cancer	Autoantibodies
Breast cancer	PCA-1, ANNA-2
Hodgkin lymphoma	PCA-Tr, N-type Ca++Ab
Ovarian cancer	PCA-1, N-type Ca++Ab
Small cell lung cancer	ANNA-1

PCA-1: type 1 Purkinje cell cytoplasmic antibody, also called anti-Yo; ANNA2: antineuronal nuclear antibody type 2, also called anti-Ri; PCA-Tr: Purkinje cell cytoplasmic antibody type Tr; N-type Ca++Ab: antineuronal calcium channel antibody of N-type specificity; ANNA-1: antineuronal nuclear antibody type 1, also called anti-Hu. Data from: Lee, HR, Lennon, VA, Camilleri, M, Prather, CM. Paraneoplastic gastrointestinal motor dysfunction: clinical and laboratory characteristics. Am J Gastroenterol 2001; 96:373

antibodies in these patients [32]. A shared epitope between these autoantibodies and neuronal components of the enteric nervous system is theorized as the explanation of the gastroparesis [33]. The two most common autoantibodies are ANNA-1 and N-type voltage-gated calcium channel antibodies. Other autoantibodies associated with paraneoplastic gastrointestinal dysmotility include antineuronal antibodies type 2 (ANNA-2 or anti-Ri), amphiphysin antibody, type 1 Purkinje cell cytoplasmic antibody (PCA-1, also called anti-Yo), PCA-2, PCA-Tr, collapsing response modifier protein (CRMP) antibodies and antineuronal calcium channel antibodies of the P/Q and N-type (Table 19.3) [34].

Although the exact mechanism for the gastroparesis has not been adequately defined, studies conducted in patients with small cell lung cancer and gastrointestinal dysmotility have demonstrated immune-mediated destruction of the interstitial cells of Cajal (the so-called intestinal pacemaker cells) [35]. Another proposed theory is that dysmotility results from a visceral neuropathy of the myenteric plexus associated with an infiltration with lymphocytes and plasma cells, and subsequent axonal degeneration within the plexus [36].

Celiac Plexus Injury

Damage to the celiac plexus due to cancer infiltration or a celiac plexus nerve block can produce effects on gastric emptying [37]. Both accelerated and delayed gastric emptying have been reported.

Diffuse Gut Dismotility

Diffuse disorders of gut motility, such as chronic intestinal pseudoobstruction can present with gastroparesis. Patients commonly manifest a wide range of clinical features, including small intestinal bacterial overgrowth, nutritional deficiencies, bowel habit abnormalities, and pneumatosis intestinalis. Primary or secondary

amyloidosis can cause neuropathic or myopathic intestinal pseudoobstruction. Stasis of the stomach is found in 19–64% of patients with chronic constipation or constipation-predominant irritable bowel syndrome and has been linked with megarectum. Intestinal pseudoobstruction can also be related to familial causes, occur after a viral prodrome, or present as a paraneoplastic phenomenon most often in association with small cell lung carcinoma. The classic infectious cause of interrupted gastric motility is Chagas' disease, in which the myenteric plexus is damaged by *Trypanosoma cruzi* infection. In addition to producing an achalasia-like picture, Chagas' disease may cause gastroparesis, megaduodenum, and chronic intestinal pseudoobstruction and several extraintestinal manifestations.

Viral Infections

Published reports have described the occurrence of gastric stasis in association with prior viral infection, particularly Norwalk virus and rotavirus [10, 15, 38]. Other viruses which may be associated with isolated cases of gastroparesis are varicella zoster (VZV), Epstein-Barr (EBV), CMV, and human immunodeficiency virus (HIV). It has been speculated that certain viruses may cause extrinsic autonomic denervation [39, 40]. A case study of seven patients suggested that a majority of postviral gastroparesis cases resolved spontaneously within 4 weeks to 12 months [41]. Five of seven patients in a retrospective study by Ohh et al. had complete resolution of gastroparetic symptoms during a mean follow-up of 32 months. The two remaining subjects had considerable improvement within the study time frame [42]. Another study in the pediatric population included 11 postviral delayed gastric motility cases; all had resolution of symptoms in 6–24 months (mean 12.2 months) [12].

Symptomatic gastroparesis in CMV and HIV are rarely seen in immunocompetent/well-controlled individuals. CMV-associated gastroparesis can become clinically relevant after organ transplant [43]. Up to one-third of patients who develop CMV infection after liver transplantation develop dyspeptic symptoms. Histological evidence of CMV is noted on endoscopic biopsies from the stomach. Similar observations have been made for HIV infection. Up to one-third of the patients with HIV infection have dyspeptic symptoms which may be exacerbated by concomitant CMV or mycobacterium avium-intracellulare in those individuals who are not well controlled. Management of these patients should emphasize antiviral and antiretroviral therapy. Recovery can be maintained with management of the underlying disorders.

Neurologic Disorders

Gastric stasis or vomiting is commonly seen with neurologic disorders (Fig. 19.1). The vagus nerve and lower thoracic spinal sympathetic outflow which regulate the upper gut's extrinsic neural control can be involved in for multiple sclerosis, brain stem stroke or tumor, diabetic or amyloid neuropathy, or primary dysautonomias.

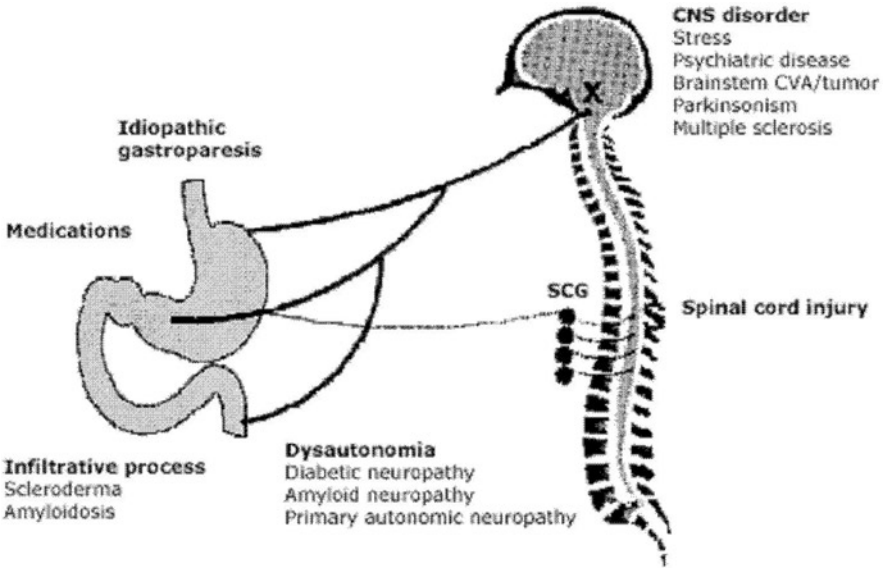

Fig. 19.1 Neuromuscular disorders impairing gastric motor function. Camilleri, M, and Prather, CM. In: Sleisenger and Fordtran's Gastrointestinal Disease, 6th ed, Feldman, M, Scharschmidt, BF, and Sleisenger, MH (eds) W. B. Saunders, Philadelphia, 1998. p. 572. Used with permission

Degenerative, diffuse neurologic processes, such as diabetes mellitus, acquired immune deficiency syndrome (AIDS) or Parkinson's disease (where Lewy bodies have been noted in myenteric neurons), can affect the myenteric plexus. Gastric stasis may also be the result of several medications used to control the neurologic disease (e.g., anticholinergics, dopaminergics, etc.).

Psychiatric Disease

Symptoms commonly associated with gastric stasis, such as nausea, vomiting, early satiety, abdominal bloating, and anorexia, are commonly present in patients with psychiatric disease, including depression, anxiety neurosis, and eating disorders, such as anorexia nervosa, bulimia, psychogenic vomiting, or can be due to side effects from a psychotropic medication. Vomiting is noted to be the most frequent complaint in these patients [44]. Documentation of gastroparesis with gastric scintigraphy or wireless motility capsule is essential in these cases as vomiting may also be self-induced in eating disorders. Treatment of these psychiatric disorders associated with gastroparesis should include behavioral and psychiatric approaches along with medication modification.

Chronic Pancreatitis

Gastroparesis has been reported with some cases of small duct pancreatitis. Delayed gastric emptying may be difficult to diagnose in these patients as the classic symptoms of nausea/vomiting/abdominal pain preclude its measurement. It is reasonable to check gastric emptying in patients who are refractory to medication after other anatomic abnormalities have been ruled out. Restoration of the gastric myoelectrical activity after administration of pancreatic enzymes has shown some promise [45].

Renal Failure

Delayed gastric emptying associated with renal dialysis or more particularly peritoneal dialysis has been noted in several patients with renal failure. This is thought to be related to electrolyte and macronutrient shifts that lead to generalized slowing of the gastrointestinal tract motility [46]. Patients who have renal failure often manifest nausea/vomiting without gastroparesis being present; therefore, the disorder often goes undiagnosed. Maintenances of proper nutrition and electrolyte balances can be the key to controlling the patient's dyspeptic symptoms.

Total Parenteral Nutrition

TPN can cause hyperglycemia which may decrease antral contractility. Hyperglycemia slows the antral phase III of the MMC, increases pyloric contractions, can cause tachygastria, decrease gastric emptying, and modify fundic relaxation [47]. Vigilant management of electrolyte and macronutrient formulations can reverse the effects of the TPN-associated gastroparesis. Lipid contents in the solution can also delay gastric emptying [48].

Conclusion

When confronted with a patient having symptomatic gastroparesis, there is a tendency to consider diabetes mellitus and vagal injury secondary to surgery as the likely cause. If neither of these conditions is present, most of the time, gastroparesis is thought to be idiopathic. The purpose of this chapter is to remind readers of many other possible causes or associations for gastroparesis. In many cases, if the cause or association is addressed, gastroparesis will improve.

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Chapter 20
Pediatric Gastroparesis

Miguel Saps and Carlo Di Lorenzo

Keywords Gastroparesis • Pediatrics • Prematurity • Food allergy • Gastroenteritis • Breath testing • Scintigraphy • Prokinetic • Gastric pacemaker

Etiology

The etiology of gastroparesis in children varies with age. In preterm infants, gastroparesis is usually related to *immaturity* of the gastrointestinal tract. Gastric electrical activity, neuromuscular coordination, gastric emptying, the development of nutritive sucking, and feeding tolerance all exhibit gradual maturation with gestational age. The frequency of normally configured migrating motor complexes (MMCs), the proportion of antral contractions associated with duodenal activity and the strength of antral contractions all increase with age. Human fetuses show initial swallowing movements at around 11 weeks of gestation with sucking developing at around 15–16 weeks of gestation. Fetal gastric emptying can be noticed as early as at 24–25 weeks gestation. Normal gastric electrical rhythm of predominant 3 cpm activity and mature patterns of liquid emptying has been reported to occur as early as at 32 weeks gestational age. Normal gastroduodenal electrical and motor activities as well as nutritive sucking are present at 34 weeks gestational age and preterm newborns exhibit little differences in gastric electrical activity and emptying on different recording days.

Postnatal maturation of gastroenteric motor function in preterm infants can be affected by early life experiences. Environmental and nociceptive factors affecting the airway and digestive tract may slow maturation. Children who experienced

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prolonged respiratory support and delayed initiation of enteral feeding are more likely to vomit and cough when fed solid foods at 6 months of age. A study using impedance to measure gastric emptying rate in full term neonates given a noncaloric liquid meal found a median gastric half emptying time of 6.9 (2.8 ± 12.5) min [1]. A study in infants aged 4 weeks to 6 months, demonstrated that gastric emptying varies with the composition of the meal. T1/2 measured by impedance gastrography was 48 min for breast milk and 78 min for infant formula [2]. Prebiotic oligosaccharides can modulate gastric emptying and gastric electrical activity in neonates. Newborns receiving formula with prebiotics have more consistent propagation of gastric electrical activity and faster gastric emptying. There is evidence that factors affecting gastric emptying in preterm infants differ from adults. While increases in osmolality, energy delivery and volume slows gastric emptying in adults, studies in 25–30 weeks preterm infants showed that while modifying each of this factors individually does not affect gastric emptying, decreasing osmolality while increasing volume accelerates emptying [3].

Children with central nervous system disorders (CNS) frequently develop gastric dysrhythmias and foregut dysmotility, possibly related to either the involvement of the enteric nervous system by the same process affecting the CNS or to abnormalities in modulation of the enteric nervous system by the CNS. A study comparing the gastrointestinal function of neurologically impaired children with healthy control children found a significant delay in gastric emptying in 14 out of 18 neurologically impaired subjects with a history of vomiting. There was no significant difference in gastric emptying between those children with CNS disorders who had no history of vomiting and controls [4]. Out of 50 children with CNS disorders evaluated, 15 had gastric dysrhythmia and 16 had both gastric dysrhythmia and gastroesophageal reflux (GER). Dietary protein allergy and especially cow's milk allergy should be considered in the differential diagnosis of preterm and full-term infants with chronic vomiting. It was reported that more than 40% of infants with GER had cow's milk allergy as the underlying cause of their symptoms. Severe gastric dysrhythmias with decreased normogastria and increased bradygastria activity and delayed gastric emptying occurred in a group of infants diagnosed with cow's milk allergy following exposure to cow's milk. In sensitized children, delayed gastric emptying may exacerbate GER by inducing reflex vomiting and leading to fundic distension and transient relaxations of the lower esophageal sphincter. Although the mechanisms are not yet clear, in sensitized patients, immune activation may result in polypeptides and proinflammatory cytokines release that in turn result in alterations of the enteric neuromusculature leading to abnormal activation and stimulation of gastrointestinal smooth muscle cells.

Postinfectious Gastroparesis

Postinfectious gastroparesis is one of the most common presentations of gastroparesis in older children. Viruses are the most common pathogenic agents but mycoplasma

Table 20.1 Etiology of gastroparesis in infants and children

Infants
Immaturity/prematurity
Cow's milk protein allergy
Pyloric stenosis
Duodenal atresia
Necrotizing enterocolitis
Meconium ileus
Children
Infectious (acute and postviral)
Surgery
Drugs
Chronic intestinal pseudoobstruction
Hirschsprung's disease
Neurodevelopmental disorders
Familial dysautonomia
Spinal cord injury
Cystic fibrosis
Celiac disease
Hypothyroidism
Acidosis/electrolye abnormalities
Diabetes
Anorexia nervosa
Bulimia nervosa
Eosinophilic gastroenteropathy
Connective tissue disorders
Muscular dystrophy
Crohn's disease
Caustic ingestion

infections have also been associated with gastroparesis. Described viruses include EBV, varicella virus, CMV [5], respiratory viruses, rotavirus, and the Norwalk agent. Postviral gastroparesis usually presents with persistent vomiting, abdominal distention, fullness, and weight loss following an acute self-limiting intercurrent illness. Vomiting may coincide with the onset of other acute gastrointestinal or extra gastrointestinal symptoms or manifest weeks to months later. A study in children and adults found that time to referral ranges from 3 weeks to 6 months after the initial episode [5]. By the time the physician is involved in the evaluation, the initial acute illness has usually resolved and no causative agents can be identified. Diagnosis is based on the history of acute onset, initial severe illness, demonstration of delayed gastric emptying, and exclusion of other causes of persistent vomiting. Treatment is supportive and antiviral therapy or other etiologic treatments have not been shown to be effective. Symptoms may persist for several months or years. Two studies that included children with postviral gastroparesis showed resolution of symptoms in less than 2 years in all cases [5, 6].

Other possible causes of gastroparesis in children are listed in Table 20.1. In patients with eosinophilic gastroenteropathy, the depth and extent of GI eosinophilic

infiltration determines the type and severity of manifestations. Vomiting may be present in cases of mucosal or transmural eosinophilic infiltration. No studies have been conducted evaluating gastric emptying in patients with eosinophilic gastroenteropathy. However, a study of children with functional dyspepsia investigated the association between antral infiltration by eosinophils and mast cells with electrogastrography and gastric emptying findings. It was found that high mast cell density was associated with slower gastric emptying and preprandial tachygastria suggesting the existence of a causal relation between antral inflammation and gastric dysfunction [7]. Gastric emptying studies show conflicting results in patients with cystic fibrosis with some authors reporting normal results [8] while others have shown delayed gastric emptying [9]. Cucchiara et al. found a significantly prolonged gastric emptying time in 26 out of 29 cystic fibrosis pediatric patients when compared with healthy control subjects. An electrogastrography study on 14 children with cystic fibrosis and 10 healthy controls, revealed postprandial gastric arrhythmias that were thought to explain the presence of delayed gastric emptying [10]. Gastroparesis significantly worsens after lung transplantation in all patients, possibly due to damage to the vagal nerves during surgery or to the use of some of the posttransplant medications.

Electrogastrographic studies in children with chronic intestinal pseudoobstruction showed persistent tachygastria during fasting probably related to the loss of intrinsic inhibitory innervation [11]. A study on full-term infants with a history of pyloric stenosis, intestinal atresia, necrotizing enterocolitis, and meconium ileus found delayed gastric emptying in all patients and differences in impedance gastric phasic activity that resolved after the resolution of the predisposing medical condition [12]. Although a common cause of gastroparesis in adults, the incidence of gastroparesis in children with diabetes mellitus has not been extensively investigated. A study showed dyspeptic symptoms in 7.2% of diabetic children with age ranging between 5 and 19 years [13]. In the few published pediatric studies, a common theme is that gastroparesis must be taken in consideration even in young diabetic patients who present with gastrointestinal symptoms. A study measuring the gastric emptying time and gastric electrical activity in 40 consecutive children with insulin-dependent diabetes mellitus (IDDM) without autonomic neuropathy and 15 healthy control subjects found a significant difference in gastric emptying time and a significantly higher prevalence of gastric electrical dysrhythmias in children with IDDM compared with controls [14]. The study showed that 65% of children in the IDDM group had delayed gastric emptying. Tachygastria was more prevalent in children with IDDM while there was no significant difference in bradygastria between both groups. EGG was similar in diabetic subjects with normal gastric emptying time and control subjects. The study found a significant correlation between HbA1c levels and gastric emptying time. There was also a significant correlation between blood glucose levels measured 180 min after meals with gastric emptying time abnormalities. A study on three adolescents with IDDM who complained of nausea, vomiting, abdominal pain, and constipation reported improvement in gastrointestinal symptoms, gastric emptying, and glycemic control using prokinetic treatment [15]. The study showed normal antral amplitude contractions after erythromycin injection during fasting but the absence of postprandial antral contractions after ingestion of a solid

meal. White et al. [16] described two adolescents with severe diabetic neuropathy, delayed gastric emptying, and poor metabolic control that improved their gastrointestinal symptoms with improved glycemic control. Studies on children with cyclic vomiting syndrome (CVS) provide conflicting results. Real-time ultrasonography showed normal gastric emptying in 9 children with CVS [17]. Another study on 16 children with CVS showed abnormal EGG with significant tachygastria in 25% of cases and abnormal gastric emptying in 75% of those children suggesting that abnormal gastric myoelectrical activity is involved in the pathogenesis of CVS syndrome [18]. Patients undergoing surgery are exposed to multiple factors that may result in gastric dysrhytmias and may delay gastric emptying. Studies in children undergoing nonabdominal surgery have demonstrated transient EGG changes associated with general anesthesia. Tachygastria associated with nausea and vomiting develops immediately after induction. Bradygastria was also described during the first half hour after general anesthesia. EGG changes return to baseline approximately 1 h after reversal of general anesthesia [19]. Vagal nerve injury and gastroparesis may occur in children undergoing upper abdominal surgery, such as fundoplication or bariatric surgery. Vagal nerve injury is also frequently reported after thoracic surgery, including lung and heart surgery [20]. Postsurgical gastroparesis is frequently transient and improves with time. Vagal reinnervation and the ability of the enteric nervous system to adapt may explain the reversal of these symptoms. A long-term follow-up report of neurologically impaired children who underwent a Nissen fundoplication found that preoperative delayed gastric emptying was associated with a less favorable surgical outcome [21]. There is also evidence that fundoplication may improve gastric emptying as suggested by a study of children with delayed gastric emptying who underwent fundoplication and an antroplasty and had a significant improvement in gastric emptying time at 90 min from 72% preoperatively to 40% postoperatively [22]. Another study measured gastric emptying of liquids before and after fundoplication without pyloroplasty and found it to be accelerated in all but one patient after the surgery [23].

Adolescents with anorexia nervosa often experience delay in gastric emptying and constipation [24]. It remains unclear whether these abnormalities are primary or secondary. Gastric electromechanical abnormalities may influence refeeding and weight restoration of this group of patients. Studies on patients with bulimia nervosa have showed delayed gastric emptying as well as abnormal gastric emptying capacity and relaxation [25]. Investigations of children and adults with untreated celiac disease have consistently shown a marked delayed in gastric emptying that corrects with gluten withdrawal [26, 27].

Diagnosis

Assessment of gastric emptying time through scintigraphic studies using a radioisotope-labeled solid meal is the gold standard for the diagnosis of gastroparesis in adults and children. Unfortunately, there are limited data on pediatric standards for this

diagnostic technique in children of different ages. Much like it is done in adults, conventional testing usually includes the use of a 99mTc sulfur colloid labeled egg sandwich followed by imaging at 0, 1, 2, and in some cases 4 h. Taste and meal preferences can make performing a "standard" test in all children somewhat problematic. A pediatric study on the preference of meals to conduct gastric emptying showed a low preference for scrambled egg on toast [28]. The study, conducted on 24 healthy children 5–10 years of age, found a mean T1/2 gastric emptying time of 107 min after the ingestion of 30 g of chocolate crispy cake (66.6% carbohydrate, 22% fat, 7% protein, energy content 616.7 kJ) [28]. Because T1/2 values of gastric emptying seem to be less accurate than the measurement of percentages of retention at fixed time points, and due to the lack of large studies investigating standards at fixed time points in normal children, pediatric centers have increasingly adopted the adult standards recently endorsed by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine [29]. The use of scintigraphy for the assessment of gastric emptying has some disadvantages. It requires expensive gamma cameras and patients are exposed to radiations, a factor that may be more concerning in young children than in adults. This has led to the development of alternative techniques of evaluation of gastric emptying in pediatrics.

Ultrasonography is widely available and noninvasive. It can also provide dynamic information on the various areas of the stomach in relation to meals, allowing simultaneous measurement of gastric emptying and gastric accommodation. The technique has been used in children of different ages and pathological conditions [30]. The largest published study on asymptomatic children evaluated 114 subjects of various weights, and it showed a similar gastric emptying curve in normal weight, overweight, and obese children [31]. Despite its multiple advantages, this technique has not become yet widely used for routine clinical purposes. Breath testing excretion of 13C-labeled octanoic acid or acetate is a noninvasive technique used to assess gastric emptying of liquids and solids. The technique is easy to conduct, reliable, cost-effective, and does not involve radiation and the expired air can be collected in any outpatient facility and mailed to a reference laboratory. Studies in children, using either acetate or octanoic acid labeled with 13C, have shown similar results to those obtained by scintigraphy [32]. The 13C breath test seems to be feasible and reliable also in neurologically impaired patients. A study on 21 healthy children given a standard liquid meal found a median T1/2 of 81 min with a range of 65–112 min using 13C-acetate breath test. The intraindividual variability in gastric emptying obtained by this technique is comparable to other techniques. Single photon emission computed tomography (SPECT) is a noninvasive and reliable scintigraphic technique [33]. It allows to assess gastric volume and the relation between gastric functions, such as accommodation and emptying. SPECT is not used for clinical purposes in children but has been used to investigate adolescents with functional dyspepsia [33]. No studies have been published on pediatric gastroparesis using SPECT. Measurement of gastric emptying time by the SmartPill® has a good correlation with gastric emptying measures obtained by scintigraphy in adults allowing discrimination between healthy adults and patients with gastroparesis [34]. SmartPill offers an attractive, nonradioactive, noninvasive ambulatory alternative to scintigraphy,

but it has not yet been approved by the FDA for use in children and its utility and safety in pediatrics is currently being investigated. The size of the capsule in the SmartPill is similar to that of the endoscopic PillCam, a device that has been FDA approved for use in children older than 2 years.

Treatment

Treatment is based on diet modifications, lifestyle changes, use of medications and, when possible, correction of the underlying conditions causing gastroparesis. Medications currently being used should be reviewed to uncover drugs that could contribute to the gastric dysfunction. Particular attention should be paid to the possible anticholinergic effects of psychotropic medication which are increasingly being used in the treatment of children with autism, attention deficit hyperactivity disorder or other psychiatric diseases. Children with gastroparesis should be managed by a multidisciplinary team that includes an experienced nutritionist. In children with severe and prolonged gastroparesis, correction of electrolyte and fluid imbalances and nutritional optimization are the mainstay of treatment. In patients with milder forms of gastroparesis, dietary modifications may be sufficient to control the symptoms. Small volume and more frequent meals (4–6 times a day) are recommended. Because lipids diminish antral pressures and increase basal pyloric pressure foods with high fat content should be avoided [35]. Meals with a high caloric content also decrease the gastric emptying rate. Fiber content should be minimized. Carbonated beverages should be avoided to limit gastric distention. Posture influences transpyloric flow and intragastric distribution of liquids. Liquids empty more slowly in the decubitus position. Postprandial walking accelerates gastric emptying.

Pharmacologic treatment may require a combination of drugs targeting different pathophysiological mechanisms and symptoms. Prokinetics are the drugs of choice for the treatment of gastroparesis, however, as symptoms may not be exclusively caused by a propulsive dysfunction, other drugs including visceral analgesics, fundic relaxants, and antiemetics may need to be considered. Prokinetics currently available in the USA include dopamine receptor antagonists and motilin receptor agonists. Dopamine receptor antagonists are domperidone, not commercially available in the USA, and metroclopramide that has received a “black box warning” by the FDA. Dopaminergic receptor antagonists have prokinetic and antiemetic properties and stimulate proximal gastrointestinal motility (lower esophageal sphincter, stomach, and proximal small intestine) without increasing gastric secretions. Metoclopramide is a central and peripheral antagonist of dopaminergic D2 receptors, an agonist of peripheral serotonergic 5-HT4 receptors, a 5-HT3 receptor antagonist, and has indirect cholinergic effects by releasing acetylcholine from the myenteric plexus. In children, metoclopramide is usually administered orally at a dose of 0.1–0.2 mg/kg/dose up to four times daily. Some of the undesirable effects of metroclopramide include extrapyramidal dyskinetic reactions, fatigue, depression,

and galactorrhea. Domperidone has similar peripheral mechanisms of action to metoclopramide but has minimal penetration through the blood-brain barrier limiting its central effects [36]. Domperidone enhances acetylcholine release, inhibits cholinesterase activity, and antagonizes adrenergic alpha-1-receptors [37]. A study in children found that oral domperidone is a safe and effective prokinetic. In pediatrics, domperidone is administered orally at a dose of 0.1–0.2 mg/kg/dose up to four times daily (max: 10–20 mg/kg/dose). Domperidone is commercially available in most of the world. In the USA, domperidone can be legally prescribed for gastroparesis by filing an investigational new drug application to the FDA [38].

Motilin is a peptide hormone secreted by the enterochromaffin cells of the small intestine. Erythromycin is a macrolide which also acts as a motilin receptor agonist with proven prokinetic effects in adults, preterm infants, and children. A placebo-controlled study on 20 preterm infants ranging from 26 to 34 weeks who received oral erythromycin 10 mg/kg every 8 h showed enhancement of antral contractility and acceleration of whole gut transit time [39]. Due to their different mechanisms of action erythromycin may be combined with metoclopramide. In children, the prokinetic dose of erythromycin is 3–5 mg/kg/dose 15–30 min prior to meals. Exposure to erythromycin in the neonatal period has been reported to result in a several fold increase in the risk of developing hypertrophic pyloric stenosis [40]. Another study found no association between maternal prenatal erythromycin exposure and infantile hypertrophic pyloric stenosis [41]. Macrolides are excreted in breast milk but results of a prospective study showed that exposure to this group of drugs during breastfeeding was not associated with an increased rate of hypertrophic pyloric stenosis or other serious adverse reactions [42].

In children with persistent nausea or vomiting, antiemetics can be added to the treatment on an as-needed basis. Those include 5-HT3 receptor antagonist agent, such as ondansetron, promethazine, or prochlorperazine in oral or suppository form. Among these drugs, ondansetron given up to a dose of 0.3–0.4 mg/kg/dose every 4–6 h on an as-needed basis is the most effective tool to control severe vomiting in children. A Cochrane review showed the use of acupoint stimulation using the P6 acupuncture point prevented postoperative nausea and vomiting [43]. The review found no difference in effectiveness between adults and children. Botulinum toxin acts by blocking acetylcholine release from excitatory nerve endings. Although no pediatric studies have been conducted evaluating the efficacy of intrapyloric injection of botulinum toxin for the treatment of gastroparesis, botulinum toxin injections are occasionally used for the treatment of this disorders. Studies in adult have shown disappointing results in the treatment of gastroparesis [44]. Due to difference in etiological factors involved in gastroparesis in children, studies in pediatrics are needed before any conclusions can be drawn on its efficacy in the younger age groups.

Patients with severe gastroparesis may benefit from gastric electrical stimulation. Gastric electrical stimulation uses an intramuscular implantable device that is placed in the stomach at the level of the greater curvature, close to the pylorus to provide low energy and high frequency electrical stimulation. The device is being increasingly used in adults and children for the treatment of gastroparesis-related

symptoms. Two studies have been published in children. Gastric electrical stimulation was shown to be safe and successful in reducing symptoms and optimizing nutrition in a 7-year-old total parenteral nutrition (TPN) dependent child, with gastroparesis, abnormal antroduodenal manometry, postprandial vomiting, and failure to thrive since birth who had daily nausea, vomiting, and intractable visceral pain and retching. One year after the implantation of the device the child had fewer symptoms and improved nutritional status but continued to require jejunostomy (J-tube) feedings [45]. A study in children with chronic nausea and vomiting who received an initial trial of temporary stimulation followed by permanent gastric stimulation device showed a sustained benefit in 7 of 9 children in symptoms and improvement in quality of life without significant electrographic or gastric emptying changes [46]. The results of the study are in line with adult studies that have shown improvement in nausea, vomiting, and nutritional status without a clear effect in gastric emptying [47]. The improvement of symptoms even in patient in whom gastric emptying has not improved significantly could be partially explained by a reduction in visceral sensitivity.

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Chapter 21
Dietary Treatment for Gastroparesis

Frank Duffy

Keywords Gastroparesis • Digestion • Absorption • Upper gastrointestinal dysfunction • Malnourishment • Dietary treatments

Introduction

Processing of ingested food by the upper gastrointestinal (GI) tract, which primarily occurs in the stomach and small intestine, is paramount to adequate digestion and absorption of nutrients. The constellation of symptoms and upper gastrointestinal dysfunction in patients with gastroparesis can create a propensity for acute or chronic malnourishment which can be debilitating or even life-threatening. Many patients with gastroparesis consume diets deficient in calories, vitamins, and minerals. Dietary treatment is indicated as a means of reducing the impact of delayed gastric emptying on food processing/absorption and is tailored to improve symptoms, making it important in the treatment of the patient with gastroparesis.

The general approach to dietary therapy for gastroparesis involves an assessment of the patient's nutritional status, identification of existent or risk of malnutrition, correction of acute nutrient deficiencies, collaboration with the patient on an adequate dietary regimen, and education on dietary principles in order to prevent malnutrition in the future. In this chapter, we elaborate on this approach for the patient with gastroparesis, and then highlight concerns specific to gastroparesis in diabetes and renal failure (RF), where dietary therapy is altered to reflect differing clinical concerns. We mention complementary therapies for gastroparesis, which straddle the areas of nutrition, medicine, and lifestyle intervention. Educational templates for use with patients with gastroparesis, as well as Internet resource information, are provided.

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Nutrition Assessment

The first step in determining the need or extent of dietary therapy in the patient with gastroparesis is a nutrition assessment, which includes taking a dietary history of the patient, weight, height, and anthropometric measurements, and laboratory tests. The patient may then be categorized as either at low, moderate, or high risk of malnutrition. Low-risk patients are able to maintain healthy nutritional status with minimal intervention and standard education on gastroparesis and diet. Moderate risk patients need more extensive diet manipulation and supplementation, with ongoing monitoring and support to maintain status. High-risk patients need ongoing monitoring, with more aggressive nutrition support regimens, including the possibility of enteral nutrition.

Weight Assessment

Nutrition assessment should begin with an estimation of lean body mass (LBM) status. A body weight (BW) history with subjective reports of food intake and strength level, along with visceral protein status and anthropometrics, can combine to ascertain LBM status and risk of debilitation and subsequent illness. Weight assessment is the most convenient gross estimate of nutritional status. Upon presentation, any patient <80% ideal body weight using Hamwi formula or Body Mass Index <20 kg/m^2 has a high risk of malnutrition. Obtaining a weight history may elucidate a trend toward malnutrition: >10% loss of usual BW over 6 months or >5% loss in 1 month indicates high risk [1]. Fluid status may confound weight assessment; patients need to be assessed for fluid retention. Dry weight is used for hemodialysis, and postparacentesis weight is used for patients with ascites. Edema can be an indicator of deficient protein status. Ascitic buildup of fluid can exacerbate gastroparesis symptoms; postprandial gastric volumes and accommodation are reduced in patients with cirrhosis and ascites, and removal of fluid increases fasting gastric volumes, volumes ingested, and caloric intake [2]. Therefore, sodium and fluid restriction may be warranted.

Patient Interview

Patient reporting on weight changes and dietary intake can be used to bolster the weight and nutritional assessments. Any significant weight loss from a patient's reported healthy weight, along with a concomitant complaint of weakness/fatigue, indicates high risk. Diet recall or calorie count can be used to correlate recent inadequate intake with overall weight loss. Nitrogen balance may be estimated in order to assess adequacy of protein intake, where excess of urinary nitrogen may reflect skeletal muscle catabolism. Other areas to screen the patient for risk

include oral food intolerance from poor dentition or dysphagia; liquid versus solid tolerance; percent of ingested food vomited; avoidance of certain foods; cyclic vs. sporadic symptoms; use of nutritional supplements; and bowel movement patterns (constipation or diarrhea) [3].

The average patient needs a caloric intake of 25 kcal/kg/day at rest. Any patient not eating 50% of their daily needs should be considered for oral liquid nutrient supplements to increase intake, e.g., Ensure Plus HN has 360 kcal/8 oz can. Inadequate intake, such as being nil per os (NPO), or impaired eating or absorption >7 days indicates high risk of malnutrition. Malnourished patients who cannot tolerate oral supplements may need enteral or parenteral nutrition support.

Laboratory Assessment

Biochemical markers of visceral protein status can be used in conjunction with weight and intake history to further establish the risk of malnutrition.

Albumin

Albumin is a protein synthesized in the liver which has oncotic and carrier properties in the bloodstream. Serum albumin, especially when low, can be used as an overall prognostic indicator, though low levels may also indicate impaired hepatic function. Although serum albumin alone does not correlate with nutritional status, it is a useful barometer for anabolism or inflammation when a concomitant C-reactive protein (CRP) level is obtained. Inflammation can induce catabolism via cytokines (e.g., interleukin-6) by inhibiting protein synthesis, increasing protein hydrolysis, and breaking down muscle protein. Inflammation may also affect anorexia and impact the GI system, as well as affect resting energy expenditure [4]. A low serum albumin level of <3.5 g/dl confers moderate risk and <2.8 g/dl high risk in a patient with other global indicators of malnutrition. Fluid shifts may confound the accuracy of albumin level and need to be accounted for. A normal albumin level cannot rule out risk, as a chronic hypocaloric intake may lead to weight and functional loss without a change in hepatic protein production. Albumin level is not sensitive to acute starvation due to its biological half-life of 19 days in adults. Albumin level has been reported to inversely correlate with prolonged gastric emptying of solids in idiopathic gastroparesis [5].

Prealbumin

Shorter half-life visceral blood proteins may indicate more acute malnutrition when added to the overall assessment of status. Prealbumin is a carrier protein for

thyroxine- and retinol-binding protein, and has a half-life of 2 days. Serum prealbumin levels drop in the acute stage of starvation and return to normal as nutritional intake becomes adequate, presumably reflecting liver biosynthesis rate [6]. Prealbumin is also low with chronic impairment of liver function. Prealbumin has high tryptophan content. Tryptophan is a regulator of protein synthesis; this may increase the sensitivity of prealbumin level to low protein intake. Serum prealbumin level may be stratified into high risk: <0.1 g/l; moderate: 0.1–0.17; and low: >0.17 [7].

Other Laboratory Parameters

Transferrin has a half-life of 8 days, and a serum level <150 mg/dl can correlate with malnutrition [8]. However, this measurement may be confounded by altered iron (Fe) metabolism, as Fe deficiency raises transferrin level. Retinol-binding protein level can reflect protein intake but is not often assayed. As with albumin, fluid status and inflammation must be accounted for in determining accuracy when assessing visceral protein status.

Other biochemical serum correlates for malnutrition include cholesterol <4.15 mmol/l, which may indicate hypocaloric intake, and total lymphocyte count <1.2 ($\times 10^9$)/l, which is also likely to be associated with diminished cell-mediated immunity [9].

Anthropometric Assessment

Anthropometric measurements can be better correlates for depleted LBM status. These are not now widely used due to the technical skill required for accurate assessment. The triceps skinfold thickness is an estimate of fat stores while midarm muscle circumference correlates to muscle protein. Triceps skinfold thickness <10th percentile and midarm muscle circumference <10th percentile indicate high risk of malnutrition [10]. Midarm muscle circumference has been found to correlate with serum albumin [11]. Handgrip strength has been also shown to predict malnutrition [12]. Other physical markers that may indicate deficient protein status include alopecia and malaise.

Micronutrient Deficiency

Patients may also suffer from micronutrient deficiencies, both from inadequate intake and impaired absorption, due to altered UGI function. Deficiencies need to be corrected and further prevented by either supplementation or increased intake of food sources, if tolerated. Three prevalent micronutrient deficiencies in gastroparesis are explored: iron (Fe), calcium (Ca), and vitamin B_{12}.

Iron

Gastroparesis can lead to deficient Fe status. Optimal Fe absorption is a function of Fe levels, food source, and digestive mechanism. Fe absorption improves as Fe reserves become deficient, with an absorption rate of 40% at a serum ferritin of 30 μg/l [13]. Food sources of Fe contain both heme Fe, found in meat products, and inorganic Fe, found in plant products. Fe from heme proteins is more soluble and absorbable than inorganic Fe; however, it must be freed via acid and protease lysis in the stomach. Bioavailability of inorganic Fe is affected by acid reduction from the ferric to ferrous state, which is available for absorption by the mucosal cells in the duodenum and proximal jejunum. Ferrous Fe is absorbed three times more effectively than ferric form. Achlorhydria from proton pump inhibitors or the use of antacids for treatment of symptoms predisposes gastroparesis patients to Fe malabsorption. Furthermore, 75% of patients with gastroparesis have been reported to have deficient intake of Fe (<6 mg/day for men and 13.5 for women; Daily Reference Intake (DRI) 8 and 18, respectively) [14]. This could be due to a decrease in red meat intake, which may be harder to digest. A disproportionate number of gastroparesis patients are women who are menstruating, which places them at risk for iron depletion. Interestingly, it has been reported that women have slower gastric emptying than men and that emptying is related to phase of the menstrual cycle [15]. Postgastric surgery patients have a higher risk of Fe deficiency as well, with the following reported incidence: vertical banded gastroplasty 0–32%; Roux-en-Y gastric bypass (RYGB) 6–52% (malabsorption correlated with Roux limb length); biliopancreatic diversion 0–100%. These rates of Fe deficiency are a function of a truncated duodenal and proximal jejunal absorptive surface following surgery [16].

Any gastroparesis patient with anemia, chronic complaint of fatigue, decreased pallor (in the face, nail bed, lips, or inner eyelid), or pica should be screened for Fe deficiency. Postgastric surgery patients should be screened at least annually. A bone marrow measurement of Fe status is considered the gold standard; however, a serum Fe panel, consisting of Fe, transferrin, and ferritin, remains the most practical measure of Fe status. Transferrin saturation <15% and a ferritin <12 μg/l indicate a need for repletion [17]. These measurements may be confounded by the presence of inflammation, e.g., transferrin saturation may be suppressed due to acute or chronic inflammation. A concomitant CRP may be drawn to evaluate for acute inflammation.

Fe repletion can be via oral, intramuscular (IM), or intravenous (IV) route. Patients should be educated about how to increase good sources of Fe in their diet, if tolerated. Oral Fe supplementation is safe and cost-effective – given in dosage of 200 mg elemental Fe per day [18]. High single doses should be avoided [19]. Administration should be spaced out 3–6 h to optimize duodenal uptake. Supplements should be taken on an empty stomach, as Fe salts bind with food, impairing absorption. Fe should be separated 2–4 h from a meal, noting that foodstuffs containing fiber, coffee, tea, or milk further impair absorption. If supplements are not tolerated on an empty stomach, the patient can take them with meals; however, doing this decreases absorption 40–50%. Vitamin C given as 500-mg tablets or orange juice can enhance absorption of Fe by 10%. For gastric bypass patients, chewable or liquid

Fe supplements may be optimal, as solid supplements have decreased solubilization in these patients [20]. Sustained-release preparations are suboptimal, as Fe is not absorbed further along the GI tract.

Intolerance to oral Fe may be a limiting factor for repletion and may itself exacerbate GP symptoms, including nausea, abdominal cramps, and constipation. Nausea and vomiting can occur as the quantity of solubilized Fe in the stomach and duodenum increases. Constipation can increase with higher dose. It may be possible to improve tolerance by starting at a small dose and gradually increasing over a few days to the full dose. If a full dose is still not tolerated, the Fe may be plateaued at a partial dose; this may be better than providing none at all, as Fe absorption is optimized at lower Fe status. Repletion should last 3–6 months or longer if the patient cannot tolerate heme Fe sources in the diet.

Parenteral Fe repletion should be considered if the anemia is refractory to oral treatment, e.g., lower stomach bypass, or if PO intolerance is intransigent. Fe dextran may be given IM or IV if there is no hypersensitivity. Fe deficit is calculated, in mg to be injected, as (15 Hgb g/dl) × BW in kg × 3. Side effects can include hypotension, urticaria, and anaphylaxis.

Calcium/Vitamin D

Gastroparesis can contribute to osteoporosis by interfering with Ca and vitamin D absorption. Ca is selectively absorbed in the duodenum and proximal jejunum mediated by vitamin D. Vitamin D is absorbed mainly in the jejunum and ileum. Any chronic insufficient Ca absorption can stimulate parathyroid hormone (PTH) release, which increases 1,25-dihydroxyVitD (1,25-$(OH)_2$D) and release of Ca from bone. Left unchecked, this can lead to secondary hyperparathyroidism (PTH greater than 100 pg/ml) – found in 29–53% of RYGB patients. Obesity is also an independent risk factor [16]. Any weight loss can further decrease bone density due to alteration in skeletal mechanical load [21]. Postsurgical gastroparesis patients have a 40% increase in the incidence of osteoporosis [22], and a 2% incidence of bone fracture [23] due to bypassing the duodenum and proximal jejunum or unnatural mixing of pancreatic and bile juice in the distal jejunum or ileum. Diabetic gastroparesis patients are also at increased risk: patients with type 1 have lower bone mineral density and type 2 with complications confers an increased risk of osteoporotic fractures despite a higher bone mineral density [24]. Intake of Ca and vitamin D is low in gastroparesis. Eighty percent of patients have deficient intake of Ca (<750 mg/day, DRI = 1,000–1,200) while 70% consume <3.75 μg of vitamin D (DRI = 5–15) [14] perhaps due to an avoidance of lactose-containing foods. It has also been reported that 50–63% of bariatric surgical patients have vitamin D deficiency [23].

Therefore, any GP patient at nutritional risk, along with a further risk of low bone density, should be screened for osteoporosis (e.g., women over 65 or young women with low BW, previous fracture, type 1 or DM complications). Screening may include dual-energy X-ray absorptiometry (DEXA) and levels of

25-OHD, (ionized)Ca, phosphorus (P), and PTH. Increased urine Ca and hydroxyproline/Cr ratio can indicate increased bone turnover.

Treatment/prevention include 1,000–1,500 mg supplemental Ca per day (and/or increasing Ca food sources); 400–800 IU vitamin D per day; sun exposure; exercise; and fall prevention. Ca should be taken in divided 500-mg doses. Ca citrate/D is optimal because it is more soluble than $CaCO_3$ in a higher pH gastric environment [25], and vitamin D should be repleted to a serum level >30 ng/ml. Magnesium should be taken as well in a 2/1 Ca/Mg ratio of intake [26]. Patients with fractures likely will need additional therapy with a bisphosphonate or consideration of estrogen or PTH therapy.

Vitamin B_{12}

B_{12} status can also be deleteriously affected by gastric surgery and gastroparesis. Normally, B_{12} absorption progresses along five steps: (1) B_{12} bound to protein is hydrolyzed by gastric acid and pepsin; (2) free B_{12} binds to R-binder glycoproteins secreted in salivary gastric, bile, and intestinal juices; (3) pancreatic proteases degrade R binders in the duodenum; (4) free B_{12} complexes with parietal intrinsic factor (IF) which can no longer be proteolyzed by trypsin; and (5) B_{12}–IF complex binds to ileal receptors for absorption [27]. B_{12} absorption may be directly reduced via decreased gastric production of acid, pepsin, or intrinsic factor. Resultant achlorhydria and blind loop formation can lead to bacterial overgrowth with subsequent B_{12} malabsorption. The use of proton pump inhibitors or histamine-2-receptor antagonists also further disrupts B_{12} absorption. Concomitant decrease in B_{12} intake (protein-bound B_{12} food sources, i.e., red meat/dairy) increases risk, as 40% of patients consume less than 1.8 μg/day (DRI = 2.4) [14]. As body storage, primarily liver, of B_{12} is approximately 2,000 μg, deficiency may progress from 1 to 9 years post surgery. Studies report that 8–40% of gastric surgical patients were B_{12} deficient (2% control), as a function of length of time post surgery [16].

Any patient post gastric surgery at nutritional risk should be screened for B_{12} status, and all patients should have B_{12} checked periodically. B_{12} repletion should be considered for any pt with serum level <221 pmol/l [28]. Crystalline oral B_{12} >350 μg/day can be given (25,000 U sublingual 2×/week [29] or 500 μg intranasal q week are other options); however, a refractory, low-serum B_{12} or suspected gross intrinsic factor deficiency indicates a repletion regimen of 1,000 μg B_{12} IM × 5d, followed by injections of 1,000–3,000 μg q 6 months [30]. Rx cost: 1,000 mcg tab: $.52 (eg. Big Mountain drugs), sublingual: $.22 (eg. West Coast Naturals); IM: $.1.5 (eg. 30ml vial North West Pharmacy.com not including syringe); intranasal: $67.19 [31].

Interestingly, B_{12} status itself has been indicated as a factor in nerve function, and as such may modulate gastric emptying. B_{12} has been shown to have a negative correlation with gastric emptying in hemodialysis patients with high B_{12}/supplement status. Perhaps B_{12} plays a deleterious role in nerve function [32]. B_{12} repletion reduces gastric emptying time in dyspeptic patients [33]. Neuropathy associated

with B_{12} deficiency may exacerbate any paralytic component of gastroparesis [34]. Optimal B_{12} status may afford for better gastric emptying. Any deficient patient should be repleted, whereas any patient with elevated B_{12} level should be supplemented only with caution.

Nutrition Support

An assessment of malnutrition expedites the decision concerning whether nutritional support is necessary. Patients at moderate risk need diet manipulation to help attenuate symptoms until medical treatments can take successful effect. Any high-risk patient may need aggressive nutritional support, including tube feeding or parenteral, both for the convalescence of acute gastroparesis flare as well as long-term maintenance. Several studies have documented that patients with gastroparesis consume diets that lead to malnutrition. Interestingly, studies suggest that dietary instruction, such as that obtained with a nutrition consultation, is often neglected in patients with gastroparesis.

For acute flare-ups of gastroparesis symptoms, nutritional support is needed in order to maintain hydration and electrolyte balance. IV fluids (IVFs) may be given, along with electrolyte repletion, until the patient can tolerate clear liquids. As the acute phase subsides, the diet may be advanced to full liquids to incorporate protein and fat, along with a multivitamin (elixir) for nutritional maintenance. Any patient who cannot tolerate diet advancement from clear liquids >7 days is at high risk and may need nutritional support. For patients stable on a full liquid diet, the diet is then manipulated further to see if the patient can tolerate a transition to a more solid diet regimen.

There are several principles of diet modifications for UGI dysmotility which have been accumulated that may alleviate symptoms and increase the nutritional quality of the diet regimen. Symptoms of gastroparesis include early satiety, postprandial fullness, abdominal distension, nausea, and vomiting. Current dietary recommendations for patients with gastroparesis include suggestions that compensate for the impairment of gastric emptying. Consuming smaller meals is suggested to reduce symptoms of early satiety and postprandial fullness. In order to maintain caloric intake, frequent small meals are suggested, generally 4–5 small meals per day. Foods that are low in fat and fiber are recommended, since fat and fiber may delay gastric emptying. Nutritional counseling is suggested for dietary therapy and addressing nutritional deficiencies.

Surprisingly, controlled clinical dietary trials have not been performed in patients with gastroparesis possibly due to the myriad of etiologies, symptoms, and dysfunction which encompass gastroparesis. Most studies that attempt to correlate gastroparesis and diet are descriptive in nature, and do not proscriptively define the type of gastroparesis or diet regimen. In addition, the complexity of extrapolating from nutrient or single food effects on gastric function to combined food or meal effects is problematic for translating experimental results to dietary prescription. The paucity of controlled trials has precluded generating an optimal dietary regimen.

Dietary therapy has relied on either culling results from ancillary diet and gastric function trials or data collection on studies of patients with gastroparesis in order to create a general template of dietary principles which can be catered to each patient's tolerance and preference.

Meal Size

Altering meal size can affect gastric emptying; meals with larger volume are emptied more slowly from the stomach. Eating small meals 4–6 times/day are usually better tolerated than less-frequent, larger meals [35]. This may alleviate bloating, nausea, and/or pain by reducing the postprandial residual volume in the stomach and should also affect a more balanced glycemic profile, which can be important for diabetic gastroparesis. Frequent, small meals are associated with moderate stimulation of gastric acid secretion [15].

Liquids

Increasing liquid intake relative to solid foods can facilitate gastric emptying. Liquids empty the stomach via propulsion generated by volume and gravity with feedback from small intestine luminal receptors [36]. A liquid diet should be the easiest for patients to tolerate. Liquid emptying is enhanced as more is added up to 600-ml gastric volume [37]; this amount might serve as an upper meal limit for patients who cannot tolerate high volume. It may also be better to separate liquid from solid food intake than to consume them together, as liquids added to a solid meal slow gastric emptying [38].

Solids

Solid foods remain in the stomach longer due to the need for the solid foods to be broken down into smaller particles (<2 mm in size). This trituration process creates a lag period for gastric emptying [9, 38]. Diet manipulation of solids aims to decrease solid food components which retard gastric emptying. Homogenized meals empty faster than solid meals [15]. Therefore, pureed, soft, or well-chewed food should facilitate stomach transit.

Fat

Fat slows gastric motility via cholecystokinin (CCK) release; low-fat foods should be easier to digest for this reason. Interestingly, medium-chain triglyceride fat does not elicit CCK, [39] and may be a therapeutic caloric source for patients who have

trouble tolerating a full liquid diet. Homogenization of a lipid meal equalizes the emptying rate of the lipid and aqueous phase, so liquids with fat content may be better tolerated [15].

Fiber

Dietary fiber slows gastric motility. Soluble fiber (e.g., cellulose, pectin, raffinose, or guar gum) delays gastric emptying, which may exacerbate symptoms [40]. One hypothesis is that soluble fiber prolongs gastric transit due to increased viscosity of gastric contents, although this seems to hold true only for the liquid phase [41]. Delayed transit of insoluble fiber may lead to bezoar formation, where nondigested food matter accretes along the GI tract and may become symptomatic, even ulcerative or obstructive [42].

While gastric phytobezoars are not common (0.4% incidence), they have been associated with motility disorders, diabetes mellitus, and prior gastric surgery [43]. Peptic ulcers are also associated with bezoar incidence, although it is unclear whether the ulcer is etiologic or rather occurs as a result of bezoar-induced pressure necrosis or gastric outlet obstruction. Any patient with a history of bezoar formation should avoid intake of the following foods: apples, oranges, persimmons, grape skins, coconuts, berries, figs, prunes, raisins, green beans, legumes, sauerkraut, Brussels sprouts, potato peels, celery, and broccoli. Oral supplements of vitamin C, $FeSO_4$, and lecithin should be taken with care, as they are also associated with bezoar formation [44]. Increased fluid intake and thorough chewing of food should help prevent bezoars. Interestingly, coca cola, which has a pH of 2.6, may be prophylactic, as normal gastric pH is between 1 and 2 and acid facilitates fiber digestion [43]. If effective, other acidic/carbonated fluids may help as well, but patients might not tolerate the intragastric release of CO_2. Any high-fiber medication/supplement should be discontinued. Laxatives/stool softeners should be used for constipation instead. Overall, a low-residue diet should be easier to tolerate for gastroparesis.

Aspects on Specific Dietary Components of Foods

Decreasing adverse gastric irritation by food or lifestyle components may also help to alleviate gastroparetic symptoms, particularly nausea and reflux. The following factors affect gastric sensation and may also affect motility as well.

Spicy foods have been shown to modulate gastric emptying [45]. Vinegar, one of the only food components to be studied in gastroparesis patients, is reported to delay gastric emptying in type 1 diabetic gastroparesis [46]. As such, vinegar should be avoided if a patient is symptomatic or at risk for hypoglycemia.

Capsaicin, the alkaloid component of red/black/chili pepper and paprika, affects afferent sensory nerves along the GI tract, including the stomach. Red and white

peppers also increase gastric acid secretion [15]. There have been conflicting results as to the direct effect on gastric motility. This may be due to a lag effect-emptying was slower over a 180 min time course, but faster over a 4 h time course [47]. Interestingly, this lag effect is also seen in postprandial glucose excursion following consumption of spicy food, which lowers the initial spike in postprandial glucose, with a prolonged plateauing of serum glucose [48]. Therefore, capsaicin may cause an initial blunting of motility – while this might exacerbate symptoms initially, if it is tolerated it may also promote greater overall motility and glycemic control. Other spices have been studied to only a small extent. Garam masala, an Indian spice mix, has been reported to speed gastric emptying [49]. Cinnamon is reported to slow gastric emptying at dose of 6 g [50].

Alcohol can increase gastric-emptying time and may need to be avoided. Alcohol can also lower blood glucose by blunting hepatic gluconeogenesis. Diabetics who are alcohol drinkers may need even more frequent glucose monitoring.

Citrus is reported to exacerbate dyspepsia [51]. Citrus should be avoided if symptomatic. Acids were reported to delay gastric emptying of liquid meals [15].

Coffee is reported to exacerbate dyspepsia [51] and decaffeinated coffee was found to have higher gastric acid stimulation than peptone [15].

Use of mineral water has been studied in patients with delayed gastric emptying. Mineral water was reported to stimulate gastric emptying via a decrease and progressive increase in phasic motor activity, sometimes ending in an activity front of the migrating motor complex [52].

Foods high in osmolarity can slow gastric emptying and is likely a significant effector of duodenal feedback [53]. This is due to the fact that there are osmoreceptors in the duodenal but not in the gastric epithelium. The osmotic effect on emptying occurs with solution >139 mM [37]. As such, osmolarity is not a major determinant of gastric tolerance, as patients may tolerate high osmolarity liquids orally, whereas tube feeding high osmolarity liquids into the small bowel may cause diarrhea or intolerance.

Foods at extreme temperatures stimulate antral and duodenal thermoreceptors and modify peristalsis. However, there have been conflicting results from experiments attempting to link food temperature and motility. Hot (60°C) foods may accelerate gastric emptying in the early phase [54] while cold foods (4°C) may decelerate emptying. Late-phase emptying is less affected as food temperature acclimates to body temperature in the stomach approximately 20 min after ingestion [55]. These effects are confounded by meal composition; nevertheless, modification may be tried especially with functional dyspepsia. Hot or room-temperature (37°C) meals may be easier to tolerate than cold.

Factors Affecting Gastric Emptying

Gastric-emptying halftimes for evening meals were longer for solids (not liquids) compared to morning emptying [56]. The effect of body posture on gastric emptying has shown conflicting results. For liquid meals, emptying is slower in the supine

than in the vertical position [57]. Solid meal emptying studies have not shown consistent results [58]. Lying down shortly after eating can exacerbate dyspepsia [57]. Walking or light exercise may increase gastric emptying while high intensity inhibits emptying [59]. Cigarette smoking delays gastric emptying of solids [60].

Dietary Foods to Be Avoided

Certain foods may need to be avoided due to exacerbation of belching/bloating.

Lactose may increase bloating if the patient is lactose intolerant. Interestingly, lactose has a faster gastric-emptying rate in patients with low intestinal lactase activity [61].

Carbonated beverages have been shown to induce gas distention of the proximal stomach [62]. At high volume of intake, symptoms occur and thereby may exacerbate dyspepsia [63]. Low-volume intake may be tolerated, as carbonation per se has not been definitively found to directly alter gastric emptying. However, high sugar content (100 g CHO/l) carbonated drinks do retard gastric emptying, and may need to be limited, especially if diabetes is present.

Use of drinking straws may increase aerophagia, which is already common in patients with GERD because of increased swallowing of saliva to compensate for the presence of gastric acid in the esophagus [64].

Chewing gum may affect satiety either by increasing gastric fluid volume [65] or via aerophagia.

Complementary Treatments

In addition to dietary manipulations and pharmacotherapies, there are complementary treatments which may help reduce gastroparetic symptoms and improve nutritional status and well-being. Several herbal supplements and lifestyle modifications have been studied. These adjuncts may be useful in patients with refractory symptoms or who are unwilling or unable to tolerate pharmacological prescription. For a thorough analysis, see "Complementary Treatments".

Peppermint oil has been found to accelerate the early phase of gastric emptying while relaxing the pyloric sphincter [66]. However, peppermint also decreases lower esophageal sphincter (LES) pressure, so a coated form may be needed if reflux is symptomatic.

STW-5 (Iberogast) is a blend of bitter candytuft plant, German chamomile flower, peppermint leaves, caraway fruit, licorice root, lemon balm leaves, celandine, Angelica root, rhizome, and milk thistle. STW-5 effects proximal gastric relaxation via the extracts of Angelica/licorice root, and chamomile flower, while increasing antral motility via the extracts of celandine, lemon balm leaves, caraway fruit, and bitter candytuft. However, there are conflicting results as to clinical efficacy.

Tangweikang has been shown to increase gastric emptying favorably versus domperidone in diabetic gastroparesis, and afforded better control of 2-h postprandial glucose as well. Conversely, the herbal supplement YGD has been reported to slow gastric emptying [67].

Music therapy has been shown to modulate gastric emptying in dyspeptic and healthy subjects. Concentrated listening to relaxing music for 90 min affected shortened gastric emptying, comparing favorably to cisapride, while improving upper GI symptoms as well [66].

Dietary Management of Gastroparesis in Diabetes/Renal Failure

Nutritional intervention applied to two chronic disease states in which gastroparesis is prevalent; diabetes mellitus and renal failure are discussed.

Diabetes

Altered glucose metabolism can affect gastric motility. Therefore, glycemic control is paramount to treating diabetic gastroparesis, both to modulate serum glucose swings (also minimizing the risk of hypoglycemia if insulin is on board) and to attenuate GI hormonal decompensation and nerve damage. The AACE treatment goal of HgbA1c < 6.5 also applies to gastroparetic patients. This HgbA1c level corresponds to an (weighted) average blood glucose of 140 mg/dl, which should be low enough to prevent hyperglycemia. Any precipitous drop in HgbA1c under treatment may signify bouts of hypoglycemia, which may be more prevalent in diabetic gastroparesis.

Establishing a consistent and tolerated meal pattern is conducive to glycemic control: spreading out daily intake into smaller feedings not only reduces volume load on the stomach, but spreads out glycemic load as well. Interestingly, it seems that diabetic gastroparesis patients consume a diet higher in fat and fiber content as compared to idiopathic gastroparetic patients [14], as high-fiber and fat content foods are known to lower glycemic index. The optimal diet for diabetic gastroparesis patients (i.e., a diet tailored to increase gastric motility or to lower glycemic index) remains to be established. The best insulin regimen is to use an insulin pump. A basal/bolus regimen is a good alternative; if postprandial hypoglycemia is a concern, regular insulin may be used to cover meals [68]. It is important for practitioners to keep in mind that the insulin regimen may change more frequently for diabetic gastroparetics based on symptoms: acute symptom periods may require a cutback in postprandial insulin; whereas when symptoms become better managed, insulin requirement may go up with any stable increase in intake or body weight [69]. For acute flare-ups, patients may need glucagon or sublingual glucose [70] if unable to correct hypoglycemia with oral liquids.

Renal Failure

An underappreciated demographic of gastroparetics are chronic renal failure patients due to the numerous etiologies for failure to thrive (FTT) in this population. Renal failure can lead to nerve dysfunction, thereby impeding gastric emptying [32]. Chronic uremia is associated with anorexia, nausea, and vomiting; renal failure is a risk factor for GI tract lesions [71]. Many of these patients are diabetics, where long duration of diabetes and poor glycemic control are risk factors for gastroparesis [72]. Ascitic fluid buildup can exacerbate gastroparetic symptoms. All renal failure patients with FTT should be screened for gastroparesis. Weight status needs to be scrutinized, as H_2O retention can mask LBM loss. Trending dry weights, as well as anthropometrics, visceral protein stores, and subjective reporting, can bolster any estimation of nutritional risk. Protein intake can be approximated using urea kinetic modeling via estimation of nitrogen appearance found in change of urea levels. As such, a normalized protein catabolic rate (PCR) <0.8 may indicate inadequate protein intake. With altered renal clearance, higher goals for albumin (4 g/dl) and prealbumin (30 mg/dl) are used [73], although again being cognizant of chronic inflammation suffered by these patients trending CRP along with visceral proteins should be more accurate [74]. Fluid retention also confounds serum lab values as well, which again necessitates trending visceral protein measurements. Folate status in hemodialysis patients was found to be correlated with gastric emptying, so any symptomatic hemodialysis patient should be screened for folate status or chronically supplemented with a B vitamin (Nephrocaps). Any patient with a high serum level of vitamin B_{12} should be supplemented with caution.

The dietary principles for general gastroparesis are also applied to renal failure patients. Potassium and phosphate restrictions are worked into the meal regimen. Fluid restriction may become problematic for symptomatic patients. Adding skim milk powder or protein powder supplements (eg. procel if hyperphosphatemic) to liquids ingested can help increase density allowing for nutritional adequacy of a restricted fluid intake. Phosphate binder regimen, analogous to insulin regimen, may be spread out for more feeding coverage, e.g., two phoslo with meals may be spread out to one with six small meals.

Conclusion

Dietary therapy is often used to complement medical treatments in order to improve the gastroparetic patient's well-being. Dietary regimen is manipulated to alleviate and prevent symptoms which can take a chronic toll on the patient's nutritional status. Thorough assessment and monitoring while including the patient in making therapeutic decisions are necessary components of a successful care plan. Included in this chapter are a general gastroparesis handout (Table 21.1) and daily meal pattern for the symptomatic gastroparesis patient, incorporating concerns for diabetic

Table 21.1 Top ten dietary information list for gastroparesis

1.	Size does not matter	Smaller, more meals/snacks
2.	Liquids are your friend	Increase liquid intake if symptomatic Puree foods (they liquefy in your stomach) Chop up food well/chew thoroughly/small swallows Separating solids and liquids may work better, e.g., solids at breakfast and liquids for lunch Limit liquid meal to 2½ cups (20 oz) if symptomatic Solids may go down easier earlier in the day
3.	Fat folly	Limit fried/greasy solids Can drink higher fat shakes (with ice cream/whole milk) if tolerated for extra calories
4.	Forego fiber	Avoid whole grains and uncooked produce, especially if you have had a bezoar Careful with fiber supplements
5.	Be sure of your sugar	If diabetic, good sugar control (80–150) may improve symptoms over the long haul If symptomatic, check sugars more often, careful with premeal insulin dose; keep glucagon available if nausea and vomiting worsen Lantus (R) insulin may be optimal regimen
6.	Super supplements	Daily multivitamin with minerals (liquid if necessary) when intake is poor or only tolerating liquids Iron supplement if anemia Take between meals with vitamin C (orange juice) Cannot tolerate iron pills? Try with meals or small doses or liquid form Calcium and vitamin D and magnesium supplement if you have risk of osteoporosis Vitamin B_{12} supplement if needed (if you have had stomach surgery)
7.	Become a blender chef	Experiment with great tasting smoothies that go down smooth Add skim milk or protein powder or ice cream (lactose free) when extra calories are needed Ideas for smoothie recipes at University of Virginia GI Web site: http://www.uvahealth.com/services/digestive-health-1/images-and-docs/gastroparesis-diet.pdf
8.	Support from others	You are not alone with a bum stomach! Find Web support groups, referring to real world support groups: http://www.gastroparesis.proboards.com/index.cgi?action=chat http://health.groups.yahoo.com/group/gastroparesis/
9.	Exercise	Exercise helps you be strong, and may increase appetite as well
10.	Weigh-in weekly	If symptomatic Keep goal weight and contact nutritionist if unable to maintain

gastroparesis (Table 21.2) and renal failure (Table 21.3). Hopefully, future research will further expand our understanding linking diet and gastroparesis, as patient and practitioner work to further improve treatment for this unfortunate, yet manageable, condition.

Table 21.2 Diet suggestions for patients with diabetic gastroparesis

Breakfast	
Take R insulin to cover for 50 g CHO	
1 cup grits or 2 slices of white toast	2 BR
1 poached egg or eggbeaters scrambled	1 MT
½ cup skim milk or lactaid if better tolerated	1/2 MK
½ cup apple juice or any noncitrus juice	1 FR
AM Snack	
Take R insulin to cover for 15 g CHO	
Carnation instant breakfast – 325-ml bottle – no sugar added	1 BR
Lunch	
Take R insulin to cover for 40 g CHO	
Broiled fish in lemon sauce 2–3 oz chopped	2 MT
½ cup mashed potatoes t margarine; salt + pepper	1 BR
1 cup skim milk or whole milk if tolerated	1 MK
½ cup canned fruit or pureed	1 FR
Afternoon Snack	
Take R insulin to cover for 35 g CHO	
½ cup frozen yogurt or yogurt drink/kefir	20 g CHO
1 banana small or ½ of a large banana	1 FR
Dinner	
Take R insulin to cover for 45 g CHO	
1 cup soup o' the day blenderized or strained	20 g CHO
6 oyster crackers crackle up into the soup	1 BR
Mozzarella cheese 2 oz	2 MK
½ cup gatorade thirst aid for when symptomatic!	7 g CHO
After Dinner Snack	
Take R insulin to cover for 30 g CHO	
1 cup (diet) puding or custard/ice cream/add skim milk powder	2 BR

Table 21.3 Diet suggestions for patients with gastroparesis and renal failure

Breakfast	
Take phos binder	
1 cup grits or 2 slices of white toast	2 BR
1 poached egg or eggbeaters scrambled	1 MT
½ cup skim milk or lactaid if better tolerated	1/2 MK
½ cup apple juice or applesauce if fluid restricted	1 FR
AM Snack	
Take phos binder	
Nepro 8 oz can	1 BR
Lunch	
Take phos binder	
Broiled fish in lemon sauce 2–3 oz chopped	2 MT
½ cup white rice t margarine; pepper	1 BR
1 cup skim milk or whole milk if tolerated	1 MK
½ cup canned peaches or any low-potassium fruit	1 FR

(continued)

Table 21.3 (continued)

Afternoon Snack	
Take phos binder	
½ cup frozen yogurt or yogurt drink/kefir	20 g CHO
½ cup applesauce or pureed low-potassium fruit	1 FR
Dinner	
Take phos binder	
1 cup soup o' the day blenderized or strained	20 g CHO
6 oyster crackers crackle up into the soup	1 BR
Mozzarella cheese 2 oz	2 MK
½ cup ginger ale or applesauce if fluid restricted	12 g CHO
After Dinner Snack	
Take phos binder	
1 cup (diet) pudding or custard/ice cream/add skim milk powder	2 BR

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Chapter 22
Prokinetic Agents for Gastroparesis

Henry P. Parkman

Keywords Gastroparesis • Prokinetic agents • Gastric emptying • Pathophysiology

Introduction

Gastroparesis is a chronic disorder characterized by delayed gastric emptying in the absence of mechanical obstruction [1]. Symptoms of gastroparesis typically include early satiety, postprandial fullness, nausea, and vomiting. Gastroparesis is confirmed in a symptomatic patient by demonstrating no organic lesions on upper endoscopy and delayed gastric emptying either by scintigraphy or wireless motility capsule or breath testing. Gastroparesis can occur in several clinical settings; it is commonly associated with diabetes, postsurgical (gastric) conditions, and idiopathic origin (i.e., without a known cause). Delayed gastric emptying in diabetic gastroparesis can interfere with the timing of gastric emptying of food into the small intestine where it is absorbed, leading to erratic glucose control in diabetic patients [2].

The general principles for treatment of symptomatic gastroparesis are (1) correction of fluid and electrolyte imbalance, (2) correction of nutritional deficiencies, (3) reversal of the cause of gastroparesis, if possible, and most importantly, (4) improvement of symptoms [1]. The treatment options for the patient vary with the severity of the disease [3]. Dietary modifications is an important aspect for patients: consuming small meals, perhaps more frequent meals to consume enough calories, avoiding food that is high in fat and insoluble fiber [4]. In the case of diabetic gastroparesis, good glycemic control is important, as hyerpglycemia inhibits upper GI motor function and limits the effects of prokinetic agents [2]. The next step is with pharmacologic agents

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to control nausea, vomiting and to improve the impaired motility using antiemetic and prokinetic agents [3, 4]. Recent reviews provide treatment plans based on severity of symptoms, degree of delay of gastric emptying, and ability to maintain hydration and nutrition by oral route [3, 5].

Gastric prokinetic agents enhance contractility of the GI tract and accelerate gastric emptying. In general, prokinetic agents increase gastric antral contractility, correct gastric dysrhythmias, and improve antroduodenal coordination. Some of the prokinetic agents, metoclopramide and domperidone, also have antiemetic properties due to their central effects. Theoretically, treatment of the symptoms of gastroparesis, a condition with delayed gastric emptying, should best be achieved with prokinetic agents that accelerate gastric emptying and should improve symptoms. These agents are prescribed with the intent of both augmenting and coordinating the contractility of gastric smooth muscle and promoting the aboral movement of food to facilitate absorption and maintain nutrition [4]. However, there is a poor correlation of symptoms with gastric emptying. Enhancement of gastric emptying may not necessarily improve symptoms [6, 7]. Not all symptoms of gastroparesis, such as abdominal pain and bloating, may be from delayed gastric emptying. For diabetic gastroparesis, several studies have reported improvement in gastric emptying with prokinetic drugs, but not any consistent effects on symptoms or glycemic control [7]. While the relationship between current measures of gastric emptying is weak, control of gastric emptying is important to regulate delivery of nutrients to the small intestine [8].

New prokinetic agents are needed to treat gastroparesis. However, it has been difficult to establish symptomatic benefit with prokinetic drugs in gastroparesis possibly because of the pathophysiological heterogeneity of the patients, the inconsistent relationships between changes in motor function and symptomatic outcome, potential side effects of medications, and a lack of well-accepted symptom end points for clinical trials [6].

Implementation of Prokinetic Treatment

At the present time, there is a paucity of prokinetic agents to treat gastroparesis (Table 22.1). Prokinetics presently available for clinical use are metoclopramide and erythromycin. Although each has been shown to improve gastric emptying and decrease symptoms, there are problems with these currently used agents. With metoclopramide, side effects, primarily involving the central nervous system, can occur in up to 20% of patients necessitating stopping the treatment. The prokinetic effects of erythromycin reduce over time due to motilin receptor tachyphylaxis. The serotonin 5-HT_4 receptor agonists, cisapride and tegaserod, increase gastric emptying and had been used to treat gastroparesis until they were withdrawn from the market.

When starting a patient on a prokinetic agent, the medications that the patient is taking and other disorders of a patient need to be considered, as these may interfere with the action of the prokinetic agent or increase likelihood of side effects.

Table 22.1 Prokinetic agents

Class of agent	Available agents	Special circumstances	Under study
Dopamine receptor antagonists	Metoclopramide	Domperidone	Itopride
Motilin receptor agonists	Erythromycin Azithromycin Clarithromycin		Mitemcinal
Ghrelin receptor agonists			TZP-101 TZP-102
5-HT_4 receptor agonists		Cisapride Tegaserod	Prucalapride Mosapride Renzapride Velusetrag ATI-7505
Cholinesterase inhibitors	Neostigmine Physostigmine		Acotiamide Nizatidine
Muscarinic agonists	Bethanechol		
Opiate receptor antagonists			Alvimopan Methylnaltrexone
Pyloric sphincter relaxant	Botulinum toxin		

In patients with diabetic gastroparesis, hyperglycemia can aggravate symptoms of gastroparesis and reduce the effectiveness of prokinetic agents [2]. Treatment of diabetic gastroparesis should also focus on blood glucose control [1]. Diabetic medications used by the patient can also affect gastric emptying. Of particular concern is the increased use in the treatment of diabetes of drugs that mimic or modify incretins, which slow gastric emptying and may potentially aggravate symptoms of gastroparesis. For example, amylin delays gastric emptying. The amylin analog, pramintide, delays gastric emptying in patients with both type 1 and type 2 diabetes [9]. Exentilde is a GLP-1 mimetic used in T2DM and can delay gastric emptying, although this effect may be less pronounced in patients in whom gastric emptying is already delayed [10]. By contrast, inhibitors of the enzyme dipeptidyl peptidase 4 (DPP-4), which break down GLP-I, do not delay gastric emptying and do not reduce food intake [11]. Although these agents can delay gastric emptying, they also improve glucose regulation, which might then improve gastric emptying and symptoms. The benefit of the drugs on glycemic control appears to outweigh the effects on gastric emptying, but these drugs need to be kept in mind when assessing an abnormal gastric emptying study [2, 8].

Medications with anticholinergic activity may themselves delay gastric emptying as well as reduce the effects of prokinetics that work by facilitating acetylcholine release [1]. Drugs with anticholinergic potential that may further decrease gastric emptying should be reduced or stopped. These include particularly the anticholinergic agents used to treat irritable bowel syndrome and spastic urinary bladder.

Several factors must be considered when choosing a prokinetic drug for the patient with gastroparesis including efficacy, side effects, availability, and cost. Promotility agents including metoclopramide, domperidone, and erythromycin have improved dyspeptic symptoms more effectively than placebo in the majority of studies [12–14]; improvement in symptoms with promotility agents has been 40–45% greater than with placebo [14]. There has been little in the way of controlled investigations directly comparing the different prokinetic medications. A meta-analysis assessing benefits of 4 different drugs in 514 patients in 36 clinical trials reported that the macrolide antibiotic erythromycin was the most potent stimulant of gastric emptying, while the dopamine receptor antagonist domperidone was best at reducing symptoms of gastroparesis [15]. However, as for all meta-analyses, concerns can be raised regarding publication bias in which negative studies are not reported as well as marked differences in study design that can prevent adequate comparisons of the different drugs [16].

Usually, prokinetic agents are administered 30 min before meals to maximize blood levels and gastric prokinetic effects at meal ingestion. In addition, a bedtime dose is often used to help assist indigestible solids emptying from the stomach [1].

When treating patients with prokinetics, side effects should be monitored. In particular, evidence of depression, anxiety, and movement disorders are monitored in patients being treated with metoclopramide or domperidone. Electrolytes (K^+ Mag^{2+}) and an electrocardiogram are obtained prior to treatment and on the follow-up visit in patients being treated with domperidone. Increasing gastric emptying by a promotility agent can increase peak postprandial glucose levels [17]. Thus, glucose control might have to be periodically monitored after starting prokinetic agents in diabetic patients.

In gastroparesis, pharmacological therapy with prokinetic agents is often needed on a prolonged basis. Because GI symptoms correlate suboptimally with gastric emptying, the response to treatment is usually judged clinically; repeating gastric emptying tests is not usually performed. In general, patients are treated for 4–6 weeks at the starting dose. In patients with a suboptimal response, the dose of the prokinetic agent can be increased; generally, the dose is doubled.

Dopamine Receptor Antagonists

Dopamine is an inhibitor of motor activity of the stomach. Two agents that act as dopamine receptor antagonists, metoclopramide and domperidone, are commonly used in the treatment of patients with gastroparesis [1, 2, 18]. Both agents act to counteract the inhibitory effects of endogenous dopamine on gastric emptying. They further act as antiemetic agents by virtue of their blockade of dopamine receptor mediated pathways in the brainstem. Domperidone and metoclopramide are equally effective in reducing symptoms of diabetic gastroparesis, particularly nausea and vomiting [19]. However, adverse CNS effects are more severe and more common with metoclopramide, e.g., somnolence and reduction in mental acuity [19].

Metoclopramide

Metoclopramide (Reglan), a substituted benzamide structurally related to procainamide, has been used since the 1970s to treat gastroparesis [18, 20]. Metoclopramide is a dompamine type 2 receptor antagonist; it also acts as a serotonin 5-HT_4 receptor agonist to stimulate cholinergic neural pathways in the stomach as well as a weak 5-HT_3 receptor antagonist. Metoclopramide has both prokinetic and antiemetic effects. Metoclopramide blocks peripheral dopamine receptors and releases acetylcholine from intrinsic cholinergic neurons. The prokinetic properties of metoclopramide are limited to the proximal GI tract, increasing gastric fundic and antral contractions and improving antropyloroduodenal coordination. Metoclopramide also has antiemetic effects resulting both from dopamine antagonism in the chemoreceptor zone and from a central action at the vomiting center.

Metoclopramide has been approved for short-term use (4–12 weeks) since 1979 for use in diabetic gastroparesis and for prevention of postoperative and chemotherapy-induced nausea and vomiting. In February 2009, the FDA had manufacturers of metoclopramide add a boxed warning to their drug labels about the risk of its long-term or high-dose use. The FDA recommends that the treatment should not exceed 3 months. Chronic use of metoclopramide has been linked to tardive dyskinesia, which may include involuntary and repetitive movements of the body.

Controlled trials have shown that metoclopramide may improve symptoms while accelerating gastric emptying of solids and liquids in patients with idiopathic, diabetic, and postvagotomy gastroparesis and in patients with gastroesophageal reflux disease (GERD) [21–24]. Metoclopramide has been reported to be effective in the short-term treatment of gastroparesis for up to several weeks [21–23]. In one 3-week double-blind trial, metoclopramide produced greater symptom improvement and acceleration of gastric emptying than placebo [22]. Individual patient improvements in gastric emptying correlated poorly with reductions in nausea and vomiting, emphasizing that symptom benefits may not result from the prokinetic actions of the drug and that antiemetic mechanisms may be important for clinical efficacy [21, 23]. An additional possible mechanism of action of metoclopramide is to normalize gastric slow-wave dysrhythmias [25].

Long-term efficacy for metoclopramide has not been clearly demonstrated; its effect on gastric emptying may diminish during long-term treatment [26]. In diabetic gastroparesis, acute administration of metoclopramide accelerates emptying, but not after 1 month of treatment [26]. However, metoclopramide may continue to relieve symptoms because of its antiemetic effects.

Side effects of long-term use of metoclopramide are of concern and often limit the use of this drug. Side effects of metoclopramide, resulting from its antidopaminergic properties, may occur in up to 30% of patients and are the major factors restricting its use. Most of the side effects of metoclopramide result from its ability to cross the blood brain barrier. Acute dystonic reactions – facial spasm, oculogyric crisis, trismus, and torticollis – occur in 0.2–2% of patients, often within 24–48 h of initiating treatment [27]. This side effect, should it occur, is treated with diphenhydramine and

stopping metoclopramide. Up to 30% of patients cannot tolerate metoclopramide due either to drowsiness and fatigue or to restlessness and irritability. Depression may occur and may range from mild to severe. Metoclopramide can aggravate underlying depression. Increased prolactin release may result in breast engorgement, lactation, and menstral irregularity. Prolonged treatment infrequently may produce Parkinsonian-like symptoms, more commonly within the first 6 months after beginning treatment, but occasionally after longer periods [27]. These symptoms usually subside within 2–3 months after discontinuation of metoclopramide. Patients with Parkinson disease should not be given metoclopramide. Tardive dyskinesia, characterized by involuntary movement of the face, tongue, or extremities, is an infrequent adverse effect of prolonged use of metoclopramide that may not reverse upon discontinuing the medication. The prevalence of tardive dyskinesia may range from 0.02 to 2% when patients take metoclopramide for at least 3 months [27]. One study reported this as high as 15% [27]. An increase in tardive dyskinesia was reported after cisapride was withdrawn from the market, presumably from patients being switched from cisapride to metaclopramide [28]. Tardive dyskinesia is more common in the elderly, especially older women, and people who have been on the drug for a long time. A recent review on the risk on metoclopramide-induced tardive dyskinesia suggested the risk to be <1% and that this might represent an idiosyncratic response to metoclopramide [29].

Possible side effects of metoclopramide should be discussed with the patient before starting this medication. Notation of this discussion should be documented in the patient's medical chart [3]. Some clinicians have patients sign an informed consent to document communicating the risks of metoclopramide. Side effects, particularly movement disorders and depression, should be monitored for during treatment.

The usual starting dose of metoclopramide in adults is 5–10 mg 30 min before meals and at bedtime. In patients not responding and without side effects, the dose can be increased to 20 mg. In severe gastroparesis, oral metoclopramide may not be adequately absorbed because of vomiting or delayed gastric emptying; metoclopramide administered intravenously may improve gastric emptying. Liquid metoclopramide may also be of benefit as liquid gastric emptying is often maintained until severely delayed gastric emptying. Recently, an oral disintegrating tablet of metoclopramide has been introduced, which may be of benefit to patients with nausea and vomiting, preventing swallowing medications [30]. For individuals with more refractory nausea and vomiting and unable to retain oral medications, subcutaneous injections of metoclopramide have shown symptomatic efficacy in patients [31]. Metoclopramide may also be administered by suppository, or even intraperitoneally in patients undergoing peritoneal dialysis [32].

Domperidone

Domperidone (Motilium) is a benzimidazole derivative and is a specific dopamine-2 receptor antagonist. The effects of domperidone in the upper GI tract are similar

to those of metoclopramide. Domperidone stimulates upper GI motility by enhancing gastroduodenal contractions and coordination. Domperidone is regarded as a peripheral dopamine receptor type 2 receptor antagonist. It does not readily cross the blood–brain barrier; therefore, it is much less likely to cause extrapyramidal side effects than metoclopramide [19]. However, domperidone also has antiemetic properties by its actions at the chemoreceptor trigger zone on the blood side of the blood–brain barrier [18].

Domperidone has been studied primarily in diabetic gastroparesis. It increases both solid and liquid emptying, especially in those patients with a severe delay in gastric emptying [33]. Symptomatic improvement may not correlate with improvement in emptying as improvement of nausea and vomiting may also result from antiemetic effects. Symptomatic benefit of domperidone can also occur in diabetic patients with normal gastric emptying [34]. In a small study of six patients with diabetic gastroparesis, symptom improvement on domperidone was associated with resolution of gastric slow wave dysrhythmias suggestive of a possible gastric antiarrhythmic effect of this agent [35].

In a phase III trial of diabetics with symptoms suggestive of gastroparesis, 269 patients initially received domperidone 20 mg four times a day for 4 weeks [36]. Seventy-seven percent of patients responded to therapy, defined as more than 30% reduction in symptoms. Responders were then randomized to double-blind continuation of domperidone versus withdrawal to placebo. Those switched to placebo had worsening of overall symptoms compared to the patients maintained on domperidone. The main symptom that had most deterioration on placebo was early satiety with trends for worsening of nausea, bloating, and vomiting.

The effect of long-term treatment with domperidone has been variable. At 6 weeks, the effect of domperidone on solid phase gastric emptying was lost, whereas the improvement of liquid gastric emptying was maintained [33]. Another study found that nausea and vomiting were improved compared with baseline values after 6 weeks of treatment, but there was no change in solid phase gastric emptying [34]. Other studies have suggested that improvement in gastric emptying and symptoms was still present after 1 year of treatment [33].

Domperidone is often used in patients whom have had side effects to metoclopramide or in those who are concerned about the possibility of developing side effects with metoclopramide. Domperidone is especially useful in gastroparetic patients with Parkinson's disease in whom it can improve gastric emptying without blocking the central dopaminergic actions of treatment for Parkinson's disease [37]. Domperidone would work peripherally for GI dysmotility and symptoms; L-dopa would still work centrally for the Parkinsonian symptoms.

In the USA, domperidone is not approved by the Food and Drug Administration (FDA) and cannot be obtained by routine prescription and is not covered by health care plans. Traditionally, domperidone has been obtainable from other countries, from Internet websites, or from compounding pharmacies within the USA. These practices have been discouraged by the FDA. Physicans who would like to use domperidone for their patients can submit an Investigative New Drug (IND) application to the FDA and their IRB to use this medication. Using this mechanism,

patients sign an informed consent document and purchase domperidone from an FDA-approved pharmacy ($50 per month for 10 mg po QID). The FDA protocol entails obtaining an electrocardiogram and electrolytes including magnesium prior to initiation of treatment and repeating them on treatment with domperidone.

Domperidone is generally started at 10 mg four times a day. If symptoms persist after 4–8 weeks, the dose is increased to 20 mg four times daily. A trial of 80–120 mg/day for up to a month is considered the time needed to assess its efficacy [4].

Because it does not cross the blood–brain barrier, domperidone has a more favorable side-effect profile compared to metoclopramide [18]. The side effects of domperidone are usually secondary to increased prolactin levels, and include breast engorgement and galactorrhea. In addition, the high prolactin levels interfere with FSH and LH, which leads to amennorhea in some patients. Generally, however, one does not monitor prolactin levels before or during treatment with domperidone. CNS side effects are minimal. Dystonias and other movement disorders are uncommon with this agent. An intravenous form of domperidone was withdrawn in the 1980s due to rare reports of fatal cardiac arrhythmias.

Other Dopamine Receptor Antagonists

Itopride, an agent with dopamine type 2 receptor antagonism properties as well as acetylcholinesterase inhibitory properties, accelerates gastric emptying in patients with diabetic gastroparesis and is used in Asia as a therapy for functional dyspepsia [38, 39]. Phase II studies of itopride in functional dyspepsia showed improvement in symptoms in patients with functional dyspepsia [40]. Unfortunately, phase III studies for itopride in functional dyspepsia did not show efficacy [41]. This agent is no longer being pursued for treatment of gastroparesis.

Motilin Receptor Agonists (Motilides)

Motilin, an endogenous peptide hormone released by the duodenal mucosa, elicits antroduodenal contractions via activation of smooth muscle L-type calcium channels after occupation of motilin receptors on enteric neurons and smooth muscle tissue [42]. Motilin plays a role initiating the gastric phase III of the MMC and is a potent stimulator of antral contractility. A number of macrolide antibiotics act as motilin receptor agonists to promote upper gut transit, including erythromycin, clarithromycin, and azithromycin (Table 22.1) [43, 44].

Erythromycin

Erythromycin has prokinetic effects because it is a motilin receptor agonist in addition to being an antibiotic [43, 45]. Erythromycin binds to motilin receptors located on

smooth muscle and cholinergic neurons; motilin receptors appear to be important for actions in vivo [46–48]. When given intravenously, erythromycin is a potent stimulant of gastric emptying among the available prokinetic drugs [49]. The regional actions of erythromycin include stimulation of cholinergic nerves in the antrum, which elicit coordinated phasic contractions, and activation of inhibitory nerves in the pylorus, which promote pyloric relaxation [46–48].

Erythromycin stimulates gastric emptying in diabetic gastroparesis, idiopathic gastroparesis, and postvagotomy gastroparesis [43, 45, 49]. Erythromycin is the most potent prokinetic agent in accelerating gastric emptying. Erythromycin accelerates gastric emptying by increasing the amplitude and frequency of antral contractions. Interestingly, erythromycin has been reported to accelerate stomach emptying in postsurgical gastroparesis in which the antrum, the primary site of its motor effect, has been respected [43]. The prokinetic effect in this situation may result from a stimulatory effect on the fundus.

Erythromycin is reported to be most effective when it is used intravenously during acute exacerbations of gastroparesis [50]. Intravenous infusion of erythromycin lactobionate (200 mg) accelerated emptying of solids in patients with diabetic gastroparesis [51]. In the same patients, after 4 weeks of oral erythromycin ethylsuccinate (250 mg orally three times daily, 30 min before meals), the magnitude of the acceleration was less than that observed in response to the single intravenous dose. Studies carried out over longer observation periods have reported a reduction of benefit over time with oral administration. Erythromycin is associated with tachyphylaxis, due to downregulation of motilin receptors, which occurs by 4 weeks of oral treatment [45].

A number of controlled and open trials have reported clinical benefits of erythromycin therapy in patients with gastroparesis. In one study, however, intravenous erythromycin significantly enhanced solid and liquid gastric emptying; however, it did not significantly reduce meal-related dyspepsia symptoms [52]. A systematic review reported symptom improvement has been noted in 43% of patients treated with oral erythromycin [53]. However, the utility of chronic oral erythromycin therapy may be limited by the development of tachyphylaxis as a consequence of motilin receptor downregulation, which can develop within days of initiating treatment [54]. For example, in a study by Dhirand and Richter, more than half of patients had a good short-term response to low-dose erythromycin suspension (50–100 mg po TID), whereas in the long term, the response rate was much lower, only 20% [55]. Hyperglycemia also attenuates the stimulation of antral contractility and gastric emptying by erythromycin [56].

When given clinically, erythromycin is usually started in low doses (125 mg orally three times daily before meals). Dosing can be titrated as needed for clinical effect. Many physicians prefer using erythromycin suspension; it takes less time to reach peak concentrations, is easier to adjust dosages, and may be better absorbed in gastroparesis [57]. Erythromycin comes as 250 mg tablets and ½ tablet could be given before meals. One center reports the use of intravenous erythromycin (100 mg every 8 h) for severe refractory gastroparesis [58].

Side effects of erythromycin therapy are common and include nausea, vomiting, and abdominal pain which may occur more prominently at higher doses. A review of a large Medicaid cohort observed a twofold increased risk of sudden cardiac

death in individuals on erythromycin therapy [59]. This risk was further increased by concomitant use of cytochrome P-450 (CYP-3A) inhibitors such as verapamil or diltiazam. Azithromycin does not have the cardiac risk and has been proposed as an alternative, although long-term data are not available [44].

Due to its antibiotic properties, long-term use may lead to resistant bacterial strains. There are other possible side effects such as ototoxicity and pseudomembranous colitis, which may limit long-term use in patients with gastroparesis [7]. Furthermore, the problem of tachyphylaxis, with reduced clinical responsiveness over time, makes long-term use less attractive [7]. Drug holidays with periods of several weeks stopping erythromycin may help.

Other and New Motilides

A focus of pharmaceutical investigation has been the development of motilin receptor agonists exhibiting prokinetic capabilities but without antimicrobial properties.

An early motilin receptor agonist ABT-229 was tested in diabetic gastroparesis and functional dyspepsia. However, ABT-229 worsened symptoms in diabetics with nausea and vomiting compared to placebo and showed no benefits in functional dyspepsia [60, 61]. It is speculated that because motilin receptor agonists increase proximal gastric tone, they may aggravate the impaired fundic accommodation in functional dyspepsia, and this could explain the worsening of postprandial symptoms with ABT-229 [61]. Follow-up gastric emptying tests were not performed to show if ABT-229 resulted in sustained improvement of gastric emptying.

Mitemcinal (GM-611) exhibits potent prokinetic action in the stomach and early results in diabetic gastroparesis show good effects [62]. Mitemcinal enhances gastric emptying and postprandial glycemic control. Poor responders included obese (BMI > 35) and diabetic patients with poor glucose control (HgbA1c > 10%). Paradoxically, response rates were higher in patients with nondelayed gastric emptying than for those with delayed gastric emptying [62, 63]. Unfortunately, this compound is not currently being investigated for approval.

Azithromycin has been suggested as an alternative to erythromycin since it does not have cardiac side effects [44]. Azithromycin is equivalent to erythromycin in accelerating the gastric emptying of adult patients with gastroparesis. Azithromycin stimulates antral activity similar to erythromycin and may have a longer duration of effect [64]. In addition, unlike erythromycin, azithromycin does not have significant drug–drug interactions. Further research should evaluate the long-term effectiveness and safety of azithromycin as a gastroparesis treatment [65].

Clarithromycin, which also has prokinetic effects, has also been suggested as an alternative to erythromycin. It is available as oral or intravenous formulations [4].

GSK962040 is a recently identified small-molecule motilin receptor agonist that selectively activates motilin receptor and is being evaluated for safety, tolerability, and efficacy in humans [66].

Serotonin 5-HT_4 Receptor Agonists

5-HT_4 receptors are important in mediating effects of serotonin on gastrointestinal motor function [67]. 5-HT_4 receptors are important drug targets for medications intended to stimulate GI motility. Older 5-HT_4 receptor agonists were less selective and may have induced adverse cardiac events. Newer 5-HT_4 receptor agonists being studied are more selective, are safer on cardiac conduction, and have been shown to be efficacious in animal or human studies, including clinical trials [67].

Cisapride

Cisapride (Propulsid) is a nonselective serotonin (5-HT_4) agonist with partial 5-HT_3 antagonist effect that facilitates release of acetylcholine from cholinergic nerves in the myenteric plexus throughout the GI tract. Cisapride stimulates antral and duodenal contractions, improves antroduodenal coordination, and accelerates gastric emptying [68, 69]. Cisapride accelerates gastric emptying and decreases symptoms in patients with gastroparesis, an effect, reported in one study, that may last for a year [70].

Cisapride was approved by the US Food and Drug Administration (FDA) for treatment of nocturnal heartburn in patients with GERD. There have been rare instances of cardiac arrhythmias and sudden death [71]. These were not due to cisapride's 5-HT_4 agonist properties, but rather they were an effect of its molecular structure on cardiac potassium channels, the human ether-a-go-go-related gene (HERG channels), prolonging the QT interval and predisposing to ventricular arrhythmias, particularly torsades de pointes. Patients with underlying cardiac disease, especially of the conduction system, and those on medications known to prolong the QT interval are the main groups of patients at risk. Cisapride is metabolized by the cytochrome P450 3A4 system; use of medications that interact with this enzyme system leads to increased cisapride blood levels and increased cardiac toxicity. Besides cardiac risks, side effects include diarrhea, light-headedness, and abdominal cramps. In patients with a seizure focus, cisapride may rarely increase seizure activity.

Cisapride was withdrawn from the US market in 2000 because of its cardiac side effects. Currently, the drug is available in the USA through a compassionate-use/limited-access program through Janssen Pharmaceutica with strict patient monitoring [72].

Tegaserod

Tegaserod is a partial 5-HT_4 receptor agonist [73]. Further evaluation showed it can also block 5-HT_{2b} receptors. Tegaserod was approved for treatment of constipation-predominant irritable bowel syndrome and chronic constipation. Although its prokinetic actions appear to be greatest in the small intestine and proximal colon,

tegaserod given at a dose of 6 mg twice daily accelerates gastric emptying in healthy volunteers [73, 74].

In an abstract publication of 163 patients with gastroparesis, tegaserod was shown to accelerate solid phase gastric emptying which was most pronounced at doses higher than those commonly used to treat constipation (6 mg three times daily and 12 mg twice daily) [75]. However, its effect on symptoms was marginal. Because of this prokinetic effect, tegaserod had been used on an off-label basis for the treatment of gastroparesis. Tegaserod was removed from the market in March 2007 due to ischemic cardiovascular side effects including heart attack and strokes.

Newer 5-HT$_4$ Agonists

Other 5-HT$_4$ receptor agonists have been developed and show efficacy in gastroparesis.

Mosapride exhibits both 5-HT$_4$ receptor agonist and 5-HT$_3$ receptor antagonist properties [6]. Mosapride accelerates gastric emptying in healthy volunteers and patients with diabetic gastroparesis [76, 77]. Furthermore, the drug may improve glycemic control in diabetics with delayed gastric emptying [77]. In contrast to cisapride, mosapride has little effect on potassium channel activity and appears to exhibit a significantly lesser cardiac arrhythmogenic potential [78].

Renzapride is a combined 5-HT$_4$ receptor agonist and 5-HT$_3$ receptor antagonist [79]. A small study showed improvement in gastric emptying of liquids but not solids in diabetic gastroparesis. Future studies are needed to determine if renzapride exhibits efficacy in gastroparesis.

Prucalapride, a highly selective 5-HT$_4$ receptor agonist, accelerates gastric, small bowel, and colonic transit [80, 81]. Prucalapride has recently been approved in Europe for the treatment of chronic constipation. Two other new 5-HT$_4$ receptor agonists being studied, ATI-7505, and Velusetrag (TD-5108), are also highly selective 5-HT$_4$ receptor agonists with dose selectivity for 5-HT$_4$ receptors over hERG channel and other receptors [67, 82, 83]. These agents have not yet been tested in gastroparesis or dyspepsia.

Muscarinic Receptor Agonists

Bethanechol is a nonspecific cholinergic muscarinic receptor agonist. It enhances amplitude of contractions throughout the GI tract [84]. Bethanechol increases phasic antral motor activity; however, the elicited contractions are not peristaltic and do not facilitate gastric emptying [85, 86]. Thus, bethanechol is not a true prokinetic agent [71]. Some clinicians employ bethanechol in low doses in combination with other prokinetic agents; however, this practice has not been subjected to a clinical trial. The typical dose is 25 mg orally four times daily. The direct muscarinic

cholinergic action of bethanechol may also stimulate secretion of gastric acid and saliva. Potential side effects of bethanechol include increased salivation, blurred vision, abdominal cramps, and bladder spasm.

Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors, such as physostigmine and neostigmine, may stimulate GI contractility by increasing acetylcholine levels with subsequent muscarinic receptor activation. Anticholinesterase agents may increase gastric contractility, but they may not increase antroduodenal coordination; therefore, they may not increase emptying [87]. In animal studies, GI transit is affected in an inverted U-shaped dose–response curve with acceleration at lower doses but inhibition at higher doses [87]. This dual effect may be related to activation of different muscarinic receptor subtypes.

Some H_2 receptor antagonists (H_2RAs), such as nizatidine, exhibit anticholinesterase activity and stimulate gastric emptying but their efficacy in long-term treatment of gastroparesis is unknown [88, 89]. Nizatidine has been suggested to enhance gastric emptying in patients with GERD [4]. Other H_2RAs, such as famotidine, and proton pump inhibitors, such as omeprazole, have been shown to delay gastric emptying in normal subjects, an effect suggested to be mediated by increase in gastrin levels [90].

Acotiamide (Z-338) is an acetylcholinesterase inhibitor and also enhances acetylcholine release in the enteric nervous system by muscarinc M1/M2 receptor antagonism of presynaptic autoreceptors regulating acetycholine release [91]. Acotiamide may enhance gastric accommodation and is associated with improvement of dyspeptic symptoms [92]. In a phase IIb study of patients with functional dyspepsia, acotiamide improved meal-related dyspeptic symptoms, particularly postprandial fullness, early satiety, and upper abdominal bloating [93]. It effect was suggested to be due to an improvement in meal-induced accommodation and possibly improving gastric emptying.

Octreotide

Somatostatin has variable effects on GI tract motor activity. Somatostatin inhibits antral motor contractions. In the intestine, somatostatin initiates ectopic myoelectric and motor fronts under basal conditions but inhibits fed motility. Octreotide is a cyclic analog of somatostatin administered by subcutaneous injection and induces small intestinal phase III-like contractile activity. Nocturnal dosing may improve small intestinal motor function in patients with scleroderma with small-bowel involvement [94]. In patients with gastroparesis, octreotide initiates phase-III activity in the small intestine but inhibits postprandial antral contractility [95]. Thus, octreotide delays gastric emptying and may worsen symptoms in patients with gastroparesis.

Clinically, it may be used for small-bowel dysmotility. In this case, prokinetic agents are administered before meals and octreotide is given at bedtime. Prolonged usage may result in gallstones from inhibition of gallbladder emptying.

Sympathetic Agents

Clonidine, an $\alpha_{2(alpha)}$-adrenergic agonist, has been reported to decrease symptoms and to accelerate gastric emptying in patients with diabetic gastroparesis [96, 97]. Other studies have shown that clonidine reduces dyspeptic symptoms by improving gastric accommodation [98]. Still other studies report clonidine delays gastric emptying [99]. A side effect is hypotension; clonidine should be used cautiously, especially in diabetic patients with autonomic dysfunction and orthostatic hypotension.

Probiotics

Probiotics are used for a variety of functional GI disorders, usually irritable bowel syndrome and small intestinal bacterial overgrowth.

Iberogast (STW 5) is a herbal preparation of nine herbs. Initial studies of Iberogast show promise in treatment of dyspeptic symptoms and for gastroparesis [100–102]. Iberogast affects gastric motility in humans, probably in a region-dependent manner. In normal subjects, Iberogast increased proximal gastric volume, increased antral contractility, but had no effect on gastric emptying of solids or intragastric distribution [100]. The stimulation of gastric relaxation and antral motility may also contribute to the reported therapeutic efficacy of Iberogast in functional dyspepsia. In a multicenter, placebo-controlled double-blind study of 103 patients with functional dyspepsia, the improvement of gastrointestinal symptoms and the proportion of patients with a treatment response were more pronounced in the STW 5 group than in the placebo group [101]. These clinical effects of STW 5 in patients with FD and gastroparesis were not directly mediated by an acceleration of gastric emptying [102].

Botulinum Toxin Injection into the Pyloric Sphincter

Gastric emptying is a highly regulated process reflecting the integration of propulsive forces of proximal fundic tone and distal antral contractions with inhibitory forces of pyloric sphincter resistance. Pylorospasm has been reported in diabetic gastroparesis and postvagotomy. Pyloromyotomy is often used in preventing gastric stasis after truncal vagotomy. Few studies have been performed to see whether inhibition of the pyloric sphincter muscle accelerates gastric emptying. Early studies with surgical pyloromyotomy did not show benefit; more recent studies have shown a beneficial response in diabetic gastroparesis [103].

Botulinum toxin is a potent inhibitor of neuromuscular transmission and has been used to treat spastic disorders of muscles by local injection into affected muscles. Initial case series included small numbers of patients with idiopathic and diabetic gastroparesis in which botulinum toxin was injected into the pylorus in an attempt to reduce gastric outlet resistance and accelerate gastric emptying [104–107]. These open label studies, showed a mild improvement in gastric emptying and modest improvement in symptoms. A subsequent, larger case series included 63 patients and demonstrated that approximately 40% of patients experienced clinical benefit from pyloric injection which lasted a median of 5 months [108]. A larger open-label study of 179 gastroparetic patients undergoing pyloric botulinum toxin injection showed a decrease in gastroparetic symptoms for 1–4 months in 51% of patients [109]. Dose (200 units), female gender, age <50 years, and idiopathic gastroparesis were factors with improved responses. In this study, a clinical response to a second injection occurred in 71% of patients who had a good response to the first injection. However, results from placebo-controlled trials have shown that while botulinum toxin injection into the pylorus may mildly accelerate gastric emptying, there is little difference in symptom improvement with botulinum toxin compared to placebo [110, 111]. Thus, despite initial enthusiasm for intrapyloric botulinum toxin injection into the pylorus, randomized, controlled trials of intrapyloric botulinum toxin type A showed little efficacy for relief of symptoms and is not suitable for long-term control of gastroparetic symptoms.

Ghrelin Receptor Agonists

Ghrelin is a hormone initially described as an endogenous ligand for the growth hormone secretogogue receptor and expressed mainly by neuroendocrine cells in gastric fundus and duodenum [112]. Endogenous ghrelin levels rise shortly before and then fall shortly after a meal, a pattern suggesting a role in triggering the urge to eat [113]. This appetite-stimulating signal from the gut to the brain acts through vagal afferent pathways. Increases in ghrelin also occur in diet-induced weight loss; this is consistent with a role of ghrelin in the long-term regulation of body weight, primarily to increase lean body mass [114].

Exogenous ghrelin administration has been shown to stimulate gastric contractility and emptying. Intravenous administration of ghrelin stimulates premature onset of the phase III of the migrating motor complex, increases proximal gastric tone, and increases gastric emptying [115]. Although there is some similarity between ghrelin and motilin, the actions of ghrelin seem to be independent of actions of motilin or its receptors [116]. Several small studies have shown that exogenous ghrelin administration accelerates gastric emptying in patients with idiopathic gastroparesis, diabetic gastroparesis, and postsurgical gastroparesis [117, 118]. Owing to ghrelin's actions in stimulating gastric emptying, signaling hunger, and increasing body mass, it is interesting to speculate that ghrelin agonists may be particularly useful in severe gastroparesis with delay in gastric emptying and marked weight loss,

since ghrelin and ghrelin receptor agonists may both increase gastric emptying and stimulate appetite.

Ghrelin receptor agonists are being developed as promotility agents, for disorders of GI motility particularly in gastroparesis and postoperative ileus. TZP-101, a small-molecule ghrelin receptor agonist, given intravenously accelerated gastric emptying in diabetic patients with symptomatic gastroparesis [119]. When given for three days in patients with diabetic gastroparesis, TZP-101 improved gastroparetic symptoms, particularly vomiting and loss of appetite [120]. Side effects were relatively minor, but did include hyperglycemia, nausea, and diarrhea. There have been no cardiac irregularities demonstrated with ghrelin infusion [121]. The agent TZP-101 is given as an intravenous infusion and might be useful for exacerbations of gastroparesis leading to hospitalizations or could be given in an outpatient infusion unit for worsening symptoms and used to prevent subsequent hospitalizations. There is also an oral formulation, TZP-102, that also shows promise for treatment of gastroparesis and could be given for longer durations, and might be useful for chronic treatment of gastroparesis.

Increasing gastric emptying by ghrelin can increase peak postprandial glucose levels, as can be seen with any prokinetic agent [17]. In addition, ghrelin itself has been reported to have effects on decreasing insulin release and increasing systemic glucose levels [114]. Thus, glucose control might have to be periodically monitored after starting prokinetic agents, in particular ghrelin receptor agonists. Bradycardia has been reported in the pharmacokinetic studies with TZP-101 in normal subjects [121], but this was not seen in the patients with diabetic gastroparesis [119, 120].

Conclusions

Prokinetic agents are used frequently in gastroparesis to help improve the underlying defect of delayed gastric emptying. These agents are attractive in treatment of gastroparesis, as they tackle the underlying pathophysiology that defines this disorder. However, response to treatment with prokinetic agents may not parallel changes in gastric emptying. Only a few prokinetic agents are available, as several have been withdrawn from the market. Several prokinetic agents, notably metoclopramide and domperidone, also have antiemetic properties. Newer agents, including ghrelin, motilin, and 5-HT_4 receptor agonists, are being investigated, which demonstrate efficacy and have few side effects.

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Chapter 23
Antiemetic Treatment for Gastroparesis

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Keywords Nausea and vomiting • Receptor agonists and antagonists • Antidepressants • Herbal remedies • Gastric emptying

Introduction

Gastroparesis is defined by symptomatic delay in gastric emptying. As a consequence, the disorder is traditionally considered to benefit most from therapy with prokinetic drugs that promote gastric emptying. However, many patients exhibit incomplete symptom responses to prokinetic agents or exhibit unacceptable side effects to these drugs. For these individuals, clinicians commonly rely on antiemetic drugs that have no stimulatory effects on gastric retention to reduce nausea and/or vomiting.

Neurotransmitter Control of Nausea and Vomiting

Vomiting from a broad range of stimuli is coordinated by the brain stem while nausea involves cerebral cortical participation as this symptom requires conscious perception. The underlying causes of nausea and vomiting in gastroparesis are not well understood, but likely involve disruption of normal gastric functions. Although the disorder is associated with increased gastric retention, vomiting severity correlates poorly with rates of gastric emptying suggesting that other factors may be pathogenic of symptoms. Antral distention elicits nausea and altered gastric myoelectric

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function, raising the possibility that abnormal intragastric distribution, increased mechanical distention, or heightened sensitivity may contribute to symptom development. This interplay between gastric sensorimotor activities and the central nervous system suggests that agents that act centrally to reduce nausea and vomiting might be as effective as drugs that work by stimulating gastric emptying.

Brain stem nuclei (including the nucleus tractus solitarius, dorsal vagal, and phrenic nuclei, medullary nuclei that regulate respiration, and nuclei that control pharyngeal, facial, and tongue movements) coordinate initiation of the act of vomiting. Neurotransmitters involved in these coordinated actions are uncertain, but neurokinin NK_1, serotonin 5-HT_3, vasopressin, endorphin, and gamma-aminobutyric acid pathways may participate [1].

Emesis occurring in response to a broad range of stimuli results from activation of several sites in the peripheral and central nervous systems. Neurotransmitters that mediate induction of vomiting are selective for these anatomic sites. Motion sickness and emesis with inner ear disorders are mediated by action on the labyrinthine apparatus, whereas gastric irritants and cytotoxic agents, such as cisplatin, stimulate gastroduodenal vagal afferent nerves. Labyrinthine disorders stimulate vestibular muscarinic M_1 and histaminergic H_1 receptors, whereas vagal afferent stimuli activate serotonin 5-HT_3 receptors. The area postrema, a brain stem medullary nucleus, responds to blood borne emetic stimuli and is termed the chemoreceptor trigger zone. Emetic stimuli acting on the area postrema include many emetogenic drugs, bacterial toxins associated with food poisoning, and metabolic factors produced during pregnancy, uremia, hypoxia, and ketoacidosis. The area postrema is richly served by nerve fibers that act on 5-HT_3, M_1, H_1, and dopamine D_2 subtypes. Nausea and vomiting in several clinical settings also likely involves cerebral cortical pathways. Transmitters in the cerebral cortex are less well understood, although cannabinoid CB_1 pathways are prominent. Optimal pharmacologic therapy of nausea and vomiting requires understanding of these receptor-mediated pathways.

Antiemetic Medications

Agents with antiemetic effects include a variety of selective neurotransmitter receptor antagonists and agonists and medications with complex mechanisms of action. These drugs do not stimulate gastric emptying; rather, they have no effect or delay gastric emptying. However, there is no published evidence that the motor inhibitory effects of such antiemetic medications exacerbate symptoms in gastroparesis. Thus, agents which delay gastric emptying are not necessarily contraindicated in gastroparesis if their symptom benefits outweigh this physiologic effect. Furthermore, some of the drugs which are considered to primarily act via their prokinetic effects may in fact reduce symptoms by antiemetic actions in a brainstem. Although widely employed in the care of gastroparesis, there is very limited evidence-based literature on the use of antiemetic drugs in this challenging condition.

Table 23.1 Selective receptor antagonists and agonists with antiemetic actions

Receptor subtype	Examples	Documented clinical utility	Literature reports of use in gastroparesis
Histamine H_1 antagonists	Dimenhydrinate, meclizine, promethazine	Motion sickness, postoperative nausea and vomiting	No
Muscarinic M_1 antagonists	Scopolamine, methscopolamine, hyoscyamine	Motion sickness, postoperative nausea, and vomiting	No
Dopamine D_2 antagonists	Prochlorperazine, thiethylperazine, trimethobenzamide	Toxins, metabolic causes, chemotherapy-induced emesis, postoperative nausea and vomiting, radiotherapy-induced emesis	Case report
Serotonin 5-HT_3 antagonists	Ondansetron, granisetron, dolasetron	Chemotherapy-induced emesis, postoperative nausea and vomiting, radiotherapy-induced emesis	Case report
Neurokinin NK_1 antagonists	Aprepitant, fosaprepitant	Chemotherapy-induced emesis, postoperative nausea and vomiting, motion sickness	Case report
Cannabinoid CB_1 agonists	Dronabinol, nabilone	Chemotherapy-induced emesis	No

Selective Receptor Antagonists and Agonists

Histamine H_1 Receptor Antagonists. Histamine H_1 receptor antagonists are most often used for the prevention of motion sickness and the treatment of emesis associated with labyrinthine disease (Table 23.1). H_1 receptor antagonists also exhibit efficacy for prophylaxis of postoperative nausea and vomiting. Agents in this class include over-the-counter drug dimenhydrinate and the prescription medication meclizine. Promethazine is a potent H_1 receptor antagonist that also exhibits antagonist effects on dopamine receptors. H_1 receptor antagonists may be administered orally, parenterally, or by rectal suppository. Less sedating antihistamines, such as cetirizine and fexofenadine have limited antiemetic activity [2]. Intramuscular promethazine has been shown to delay gastric emptying [3]. The main side effects of this drug class are sedation and dryness of the mouth and eyes. There are no literature reports describing the use of H_1 receptor antagonists in gastroparesis.

Muscarinic M_1 Receptor Antagonists. As with the H_1 receptor antagonists, muscarinic M_1 receptor antagonists are indicated for prophylaxis of motion sickness (Table 23.1). In meta-analyses, muscarinic antagonists are superior to placebo and

comparable in efficacy to antihistamines in preventing motion-induced emesis [4]. Numerous reports documenting efficacy of M_1 receptor antagonists in postoperative nausea and vomiting also have been published. In a systematic review, M_1 receptor antagonists exhibited 17% superior reductions in postoperative symptoms compared to placebo [5]. Agents in this class include the antiemetic drug scopolamine as well as atropine and the antispasmodics methscopolamine, clidinium, and hyoscyamine. M_1 receptor antagonists may be given orally, transdermally, or intravenously. Retardation of gastric emptying has been observed with atropine, hyoscyamine, and clidinium [6]. Atropine also reduces phasic antral contractile activity, but can prevent gastric slow wave dysrhythmias elicited during experimental motion sickness [6, 7]. These medications can cause dryness of the mouth and eyes, sedation, impaired concentration, headaches, constipation, and urinary retention. Benefits of M_1 receptor antagonists in gastroparesis have not been described.

Dopamine D_2 Receptor Antagonists. Dopamine D_2 receptor antagonists are the most widely prescribed general antiemetic drug class, exhibiting efficacy against vomiting elicited by toxins, metabolic conditions, pregnancy, abdominal irradiation, surgery, and some forms of chemotherapy (Table 23.1). D_2 receptor antagonists also show benefits in prevention of postoperative nausea and vomiting as well as chemotherapy-induced emesis. Agents in this drug class include prochlorperazine, thiethylperazine, and trimethobenzamide as well as the butyrophenones (droperidol, haloperidol). D_2 receptor antagonists are administered orally, parenterally, or by rectal suppository. Intravenous chlorpromazine at a dose of 25 mg does not affect gastric emptying [8]. D_2 receptor antagonists freely cross the blood-brain barrier and can cause anxiety, sleep disturbances, mood changes, dystonic reactions, hyperprolactinemic effects (galactorrhea and sexual dysfunction), and irreversible tardive dyskinesia. In a single case report, the D_2 receptor antagonist thiethylperazine exhibited benefits in a patient with gastroparesis [9]. Dopamine D_2 receptor antagonists with prokinetic action, such as metoclopramide and domperidone, also have antiemetic actions and are discussed below.

Serotonin 5-HT_3 Receptor Antagonists. Serotonin 5-HT_3 receptor antagonists are approved for prophylaxis of acute chemotherapy-induced emesis, radiotherapy-induced emesis, and postoperative nausea and vomiting (Table 23.1). These agents may not be more potent than D_2 receptor antagonists in conditions other than these. Examples of 5-HT_3 receptor antagonists include ondansetron, granisetron, and dolasetron which can be given orally or intravenously. A new transdermal granisetron preparation shows efficacy in chemotherapy-induced emesis prophylaxis and may be useful for individuals with severe vomiting who cannot retain oral medications [10]. The newer 5-HT_3 receptor antagonist palonosetron exhibits a longer half life and higher receptor binding affinity and has greater efficacy in those with delayed chemotherapy-induced emesis than first generation 5-HT_3 receptor antagonists [11]. Ondansetron has not been shown to have significant effects on gastric emptying while tropisetron reportedly promotes gastric retention and blunts antral contractions [12]. Side effects of this drug class include constipation, headaches, and rare elevated liver chemistries. Intraperitoneal ondansetron has been successfully used to treat nausea and vomiting in a gastroparesis patient on peritoneal dialysis [13].

Neurokinin NK_1 Receptor Antagonists. Neurokinin NK_1 receptor antagonists are the most recently developed receptor antagonists for use in conditions with nausea and vomiting (Table 23.1). NK_1 receptor antagonists are approved for acute and delayed chemotherapy-induced emesis and also exhibit benefits in postoperative nausea and vomiting, motion sickness, and vomiting after apomorphine, copper sulfate, nicotine, and ipecacuanha [1]. In indicated clinical settings, investigations suggest that NK_1 receptor antagonists are more potent than $5\text{-}HT_3$ receptor antagonists. These agents permit the majority of patients to complete chemotherapy without significant gastrointestinal morbidity [14]. Older studies report reductions in nausea in addition to decreased vomiting; however, this has not been observed in many recent investigations [15]. Examples of this drug class include the oral agent aprepitant and the parenteral medication fosaprepitant, which is the water soluble phosphoryl prodrug of aprepitant. A third drug, casopitant, is in testing. Side effects include anorexia, bowel pattern disturbance, and singultus. Aprepitant also exhibits inhibitory effects on CYP3A4 activity and can lead to altered levels of other medications, including those that inhibit (ketoconazole, diltiazem) or stimulate (rifampin) CYP3A4 [1]. The drug also can influence levels of drugs metabolized by CYP2C9, including phenytoin and warfarin [1]. The effects of NK_1 receptor antagonists on gastric emptying are uncertain. In a 31-year-old type I diabetic woman with gastroparesis refractory to standard antiemetic and prokinetic therapies, aprepitant substantially improved symptoms over a 4-month period [16]. A multicenter, controlled trial of aprepitant for refractory gastroparesis has been initiated.

Cannabinoid CB_1 Receptor Agonists. In contrast to other antiemetic drugs with predominant antagonist actions on single receptor subtypes, it is the agonists of the cannabinoid CB_1 receptor that show benefits in patients with vomiting. These agents were initially approved to treat chemotherapy-induced emesis (Table 23.1). In meta-analyses of studies of chemotherapy patients, cannabinoids showed superiority versus placebo as well as other antiemetics and were preferred over other treatments for nausea and vomiting [17]. Examples of oral CB_1 receptor agonists include dronabinol and nabilone. This drug class exhibits retarding effects on gastric emptying compared to placebo [18]. Side effects of CB_1 receptor agonists include somnolence, cognitive dysfunction, ataxia, syncope, seizures, and hallucinations which may be more prominent in older patients. The benefits of CB_1 receptor agonists in gastroparesis have not been investigated.

Agents with Complex Mechanisms of Action

Tricyclic Antidepressant Agents. Medications in the tricyclic antidepressant class exhibit impressive benefits in several conditions with associated nausea and vomiting (Table 23.2). Tricyclic agents act primarily to inhibit neuronal norepinephrine reuptake but also act as antagonists on selected muscarinic, histaminergic, serotonergic receptor subtypes. In a review of 37 patients with functional vomiting given tricyclic agents for a mean of 5.4 months, moderate reductions or complete remissions

Table 23.2 Other medication classes with potential antiemetic effects

Medication class	Examples	Possible mechanisms of action
Tricyclic antidepressants	Nortriptyline, desipramine, amitriptyline	Norepinephrine reuptake inhibition, histamine, muscarinic, serotonin antagonist
Tetracyclic antidepressants	Mirtazapine	Histamine, muscarinic, adrenergic, serotonin antagonist, inhibit norepinephrine transporter
Neuroleptics	Olanzapine	Histamine, muscarinic, dopamine, serotonin, gamma-aminobutyric acid antagonist
Anticonvulsants	Levetiracetam, zonisamide	Unknown
Neuropathic pain modulators	Gabapentin	Gamma-aminobutyric acid, N-type calcium channels
Benzodiazepines	Lorazepam, alprazolam, diazepam	Sedative
Corticosteroids	Dexamethasone, prednisone, methylprednisolone	Unknown
Herbal	Ginger	Serotonin antagonist
	Iberogast	Serotonin antagonist and agonist

of symptoms were observed in 84% [19]. Likewise, this drug class is well established for symptom prophylaxis in patients with cyclic vomiting syndrome [20]. Examples of tricyclic drugs include amitriptyline, nortriptyline, desipramine, imipramine, and doxepin which are taken orally. Side effects of these agents include sedation, constipation, dryness of the mouth, and weight gain. Secondary amines (nortriptyline, desipramine) may elicit fewer side effects. The benefits of tricyclic drugs in gastroparesis are unproved. However, in an assessment of 24 diabetic patients with refractory nausea and vomiting, tricyclic administration at a mean dose of 50 mg daily produced moderate or better symptom reductions in 77% and remissions in one third [21]. Although this investigation did not strictly target gastroparetics, 29% of patients exhibited delayed gastric emptying. A placebo-controlled, multicenter trial of the tricyclic agent nortriptyline in patients with refractory idiopathic gastroparesis is ongoing.

Other Antidepressants and Neuroleptic Drugs. Agents with antidepressant or neuroleptic effects in the central nervous system are anecdotally reported to reduce nausea and vomiting in certain settings (Table 23.2). The tetracyclic agent mirtazapine has shown efficacy in individuals with a range of conditions with associated nausea and vomiting. Mirtazapine has a complex mechanism of action, including antagonism or inverse agonism of 5-HT_3, 5-HT_7, alpha adrenergic, H_1, and muscarinic receptors as well as several 5-HT_2 subtypes and inhibition of the norepinephrine transporter. In one case report of a gastroparesis patient refractory to conventional prokinetics, mirtazapine produced complete remission of nausea, vomiting, and abdominal pain within one week of starting therapy [22]. Mirtazapine has fewer cardiac side effects than tricyclic drugs, but can promote significant weight gain.

The antipsychotic drug olanzapine exhibits antagonism against several receptor subtypes in the dopamine, serotonin, muscarinic, histamine, and gamma-aminobutyric acid classes [1]. As part of a regimen including palonosetron and dexamethasone, olanzapine provided complete prophylaxis of chemotherapy-induced emesis [23]. Olanzapine also has shown efficacy in reducing nausea in other medication-refractory patients [24].

Miscellaneous Antiemetics. Several other prescription agents with uncertain mechanisms of action reduce nausea and/or vomiting in selected clinical settings (Table 23.2). Benzodiazepines are most useful for anticipatory nausea and vomiting occurring before cancer chemotherapy, and commonly are given during the prodromal phase or the acute attack in cyclic vomiting syndrome [20]. Benzodiazepines also are included in some multidrug regimens to prevent chemotherapy or postoperative vomiting. Agents in this drug class include lorazepam, diazepam, chlordiazepoxide, and alprazolam. Diazepam has no effect on gastric emptying [25]. The utility of benzodiazepines in gastroparesis have not been studied. Corticosteroids exhibit significant efficacy for prophylaxis of postoperative nausea and vomiting and chemotherapy-induced emesis, particularly during the delayed phase. Corticosteroids are often combined with one or two other drugs prior to surgery, radiotherapy, or emetogenic chemotherapy for optimal antiemetic effect [1]. Examples of corticosteroids include dexamethaxone, prednisone, and methylprednisolone. Effects of corticosteroids on gastric emptying are uncertain. In an unpublished report, dexamethasone reportedly reduced symptoms in three patients with idiopathic gastroparesis. In another study, an individual with idiopathic myenteric ganglionitis reported improved vomiting on corticosteroids [26]. The anticonvulsants levetiracetam and zonisamide and antimigraine therapies, such as sumatriptan, show benefits in the prophylaxis and the treatment of cyclic vomiting syndrome, respectively [27]. Gabapentin and the anticonvulsant carbamazepine have been reported to exhibit antiemetic effects in case reports; the utility of these drugs in gastroparesis has not been studied [28]. The peripheral opioid antagonist methylnaltrexone is effective for the treatment of constipation secondary to narcotic use [29]. However, its efficacy in gastroparesis patients on chronic opiate agents has not been studied.

Herbal remedies also exhibit antiemetic benefits in some clinical settings, including postoperative nausea and vomiting and first trimester nausea and vomiting of pregnancy (Table 23.2). The mechanisms of action of ginger are not completely defined. However, components of ginger exhibit 5-HT_3 receptor antagonist properties. In animal and human models, ginger can reverse experimental gastroparesis and prevent metabolically induced tachygastria [30]. The utility of ginger in gastroparesis is uninvestigated. In a study of 137 patients with functional dyspepsia and dysmotility symptoms, the herbal extract iberogast showed equivalent efficacy to the prokinetic drug cisapride in reducing symptoms [31]. Iberogast exhibits several properties that would suggest possible benefits in gastroparesis, including partial 5-HT_4 receptor agonism, 5-HT_3 receptor antagonism, reduction of gastric acid secretion, and increases in selected mucosally protective prostaglandins. Iberogast prolonged the half time of gastric emptying in patients with gastroparesis and functional dyspepsia in another study.

Prokinetic Agents with Antiemetic Effects

Prokinetic medications are the agents considered to be the first-line therapy for gastroparesis, based on their abilities to accelerate delayed gastric emptying. However, there is limited evidence supporting the postulate that these agents reduce symptoms by this mechanism. Indeed, some studies show poor correlations between symptom reductions and motor stimulatory effects of metoclopramide [32]. Likewise, improvements in nausea and vomiting in patients with diabetic or idiopathic gastroparesis given domperidone are observed in the absence of documented improvements in gastric emptying [33]. These prokinetic agents with dopamine D_2 receptor antagonist effects also exhibit independent antiemetic actions on the area postrema. It is possible that these central actions are more crucial for symptom control than stimulatory effects on the stomach. In contrast, the prokinetic medication erythromycin, which has no central antiemetic effect, has reported benefits in only 43% of patients with gastroparesis suggesting that agents without effects on brain stem emetic pathways may be less useful [34].

Summary of Clinical Implications

Although there are limited data supporting the use of antiemetic agents in patients with gastroparesis, it is reasonable to recommend these medications for patients who do not respond or do not tolerate traditional prokinetic drugs. Indeed, the authors of a recent American Motility Society Task Force on Gastroparesis document issued a consensus opinion that antiemetic drugs may be beneficial in such cases [35]. Given that many of the available agents are inexpensive, generically formulated, and relatively safe, it is probable that controlled trials of these antiemetic treatments of gastroparesis will never be performed. Additional suggestions can be made for selected patients with refractory vomiting based on experiences with chemotherapy-induced emesis and postoperative nausea and vomiting. These include ingestion of liquid formulations as opposed to solid pills or use of preparations that do not require small intestinal absorption, such as orally dissolving tablets, rectal suppositories, intramuscular injections, or transdermal patches. Furthermore, it is possible that concurrent use of multiple antiemetic agents with disparate mechanisms of action or combining antiemetic therapy with a prokinetic drug may be more effective in severe gastroparesis flares than administration of a single medication.

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Chapter 24
Pain Management for Gastroparesis

Henry P. Parkman

Keywords Gastroparesis • Pain management • Gastric emptying • Functional dyspepsia

Gastroparesis and Functional Dyspepsia

Gastroparesis is a chronic disorder characterized by delayed gastric emptying in the absence of mechanical obstruction [1]. Symptoms of gastroparesis typically include early satiety, postprandial fullness, nausea, and vomiting. Gastroparesis can occur in several clinical settings; it is most commonly associated with diabetes, postsurgical and idiopathic (that is, without a known cause) [2]. The diagnosis of gastroparesis is generally made with a gastric emptying test – with scintigraphy, wireless motility capsule, or breath test [1].

In contrast to gastroparesis characterized by symptoms with delayed gastric emptying, functional dyspepsia is characterized by symptoms – postprandial fullness, early satiation, or epigastric pain or burning with no evidence of structural disease on upper endoscopy [3]. Functional dyspepsia is now divided into two subgroups: postprandial distress syndrome (early satiation or postprandial fullness) and epigastric pain syndrome (pain or burning in the epigastrium) [3]. Functional dyspepsia is heterogeneous. Pathophysiology of functional dyspepsia includes impaired gastric emptying (either delayed or rapid), impaired fundic accommodation, visceral hypersensitivity, and rarely, helicobacter pylori infection. There is overlap between gastroparesis and functional dyspepsia as both symptoms and gastric emptying results may meet definitions for both in some patients [4]. Some patients with abdominal

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pain, nausea, vomiting, and evidence of delayed emptying are considered to have functional dyspepsia by some clinicians and gastroparesis by others. Since the symptoms of functional dyspepsia are nonspecific and cover gastric symptomatology and patients with idiopathic gastroparesis have gastric symptoms, it is not surprising that many gastroparetic patients meet criteria for functional dyspepsia. In a recent article on idiopathic gastroparesis, 86% of patients with idiopathic gastroparesis met criteria for functional dyspepsia [5]. Over 90% had postprandial distress syndrome and the presence of postprandial distress syndrome increased with the severity of the delay in gastric emptying.

Abdominal Pain in Gastroparesis

While gastroparesis usually presents with nausea or vomiting, abdominal pain may also be part of the patient's symptoms. Abdominal pain, however, is not classically regarded as a symptom of gastroparesis. It is often taught that if a patient has significant abdominal pain, one should think about other disorders besides gastroparesis. Conditions to be considered in the differential diagnosis of abdominal pain in this scenario may include peptic ulcer disease, chronic pancreatitis, biliary tract disease (gallstones or biliary dyskinesia), fibromyalgia, functional disorders, such as irritable bowel syndrome and functional dyspepsia, and rarer disorders, including cyclic vomiting syndrome, median arcuate ligament syndrome, and reflex sympathetic dystrophy [4, 6].

The relationship of abdominal pain to delayed gastric emptying can be difficult to understand in some patients. Narcotic analgesics, sometimes used for abdominal pain, can cause symptoms of nausea and vomiting, by their central effects on the chemoreceptor vomiting center. In addition, these agents can delay gastric emptying and, in turn, cause symptoms of nausea and vomiting. Thus, in some patients with abdominal pain from nongastroparesis etiologies who take narcotic analgesics for pain, a gastric emptying test can be delayed, not because they have gastroparesis, but because the narcotic analgesic is delaying gastric emptying. For evaluation, it is suggested that patients do not take narcotic analgesics for 48 h prior to the gastric emptying test [7].

The gastroparesis cardinal symptom index (GCSI) was designed to quantitate the severity of symptoms of gastroparesis [8]. Interestingly, abdominal pain is not one of the symptoms in the GCSI. In patient interviews for the development of the daily diary form of the GCSI (GCSI-DD), less than half the patients with gastroparesis felt abdominal pain was an important symptom of gastroparesis [9]. The Patient Assessment of GI Symptoms (PAGI-SYM) is a questionnaire that captures symptoms of gastroparesis, functional dyspepsia, and gastroesophageal reflux disease [10]. The 20 question PAGI-SYM contains the 9 symptoms of the GCSI. Using the PAGI-SYM, upper abdominal pain scores in patients with gastroparesis averaged 2.21 on a scale from 0 to 5 [10]. This value was similar to conditions more classically

associated with pain, including dyspepsia [2.27]. The PAGI-SYM also asks about abdominal discomfort, a term that can be difficult to interpret as it may be interpreted by patients as mild abdominal pain or other symptoms, such as stomach fullness.

In some patients with gastroparesis, pain represents a prominent symptom and can produce significant morbidity and utilization of health care resources [2, 11]. Case series of gastroparesis report prevalence rates of pain ranging from 46 to 71% [2, 12] and many individuals state that their pain is of moderate to severe intensity [12]. Few prior studies have specifically investigated abdominal pain in patients with gastroparesis. The importance, cause, and treatment of pain in gastroparesis are largely unexplored. There have been three studies/articles that specifically address the presence of abdominal pain in patients with gastroparesis [13–15].

In one of the first studies focusing on pain in gastroparesis, Hoogerwerf et al. reported the prevalence of abdominal pain in GP to be 89% [13]. This prevalence of pain [89%] was similar to that of nausea [93%] and early satiety [86%] and was greater than that of vomiting [68%]. Pain was characterized as crampy, burning, or vague in character. Abdominal pain was localized to the epigastrium in only 36% of cases. Meals exacerbated symptoms in 80% but provided relief in 15% of patients. Up to 80% of gastroparetic patients experienced some pain at night.

In the recent article by Cherian et al., abdominal pain was present in 89.7% of patients with gastroparesis, a prevalence rate compared to nausea which was present in 95.6% [14]. Abdominal pain was generally midline: epigastric in 42.6%, umbilical in 13.1%, and hypogastric in 11.5%. Intermittent abdominal pain was experienced by 62% of patients and 43% had daily abdominal pain. Many patients also complained of nocturnal pain (73.8%) with interferance of sleep (65.6%). Using the 5-point PAGI-SYM symptom score, the severity of upper abdominal pain (3.04), although lower than nausea (3.57), was greater than the severity of vomiting (2.21). Abdominal pain severity did not correlate with gastric emptying retention at 2 or 4 h. Abdominal pain was also present in 98.1% of patients with functional dyspepsia and normal gastric emptying compared to 90% in patients with gastroparesis. The abdominal pain severity was greater in functional dyspepsia as compared to gastroparesis (3.63 vs. 3.04). The upper abdominal pain subscale was significantly higher in idiopathic than diabetic gastroparesis (3.36 vs. 2.68), whereas the nausea/vomiting subscale showed no significant difference between the two groups. There were also significant moderate correlations between abdominal pain and impaired quality of life in multiple aspects of life and daily living.

Recently, the importance of abdominal pain as a symptom in gastroparesis was evaluated by the NIH Gastroparesis Consortium [15]. Of 339 patients with gastroparesis, 243 patients (72%) noted abdominal pain. Abdominal pain was the predominant symptom in 65 (19%) compared to nausea or vomiting in 194 (57%). Higher percentages of those with pain were present in idiopathic gastroparesis (70%) compared to diabetic gastroparesis (54%). Quality of life assessed by Patient Assessment of GI Quality of Life (PAGI-QOL) and SF-36 were lower in patients with pain. Gastric retention was similar in patients with pain vs. no pain. Opiate use was higher with pain while antidepressant, neuropathic pain modulator, prokinetic,

and antiemetic use did not significantly differ. Importantly, this study showed that abdominal pain is present in 72% of patients with gastroparesis and was predominant symptom in 1 in 5 patients.

These three studies suggest that upper abdominal pain is a symptom in many patients with gastroparesis with comparable severity to nausea and vomiting. Abdominal pain, like nausea and vomiting is also significantly correlated with impaired quality of life. Interestingly, abdominal pain does not correlate with delay in gastric emptying. Abdominal pain was worse in idiopathic compared to diabetic gastroparesis. Further investigation is needed to identify the causes of abdominal pain in patients with gastroparesis to help determine how best to treat this symptom in patients.

Pathogenesis of Abdominal Pain in Gastroparesis

The pathogenesis of pain in gastroparesis is poorly understood, leaving treatments for this symptom largely empirical and often unsatisfactory. A limited number of investigations have addressed the underlying causes of pain in gastroparesis. However, it is plausible that it can be the manifestation of autonomic neuropathy and/or visceral hyperalgesia [6].

Several studies have shown that there is no correlation between delay in gastric emptying and severity of abdominal pain in patients with gastroparesis [14–16]. The relationship between symptom patterns, assessed by the PAGI-SYM questionnaire, and gastric sensorimotor dysfunction was also studied in functional dyspepsia [17]. Gastric emptying was correlated with symptom subscores for nausea/vomiting, fullness/satiety, bloating, heartburn/regurgitation, but not upper abdominal pain.

The lack of correlation between abdominal pain and gastric emptying suggests that other mechanisms may be responsible for the abdominal pain in patients with gastroparesis, such as changes in gastric accommodation, gastric distension, and/or visceral hypersensitivity [18]. In patients with idiopathic gastroparesis, the symptom pattern has been suggested to be determined by proximal stomach dysfunction rather than by the severity of delayed emptying [12]. The prevalence of pain has been found to be similar in symptomatic individuals with normal versus impaired gastric fundic accommodation [12, 18]. Hypersensitivity to gastric distension was associated with higher prevalences of epigastric pain, early satiety, and weight loss. Impaired accommodation was associated with higher prevalence of early satiety and weight loss. Thus, visceral hypersensitivity may be one of the causes for abdominal pain in patients with gastroparesis.

In diabetics with gastroparesis, pain has been considered to be a consequence of autonomic neuropathy. However, one small study found that more severe forms of visceral afferent neuropathy were associated with fewer rather than more severe symptoms in diabetic gastroparesis [19].

Unexplored as a factor in abdominal pain in patients with gastroparesis are central mechanisms. Using positron emission tomography, altered central nervous system processing to gastric distension has been found in patients with functional dyspepsia [20].

Management of Pain in Gastroparesis

Pain has been neglected in the management gastroparesis. Unfortunately, abdominal pain can be prominent and may be the most difficult symptom to control. There have been few, if any, studies to address the effectiveness of any therapy of abdominal pain in patients with gastroparesis. Administration of the usual treatments for gastroparesis (prokinetic and antiemetic agents) may not satisfactorily treat abdominal pain [21]. Specific pharmacotherapy for the management of pain in patients with gastroparesis is complicated by potential drug side effects as well as drug properties which can delay emptying and/or worsen symptoms, thereby counteracting the benefits of prokinetic and antiemetic medications often used in these patients [6]. Before prescribing analgesics, consideration should be given to the potential effects of the medication on gastric emptying and potential for side effects and drug interactions [6].

Multiple mechanisms may be involved in the pathogenesis of visceral pain [4]. A drug that selectively targets a specific mechanism may not be able to resolve pain alone. Severe visceral pain in gastroparesis may need to be managed in a multidisciplinary approach. Various approaches are available [22, 23], including the following: (1) targeting coexistent dysmotility problems; (2) targeting peripheral receptors and neuromodulators; (3) targeting central circuits; (4) targeting somatic hypervigilance and related conditions; (5) targeting inflammatory response; and (6) targeting of all of the above.

Prokinetic Agents

Prokinetic agents aim to improve gastric emptying. Symptoms associated with delayed gastric emptying, such as nausea, vomiting, and fullness, are generally targeted with prokinetic agents and may improve with treatment. In some patients, the abdominal pain may be relieved through the prokinetic effect of drugs [24]. Some uncontrolled series with prokinetic treatments, including cisapride and domperidone have observed decreases in pain that track reductions in traditional symptoms of gastroparesis, such as nausea, vomiting, and fullness [24, 25].

Nonsteroidal Anti-inflammatory Drugs

Several medication classes offer theoretical benefits for reducing pain in the gastroparesis patient. Nonsteroidal anti-inflammatory agents ameliorate gastric slow wave dysrhythmias in several healthy human studies [26]. Oral indomethacin and intravenous ketorolac have been reported to resolve slow wave abnormalities in diabetics and patients with dyspeptic symptoms [27, 28]. In general, nonsteroidal anti-inflammatory drugs (NSAIDs) are given on an intermittent basis for mild to

moderate abdominal pain. Although selected patients can be considered for these drugs, their routine use on a daily basis cannot be advocated due to their potential for side effects, particularly the development of ulcers or worsening renal function [21].

Psychotropic Agents

Tricyclic and tetracyclic antidepressants and pain modulators, such as gabapentin and pregabalin exhibit beneficial effects in reducing chronic abdominal pain of varied etiologies, but their effects on gastroparesis pain are largely unknown [4, 21]. These agents can also help improve nausea and vomiting. Investigations focusing on the specific effects of these and other treatment modalities on pain in gastroparesis are warranted.

Tricyclic Antidepressants (TCAs). TCA medications in low doses may reduce pain associated with gastroparesis much as they do in other forms of neuropathic pain [29]. TCAs have been suggested to decrease nausea, vomiting, and abdominal pain in patients with functional GI disorders [30–33] and in patients with diabetes, including patients with diabetic gastroparesis [34]. The mechanisms that TCAs reduce gastrointestinal symptoms are unknown, but believed to be mediated centrally [33]. It has been proposed that low doses of TCAs, such as amitriptyline (Elavil) reduce sensory transmission and reduce visceral hypersensitivity. On the other hand, TCAs can also slow gastric emptying by virtue of their anticholinergic activity.

TCAs may suppress symptoms in patients with gastroparesis and functional dyspepsia; studies suggest that they may decrease nausea and vomiting and abdominal pain [30]. In one retrospective analysis of open label treatment, TCAs reduced symptoms in patients with functional vomiting [31]. The effective dose averaged 50 mg/day – lower than used for depression. In two studies in functional dyspepsia, low-dose TCAs decreased dyspeptic symptoms and abdominal pain [32, 33]. In a retrospective evaluation of diabetic patients with nausea and vomiting, low-dose TCAs provided better symptom reduction than prior trials of antiemetic and prokinetic drugs [34]. Nearly one third of patients exhibited delayed gastric emptying, suggesting that the presence of impaired motor function is not a contraindication for TCAs.

Desipramine was helpful on a per protocol basis, but not on an intention to treat basis, in female patients with functional bowel disorders, primarily irritable bowel syndrome [35]. In this desipramine study, dose escalation occurred every week – initial dose was 50 mg po qhs, then 100 mg, and then 150 mg/day. On the per protocol basis, the response rate to desipramine (69%) was greater than to placebo (49%) when patients who did not take their medication due to side effects or other reasons were excluded. Adverse events occurred with desipramine in 17% of patients.

The classification of TCAs is based on their structure. Tertiary amines, including amitriptyline, imipramine, doxepin, have more anticholinergic activity and more side effects. Secondary amines, including nortriptyline and desipramine, have less

anticholinergic activity and fewer side effects. Atypical TCAs include trazadone. In general, when treating patients with gastroparesis, TCAs are used at low doses and ones are used with lower anticholinergic activity, such as desipramine or nortriptyline. A reasonable starting dose for a tricyclic agent is 10–25 mg at bedtime. If benefit is not observed in several weeks, doses are increased by 10- to 25-mg increments up to 50–75 mg. Side effects may require a change in medication in some patients [30].

SSRIs, SNRIs, SSNRIs. Other antidepressant classes, including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and combined serotonin/norepinephrine reuptake inhibitors may have benefits as well; however, there are no data on their actions on visceral nerve function. Duloxetine, a combined serotonin/norepinephrine reuptake inhibitor, was recently approved for diabetic neuropathy [36]. Among SSRIs, paroxetine may selectively accelerate small intestinal transit [37, 38]. The effects of serotonergic psychoactive agents on gastrointestinal functions in healthy human subjects were evaluated using buspirone, a 5-HT(1A) receptor agonist (10 mg twice daily); paroxetine, an SSRI (20 mg daily); venlafaxine-XR, a selective serotonin and norepinephrine reuptake inhibitor (75 mg daily); or placebo for 11 days [37]. No effects on gastric emptying or colonic transit were observed with any agent. Small bowel transit of a solid meal was accelerated by paroxetine. Buspirone decreased postprandial aggregate symptom and nausea scores. Venlafaxine-XR increased the postprandial change in gastric volume. Thus, buspirone, paroxetine, and venlafaxine-XR affect upper gastrointestinal functions in healthy humans.

A recent study found that venlafaxine, an SNRI antidepressant, improved symptoms in young adult patients with functional chest pain [39]. In another study, however, venlafaxine was not effective in patients with functional dyspepsia and was associated with side effects [40].

Antiepileptic Agents. Other agents with efficacy in peripheral neuropathic pain include the anticonvulsants gabapentin and topiramate. Although they have unknown actions in patients with pain associated with gastroparesis, they are occasionally used to treat pain in diabetic patients with peripheral neuropathy [41, 42]. Antiepileptic agents have not been widely used in visceral pain, except for the gabapentinoids [4]. Although each agent has different mechanisms of action, antiepileptic agents have some common features which include: sodium channel blockade, inhibition of glutamatergic transmission, and increasing GABA concentration. These agents have much less effect on gastrointestinal motility and could be very valuable therapeutic options.

Gabapentin binds to the α (alpha)-2 δ (delta) subunit of voltage-gated calcium channels preventing the release of nociceptive neurotransmitters, including substance P, norepinephrine, and glutamate. It is used as an effective analgesic for patient with neuropathic pain and chronic pain syndromes. Gabapentin is approved for diabetic peripheral neuropathy [41, 43]. Diabetic peripheral neuropathy is a common complication of diabetes that can cause significant morbidity and mortality [41]. Antiepileptic drugs are an effective treatment for various forms of neuropathic pain of peripheral origin, although they rarely provide complete pain relief [43].

Sensorimotor neuropathy is marked by pain, paresthesia, and sensory loss. Gastroparesis is the most debilitating complication of gastrointestinal autonomic neuropathy. The pathology of diabetic neuropathy involves oxidative stress, advanced glycation end products, polyol pathway flux, and protein kinase C activation; all contribute to microvascular disease and nerve dysfunction. Glycemic control remains the foundation of prevention and the prerequisite of adequate treatment. Diabetic neuropathy is a many-faceted complication of diabetes that can be managed symptomatically with an array of drugs. For symptom management, current evidence from clinical trials supports the use of desipramine, amitriptyline, capsaicin, tramadol, gabapentin, bupropion, and venlafaxine. Trials have also shown efficacy of gabapentin and pregabalin for postherpetic neuralgia and painful diabetic neuropathy [43]. These drugs can be rapidly titrated and are well tolerated.

Topiramate, lamotrigine, carbamazepine, and oxcarbazepine are alternatives for the treatment of painful diabetic neuropathy [43]. These agents should be titrated slowly. Carbamazepine is the drug of choice for trigeminal neuralgia; however, oxcarbazepine and lamotrigine are potential alternatives. There is need for large-scale randomized controlled trials on the efficacy of antiepileptic drugs in neuropathic pain. Long-term follow-up is needed to establish the long-term efficacy of antiepileptic drugs in neuropathic pain.

Opiate Analgesics

Careful use of opiates may need to be considered for the treatment of refractory pain in selected patients. Unfortunately, many patients with pain do not respond to more conservative therapies and are given intermittent or chronic therapy with opiate agents for pain control [4, 21]. In general, opiates are good for acute, short duration pain, such as from a surgical procedure. Although narcotic agents produce generalized analgesia, their efficacy in gastroparesis is unproved. Furthermore, opiates exert potent inhibitory effects on gastrointestinal transit inhibiting gastric emptying and colonic transit [44–46]. Chronic narcotic use may result in tolerance to its analgesic effects, physical dependence, and addiction. Thus, the routine use of opiate agents for the management of pain with gastroparesis is not advocated.

The weak opiate agonist tramadol, which can also affect serotonin and norepinephrine reuptake, appears to be a reasonable first choice. Tramadol is a centrally acting opioid analgesic, used in treating moderate to severe pain. Tramadol possesses weak agonist actions at the mu-opioid receptor, releases serotonin, and inhibits the reuptake of norepinephrine and serotonin [47]. In contrast to morphine which slows gastric emptying, tramadol seems to have little effect on gastric or small bowel transit [44–46]. However, many patients do not have optimal control of pain with this agent if the pain is moderately severe [6].

Some patients unfortunately require narcotic opiate analgesics for the management of pain. These agents not only cause a delay in gastrointestinal transit, but also have the potential for tolerance, dependence, and addition [6]. In addition, side

effects, particularly constipation can occur. Longer acting compounds, such as methadone or continuous release preparations such as transdermal fentanyl, may elicit less constipation than other narcotics [48, 49]. A current area of drug development is the generation of peripheral opioid receptor antagonists which block peripheral effects of narcotic drugs but preserve the central analgesic effects [50, 51]. A study of the novel peripheral mu-opiate receptor antagonist alvimopan observed reversal of the inhibitory effects of codeine on the small intestine and colon but not the stomach [52]. Methylnaltrexone, a mu-opioid receptor antagonist, has less penetration into the CNS and is used for refractory constipation in patients taking narcotic analgesics [51].

A condition that needs to be recognized by physicians in patients treated with chronic opiate analgesics is narcotic bowel syndrome, a condition of opioid bowel dysfunction that is characterized by chronic or frequently recurring abdominal pain that paradoxically worsens with continued or escalating dosages of narcotics [53]. Narcotic bowel syndrome can occur in patients with no prior gastrointestinal disorder who receive high dosages of narcotics after surgery or acute painful problems, and among patients with functional gastrointestinal disorders or other chronic gastrointestinal diseases. This disorder is a manifestation of enhanced pain perception through hyperalgesic effects of chronic opioid administration. The key to the diagnosis of narcotic bowel syndrome is the recognition that chronic or escalating doses of narcotics lead to continued or worsening symptoms rather than benefit. Continued treatment with narcotics leads to a vicious cycle of pain, use of more narcotics, and continued or worsening pain. Treatment involves early recognition of the syndrome and graded withdrawal of the narcotic according to a specified withdrawal program with the institution of medications to reduce withdrawal effects (TCAs, benzodiazepines, and clonidine).

Kappa opioid agonists have been studied for the treatment of GI symptoms, primarily in patients with functional disorders. The kappa agonist asimadoline reduced satiation and enhanced the postprandial gastric volume in female volunteers [54]. However, there were no significant effects on gastrointestinal transit. In a clinical trial in 40 patients with functional dyspepsia, asimadoline did not significantly alter satiation or symptoms over 8 weeks. However, asimadoline, 0.5 mg, significantly decreased satiation in patients with higher postprandial fullness scores, and daily postprandial fullness severity over 8 weeks.

Targeting Sympathetic Pathways

Clinical observations suggest that clonidine, an alpha-2 adrenergic agonist, may improve diabetic gastropathy symptoms [55]. Clonidine exhibits visceral antinociceptive effects, but its effects on pain with gastroparesis are uncertain [56]. Clonidine, given as a single dose of 0.3 mg orally, has no gastric prokinetic effects [55]. Thus, it may act on gastric afferent innervation or, more likely, at a central site to reduce nausea and vomiting.

A patient is described with relief of pain using intravenous phenotolamine in a patient with chronic idiopathic gastroparesis [57]. The mechanism of phentolamine is believed to be receptor blockade at alpha-1 adrenergic receptors and therefore inhibition of the peripheral sensitizing effects of circulating norepinephrine. Intravenous phentolamine has been used as a marker for and the treatment of syndromes involving sympathetically maintained pain.

The celiac and superior mesenteric ganglia provide postganglionic sympathetic innervation to the stomach and small intestine [58]. Neurolytic celiac plexus blocks are being performed for the treatment of chronic abdominal pain from intra-abdominal malignancy and from benign processes, such as chronic pancreatitis [59]. Celiac plexus block probably interrupts visceral afferent input [60]. The procedure entails the installation of ethanol and bupivacaine into the plexus via fluoroscopic, computed tomography, or endoscopic ultrasound guidance. This procedure has been used antidotally in patients with abdominal pain and gastroparesis. Interestingly, gastroparesis has been reported after celiac plexus block in a patient with pancreatic carcinoma [60].

Gastric Electric Stimulation

Gastric electrical stimulation is being used for the treatment of patients with refractory symptoms of diabetic and idiopathic gastroparesis [61, 62]. The stimulation performed is not gastric pacing, but high frequency, low energy gastric electric stimulation. Long-term open label studies have shown reduction of symptoms of vomiting [62]. Double-blind studies on the efficacy of gastric electric stimulation have been disappointing. The pivotal double-blind study revealed reduction in vomiting episodes in patients with gastroparesis, primarily patients with diabetic gastroparesis [61]. More recent double-blind studies showed only nonsignificant trends toward a decrease in symptoms of vomiting in patients with diabetic and idiopathic gastroparesis, but a significant reduction in symptoms in long term (1 year) on an open label, unblinded basis [63, 64]. The single-center clinical practice experience with Enterra gastric electric stimulation for the treatment of patients with refractory gastroparesis reported clinical symptomatic improvement in 50% of patients [65]. Three clinical parameters were found to impact on clinical response: etiology of gastroparesis, main symptom, and use of narcotics. Nausea and vomiting were the main symptoms that were reduced and not abdominal pain, postprandial fullness or bloating. Diabetic gastroparetics had a more favorable outcome than idiopathic patients. Patients whose main symptoms were nausea and/or vomiting experienced a more favorable response than those with abdominal pain as their main symptom. Lastly, patients not taking narcotic analgesic medications had better outcome than those patients using narcotics at the study outset. The subgroup that did best was diabetic patients with nausea and vomiting.

Other Treatments

Acupuncture and biofeedback can also be very helpful in these conditions, and with few side effects [66, 67]. Possible future directions include the increased use of dorsal cord stimulators, and repetitive transcranial magnetic stimulation [68]. Ketamine, an inhibitor of NMDA receptors, which reduces central sensitization, is being investigated as an alternative for narcotic analgesics for acute and chronic postoperative pain and neuropathic pain [69].

Summary

Patients with gastroparesis can have abdominal pain. In some patients with gastroparesis, abdominal pain can be the prominent symptom. The treatment of abdominal pain in gastroparesis is difficult, as is any type of pain. Some of the treatments may adversely impact on gastric emptying and other symptoms of gastroparesis.

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Chapter 25
Psychiatric Aspects of Gastroparesis

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Keywords Gastroparesis • Psychologic symptoms • Metoclopramide • Antidepressant agents • Psychiatric consultation

Introduction

Patients with gastroparesis have chronic upper gastrointestinal (GI) symptoms related to meal ingestion. Many patients also have associated psychologic/psychiatric symptoms. These symptoms can result from their chronic gastrointestinal symptoms (secondary psychiatric symptoms) or can be from a primary psychiatric disorder. Differentiation between these two can be difficult. In addition, medications used to treat gastroparetic symptoms, such as metoclopramide, may cause psychiatric symptoms, such as depression and/or anxiety. Many of the refractory symptoms of gastroparesis, particularly nausea and vomiting, are treated with psychiatric medications, particularly antidepressant agents. Psychiatric consultation may be obtained in patients with gastroparesis for a number of these reasons. This chapter reviews pertinent psychiatric aspects of gastroparesis. In addition, a proposed psychiatric evaluation form for patients with gastroparesis is presented at the end of the chapter (Table 25.1).

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Table 25.1 Proposed psychiatric evaluation for patients with gastroparesis

Name: D.O.B.:
Age:
Sex: Marital status/kids:
Chief complaint:
HPI:
Past medical/surgical/obstetrical Hx: also LMP
Current medications/allergies
Past psychiatric Hx:
D&A Hx:
Family Hx:
Social Hx: education; upbringing; work; finances; support; hx of trauma
Natural history of the symptoms of gastroparesis:

I. Onset
   a. Age of onset
   b. Place and environment while it took place and prior to
   c. Prior dietary restrictions, allergies, or reactions
   d. Relationship with food before onset
      a. Use of restriction
      b. Use of binging
      c. Use of exercising
      d. Use of food rituals
      e. Use of purging
      f. Relationship between management of stress and food

II. Course of the illness
   e. Weight
      a. Current (BMI)
      b. Lowest/highest/acceptable for the patient
      c. Relationship with the body image
         i. Before onset
         ii. Current
   f. Quality of the sxs (n/v/abdominal pain; timing; contents of vomit; problems w/liquids or solids)
   g. Frequency of symptoms:
      a. Any relationship with the menstruation
      b. Can you predict when are the sxs starting? (aura)
      c. Triggers
   h. When and how was it dx?
   i. Comorbid medical/psychiatric sxs: e.g., migraines; PTSD
   j. Treatments
      a. Dietary
      b. Medications
         i. Prescribed
         ii. Drugs or alcohol (MJ to increase appetite)
      c. Interventions (Botox, gastric stimulator)
      d. Results
      e. Longest period without Sxs
         i. What helped?

(continued)

Table 25.1 (continued)

- f. Triggers to have sxs resume:
  - i. Stopped Tx
  - ii. Stress
    1. Recent trauma
    2. Comorbid active psychiatric disorder (e.g., MDD)
       - a. Leading to somatization
       - b. Leading to decreased pain threshold or intense perception of pain
    3. Psychiatric differential diagnosis (e.g., somatization)
  - iii. Stopped narcotics cold turkey
  - iv. Dependence to narcotics now
    1. Past Hx and tx (psychological/physiological)
    2. Are the narcotics exacerbating the disease?
       - a. Delaying gastric emptying
       - b. Increasing pain sensation

sxs symptoms, *hx* history, *dx* diagnosis, *D&A* drugs and alcohol, *MJ* marijuana, *LMP* last menstrual period, *Tx* treatment, *MDD* major depressive disorder, *HPI* history of present illness

Gastroparesis

Definition and Causes of Gastroparesis

Gastroparesis is a disorder characterized by the impaired transit of food from the stomach to the duodenum in the absence of a mechanical obstruction [1]. It is classically associated with diabetes mellitus, but also has been observed after injury of the vagus nerve from surgery, in hypothyroidism, Parkinson's disease, connective tissue diseases (e.g., scleroderma), autoimmune diseases (e.g., SLE), and multiple sclerosis.

Delayed gastric emptying can be seen with the use of medications, including narcotic analgesics, tricyclic antidepressants, lithium, calcium channel blockers, antacids with aluminum hydroxide, and from oral contraceptive agents from the elevated levels of progesterone [2]. Idiopathic cases of gastroparesis represent a third of the cases [3] in which several etiologic events may play a role for the chronic impairment of gastric emptying: a prior infection, such as viral infections or Lyme's disease, and a history of an eating disorder. Viruses, like parvovirus-like agents, cytomegalovirus (CMV), Epstein–Barr virus (EBV), varicella virus, herpes family viruses, and the Norwalk, have also been mentioned as possible causes (2).

Epidemiology of Gastroparesis in the USA

The sex-specific, age-adjusted incidence per 100,000 person-years for definite gastroparesis from 1996 to 2006 was found to be 9.8 (95% CI, 7.5–12.1) in women and 2.4 (95% CI, 1.2–3.8) in men as per the Rochester Epidemiology Project (1).

Symptoms, Diagnosis, and Treatment

Gastroparesis presents with nausea, vomiting, abdominal pain, early satiety, postprandial abdominal distension/bloating, and weight loss. In severe cases, dehydration, malnourishment, and electrolyte abnormalities have been seen.

The diagnosis of gastroparesis is entertained in a patient with the appropriate symptoms, generally after an upper endoscopy fails to find a cause of the patient's symptoms especially when the endoscopy reveals food in the stomach despite an overnight fast. A gastric emptying test is performed to demonstrate delayed gastric emptying [4].

Treatment is primarily with dietary management, antiemetic agents, and prokinetic agents. Metoclopramide (Reglan) is the only approved prokinetic agent for this disorder. It is associated with side effects in about 20% of patients. Acute dystonic reactions can occur. Prolonged treatment over days to months can be associated with symptoms of depression and/or anxiety. Long-term use has been associated with tremors similar to Parkinson's disease, and with tardive dyskinesia. Other agents are used for persistent refractory symptoms. These include the older tricyclic antidepressant agents, such as desipramine and nortriptyline, which can reduce symptom transmission from the GI tract to the cerebral cortex. Newer psychotropic medications, such as mirtazapine, are now being used in cases.

Psychiatric Comorbidities

Major depressive disorder (MDD) influences the autonomic nervous system (Yeragani et al. 2002) [5]. A decreased parasympathetic and increased sympathetic function may be seen affecting cardiac regulation of the depressed patients [6]. Constipation was found in almost a third of depressed patients (5). Patients with dyspepsia with dysthymic symptoms exhibit more dysrhythmic events of the gastric pacemaker which can be assessed using the noninvasive electrogastrography (EGG) (5). The EGG measures the electrical activity of the slow waves: a frequency of 3 cycles per minute being the normal frequency.

Delayed gastric emptying, as seen in diabetic gastroparesis or dyspepsia, is associated with tachygastria (5). However, bradygastria might indicate enhanced parasympathetic modulation, which can be seen in anorexia nervosa (5).

Psychiatric Differential Diagnosis of Gastroparesis

Eating Disorders

Patients with eating disorders can present with dietary restrictions and/or purging behaviors. They are often malnourished; patients with anorexia nervosa have a BMI lower than 17.5. As a consequence of the eating disorder behaviors, patients can

exhibit gastrointestinal complications as erosive esophagitis, esophageal ulcers, constipation, and in severe cases, delayed gastric emptying. They also have episodes of dehydration, electrolytes abnormalities, and peripheral edema [7]. Women exhibit irregular menstrual cycles.

Amenorrhea (for 3 consecutive cycles) one of the diagnostic features of anorexia nervosa. The marked weight loss seen in these conditions can be associated with delayed gastric emptying, which has been reported to improve with an increase in body weight during treatment of the eating disorder.

These patients have a fear to eat due to fear of gaining weight since they associate it with poor self-esteem and social isolation. They are usually not forthcoming with the disorder since they are really used as coping skills. Eating disorders are associated with other psychiatric illnesses, such as posttraumatic stress disorder (PTSD) and drug and alcohol dependence and/or abuse. The age of onset is usually between the ages of 13 and 25, but some patients are diagnosed later despite chronic symptoms. The disorders are more common in women than men.

Psychiatric Treatment of Anorexia Nervosa. The goal in treating anorexia nervosa is the restoration of normal weight. This is important for physical health and is a crucial first step in psychological recovery as well. Cognitive behavioral therapy is used in patients that are more in touch with their emotions and can identify triggers to their symptoms. Unlike bulimia nervosa, there are no FDA-approved medications for the treatment of anorexia nervosa.

There is a strong genetic-familial component associated with anorexia nervosa in 50% of its cases. Family therapy is indicated [8]. This familial type is associated with a premorbid personality characterized by perfectionism, obsessive behaviors, restriction in the expression of affect, and the use of systematized methods with the illusion that their life is bound by rules and no emotions [9]. Types of treatment used are expressive psychotherapies as art, music, exercise, and psychodrama to help the patient integrate and accept the sensation and expression of feelings [10].

Psychiatric Treatment of Bulimia Nervosa. The goal for bulimia nervosa is symptom management, stopping the binge/purge behaviors. Two treatments have been documented to have good success rates, at least in the short term. The first is cognitive behavioral therapy (CBT), and the second is high-dose fluoxetine (60–80 mg daily). Results are roughly comparable, with a suggestion that the two together may be better than either one alone. Since only a quarter of patients achieve symptom remission with these approaches, further treatment is generally needed.

As with anorexia nervosa, patients with bulimia benefit from family therapy and group psychotherapy to learn interpersonal skills to avoid the isolation generated by the disorder. Cognitive behavioral psychotherapy is recommended.

Contrary to anorexia nervosa, bulimic patients often have a premorbid personality characterized by impulsiveness, labile affect, intense expression of emotions, and risk of getting involved in other acts of self-injury, like cutting behaviors. The latter can be treated with naltrexone, [11] a medication that has been proposed to help control the habit of self-induced vomiting. Naltrexone is an opioid antagonist that can also trigger withdrawal in patients that have physiological dependence to narcotics.

Somatization Disorders

The diagnosis of somatization disorder requires the presence of two gastrointestinal symptoms, four pain symptoms, one neurological symptom, and one sexual symptom. The symptoms cannot be medically explained and serve the function of symbolic communication of internal conflicts that the person has mostly at the unconscious level. The disorder is more common in women. It is usually seen before the age of 25 and is often associated with PTSD. The treatment consists primarily of psychotherapy [12].

Major Depressive Disorder

This disorder is characterized by changes in appetite, sleep, concentration, and psychomotor activity. Other symptoms include fatigue, guilt, and anhedonia (an inability to experience pleasurable emotions from normally pleasurable life events, such as eating, exercise, social interaction, or sexual activities). In severe cases, homicidal and suicidal behaviors can develop as well as psychosis. These patients can lose or gain weight and in severe cases catatonia or melancholia can lead to malnourishment. Important in the evaluation of a depressed patient with gastroparesis is to evaluate for medication side effects; metoclopramide (Reglan) can cause reversible symptoms of depression and/or anxiety.

The treatment is with selective serotonin reuptake inhibitors (SSRIs). Paroxetine, at high dosages, is associated with anticholinergic side effects which can slow the gastric emptying. Sertraline is associated with more gastrointestinal distress as nausea and diarrhea. Selective serotonin–norepinephrine reuptake inhibitors (SSNRIs), such as velanfaxine, can be used if the patient fails SSRIs. For MDD associated with neuropathic pain, duloxetine may be helpful. For patients with lack of appetite, mirtazapine can be beneficial due to its H1 blockade effect.

Patients with melancholic depression may benefit more of tricyclic antidepressants (TCAs). Amitriptyline has anticholinergic side effects and can cause constipation and urinary retention, whereas less-anticholinergic side effects are present with the TCAs nortriptyline and desipramine. The dosages of the TCAs recommended for therapeutic effect for depression are around 150–300 mg daily, whereas the dosages of the TCAs to treat gastrointestinal symptoms are lower, around 30–75 mg daily.

If the patients have an atypical depression (e.g., binge eating, hypersomnia), they may benefit from bupropion. Bupropion is associated with dose-dependent seizures in 0.5% of the cases at dosages higher than 300 mg daily, so it is recommended to use the SR or XL formulations. Its use is contraindicated in patients with electrolyte abnormalities.

Monoamine oxidase inhibitors (MAOs) are also indicated in the treatment of atypical depressions. A diet low in tyramine needs to be followed. The restriction of cheese (with the exception of cream cheese and cottage cheese), red wine, sherry, liqueurs, pickled fish, overripe (aged) fruit, brewer's yeast, fava beans, beef and

chicken liver, and fermented products is followed. Other diets also recommend restriction of all alcoholic beverages, coffee, chocolate, colas, tea, yogurt, soy sauce, avocados, and bananas.

If the patient has a bipolar disorder, the treatment is with mood stabilizers, such as lithium, valproic acid, or carbamazepine. Lamotrigine is FDA approved for depressive states. Lithium toxicity needs to be monitored especially in patients that are dehydrated.

During the manic phase, patients can lose weight as a consequence of their increased psychomotor activity and insomnia leading to neglect, including not eating.

Schizophrenia

This disorder presents with hallucinations, delusions, disorganized behavior, and thought process as well as negative symptoms as apathy, abulia (a lack of will or initiative), and avolition (a general lack of desire, drive, or motivation to pursue meaningful goals). The patients can avoid eating due to paranoid delusions (e.g., the food is poisoned), disorganized behavior (e.g., do not remember how to eat), or catatonia. The treatment is with antipsychotics, either conventional (e.g., haloperidol) or atypical (e.g., olanzapine). The onset is usually from 15 to 25 years old.

Panic Attacks

The patients present with abrupt episodes of intense fear or discomfort that peaks within 10 min. Associated are at least four symptoms, including nausea or abdominal distress, lightheadedness, paresthesias, chills or hot flashes, feeling of choking, chest pain, sweating, and trembling. Other symptoms are derealization, depersonalization, fear of losing control, of dying, shortness of breath, or palpitations. The episodes can be seen as part of PTSD, adjustment disorders, specific phobias, obsessive compulsive disorders (e.g., obsession about contamination of the food), separation anxiety, general medical conditions (e.g., hyperthyroidism), substance-induced intoxication (e.g., cocaine) or withdrawal (e.g., benzodiazepines or alcohol), and panic disorder.

OCD, PTSD, panic disorder, and phobias are treated with a combination of cognitive behavioral therapy, exposure therapy, and SSRIs. Benzodiazepines can be used for the fast control of panic attacks in combination with the other therapies with careful monitoring of development of physiological dependence.

Opioid Withdrawal

Opioid withdrawal symptoms can develop from hours to days after stopping opioids when they had been used chronically depending on the half-life of the narcotic.

The symptoms include nausea, vomiting, abdominal pain, diarrhea, increased vital signs, mydriasis, piloerection, myalgias and arthralgias, lacrimation, rhinorrhea, and yawning.

Psychiatric Complications of Gastroparesis and Their Proposed Treatment

General

Gastroparesis patients may have associated psychological disorders. Higher depression and anxiety scores are associated with increasing gastroparesis severity [13]. Psychological dysfunction does not vary by etiology or degree of gastric retention. Psychological features should be considered in managing gastroparesis. It is not clear if the psychological abnormalities are a cause or a consequence of the severe GI symptoms. Future longitudinal studies will provide insight into the function of psychological dysfunction in the genesis of symptoms in gastroparesis and if directed therapy of depression and anxiety reduces gastrointestinal manifestations of gastroparesis. Both physical and psychological features should be considered in developing individualized treatment plans for gastroparesis.

Phobia to Eat

Phobia to eat is due to fear of getting sick as seen in the classical conditioning of Pavlov. The consequence is the aversion or avoidance to eat.

Panic Attacks

Panic attacks can be triggered to stimuli associated with food as expecting meal times, the smell of food, seeing food, or even when tasting it without swallowing. The patients can react with nausea and vomiting or "globus" or swallowing difficulties due to panic. The use of benzodiazepines half an hour before meals can be beneficial for a short period of time in combination with SSRIs chronically. The benzodiazepines can be given parenterally initially until the patient is able to tolerate oral medications. Unfortunately, the SSRIs come in pills or liquid form only. One alternative is to use mirtazapine sublingual [14]. This is a potent serotonin 2 (5-HT2), serotonin 3 (5-HT3), and central 2-adrenergic receptor antagonist.

Adjustment Disorders

Adjustment disorders can present with change in conduct, depressive, or anxiety features within 3 months of the stressor, in this case lack of control due to a medical illness (e.g., gastroparesis). It can be acute or chronic depending on whether the symptoms last less or more than 6 months. The treatment is based on psychotherapy to help the patient accept and cope with the disease. There are no medications indicated for the disorder, but adjunctive treatment for anxiety and insomnia can be provided.

Opioid Dependence

The chronic use of opioids can lead to physiological dependence that leads to the patient need for higher dosages of opioids or withdrawal if the levels are suddenly dropped. As part of the anxiety and or depression derived from the experience with gastroparesis, the patients can self-medicate with opioids to induce anxiolysis and as a method to avoid experiencing the disease by inducing a toxic-euphoric effect or somnolence. The chronic use of opioids can induce paradoxical increment in the pain sensation. On the other hand, patients with depression and anxiety experience pain in a more intense way and have lower pain thresholds [15].

Benzodiazepine Dependence

As with the use of opioids, development of physiological dependence to benzodiazepine can be seen. Be careful with the withdrawal since it can present with delirium, seizures, psychosis, unstable vital signs, tremors, insomnia, agitation, and state of panic within minutes or hours depending on the half-life of the agent.

Personality Changes

After chronic exposure with the disease, changes in personality can occur as part of the coping skills developed by the individual. Maladaptive coping skills can be seen in a complicated grieving process that will prevent the patient from moving through the phases of bereavement as denial, anger, bargaining and to reach acceptance.

Psychiatric Side Effects of the Treatment for Gastroparesis

Antiemetics

Metoclopromide, promethazine, and prochlorpenazine are associated with extrapyramidal symptoms, such as dystonic reactions, akathisia, and Parkinsonism tremors. Also, they are associated with tardive dyskinesia when chronically used.

Clinical Evaluation of Patients on Psychiatric Aspects of Gastroparesis

A proposed psychiatric evaluation form for patients with gastroparesis is presented at the end of the chapter (Table 25.1).

Potential Topics for Research in Psychiatric Aspects of Gastroparesis

Several topics for research on psychiatric aspects of gastroparesis are listed here.

1. The association among progesterone, depression, and gastroparesis.
2. The association of somatization in patients that have PTSDs and gastroparesis.
3. The association between exacerbation of gastroparesis and postpartum depression.
4. How patients with opioids dependence and gastroparesis benefit from detoxification with buprenorphine?
5. Development of antidepressants that can be used parenterally.

Conclusion

Gastroparesis is a disorder characterized by the impaired transit of food from the stomach to the duodenum in the absence of a mechanical obstruction [1]. Several psychiatric symptoms are suggested to be associated with the neurological mechanisms associated with gastroparesis. MDD influences the autonomic nervous system [5]. As well, many psychiatric disorders can mimic the symptoms of gastroparesis, like anorexia nervosa. The disorder has been associated with exacerbation of psychiatric symptoms, like anxiety and depression. Also consider the psychiatric side effects from medications used in gastroparesis, like dystonic reactions with antiemetics. Last, be careful with the use of psychotropics in these populations due to the electrolyte abnormalities seen, e.g., lithium toxicity triggered by dehydration.

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Chapter 26
Sensory Neuromodulators in Disorders with Delayed Gastric Emptying

Gregory S. Sayuk and C. Prakash Gyawali

Keywords Neuromodulator • Antidepressant • Antiepileptic agent

Introduction

Nausea, vomiting, bloating, and abdominal pain are symptoms that are shared between true gastroparesis from gastric neuromuscular dysfunction, mechanical gastric outlet obstruction, and functional foregut disorders associated with a delay in gastric emptying. Excluding mechanical gastric outlet obstruction, abnormal delay in gastric emptying with compatible postprandial symptoms is reported in up to 4% of the general population [1, 2]. Attention frequently focuses on the gastric emptying delay, and consequently treatments are frequently directed toward improving gastric emptying. However, it is well-known that there is a considerable overlap in clinical presentation among true gastroparesis, functional dyspepsia, and functional foregut disorders associated with nausea and vomiting, all of which can be associated with a delay in gastric emptying. The prevalence of each of these disorders within the broader realm of delayed gastric emptying is difficult to estimate. Since sensory modulators (antidepressants, antiepileptic agents) are beneficial in suppressing symptoms in functional disorders, there is potential for benefit in symptomatic foregut disorders, especially where delayed gastric emptying is inherent to the functional syndrome rather than a direct cause for symptoms.

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Sensory Neuromodulators: Rationale for Use

Reports in the literature suggest discordance between foregut symptoms and the rate of gastric emptying as assessed by a nuclear medicine gastric emptying study. For instance, symptoms compatible with delayed gastric emptying, including nausea and vomiting, are reported by 11–18% of diabetics [3, 4], but the prevalence of documented delayed gastric emptying is much higher, seen in as many as 48–65% of diabetics at a tertiary care center [5]. Further, foregut symptoms, especially nausea and vomiting, correlate poorly with the degree of gastric emptying delay in both short- and long-term follow-up of these patients [5–7]. As many as one-third of patients with functional dyspepsia exhibit gastric emptying delays, particularly in the presence of reported postprandial fullness and vomiting. Heightened visceral sensitivity from gastric distension may trigger symptoms in both diabetics and patients with functional dyspepsia [8, 9]. Therefore, foregut symptoms that overlap with those from gastroparesis can be produced by both motor dysfunction (neuromuscular dysfunction leading to delayed gastric emptying, mechanical gastric outlet obstruction) and sensory dysfunction (heightened visceral perception) (Fig. 26.1). When delay in gastric emptying is the predominant abnormality, nutrition may be affected and patients may manifest weight loss in addition to vomiting and reflux symptoms. In contrast, patients with predominantly perceptive symptoms may overlap with functional dyspepsia and typically report absence of significant weight loss, or

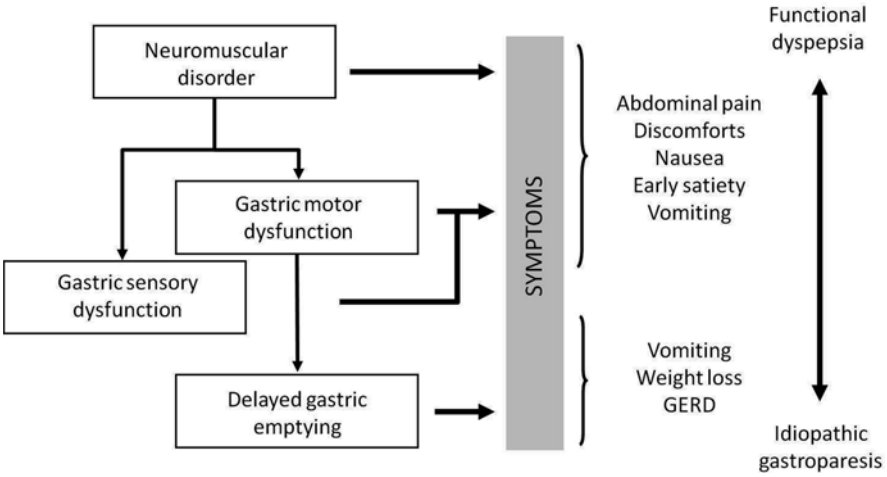

Fig. 26.1 Pathophysiologic basis for symptoms in the setting of delayed gastric emptying. The symptoms associated with gastric emptying delay may derive from both motor and perceptive (sensory) abnormalities. Considerable overlap in these two components of symptom presentation often is seen. Irrespective of the underlying pathophysiology, perceptive symptoms (discomfort, nausea, etc.) typically respond well to neuromodulator use. However, in the presence of weight loss and more profound objective delays in gastric empting, these approaches alone are insufficient, and attention to the nutritional aspects of care is warranted

Table 26.1 Relative receptor and monoamine binding affinities of common antidepressants used as neuromodulators in the management of gastroparesis [10, 11, 52]

Pharmacotherapeutic agent	Cholinergic (M)	Histaminergic (H_1)	Norepinephrine (NE)	Serotonin (5-HT)
Amitriptyline	+++++	+++++	+++	+++
Nortriptyline	++++	++++	+++++	++
Desipramine	++	+++	++++	++
Sertraline	++	0	+	++++
Paroxetine	+++	+	++	+++++
Fluoxetine	++	++	0	++++
Bupropion	0	0	0	0
Venlafaxine[a]	0	0	++	++++
Duloxetine	++	+	+++	++++

M muscarinic receptors; relative scale ranges from 0 (no binding affinity) to +++++ (strong binding affinity)

[a] At lower doses, venlafaxine exhibits predominant serotonergic effects; with increasing doses, greater NE effects are observed

in some cases even weight gain. Therefore, a proportion of patients may have an alternate functional etiology for foregut symptoms despite the presence of delayed gastric emptying, and this appears to be the case even in diabetic patients. Since foregut symptoms may not serve as reliable indicators of true neuromuscular abnormalities causing a delay in gastric emptying and since functional foregut disorders may inherently demonstrate delayed gastric emptying, a trial of sensory neuromodulators has clinical merit in managing symptomatic states associated with delayed gastric emptying. This approach typically is implemented in situations, where an impact on nutritional status is not present.

Sensory neuromodulators have been postulated to exert their benefit in patients with gastric emptying delay in several different ways, from both central and peripheral actions. The peripheral receptor- and neurotransmitter-specific influences on symptom improvement may more closely relate to changes in gastrointestinal transit, fundic tone, and analgesia, as a consequence of known roles of their neurotransmitter effects on gastrointestinal physiology; these receptor- and neurotransmitter-specific influences also allow anticipation of side effects of these pharmacotherapies (Table 26.1). Central effect may result from improvement in depression and anxiety states, sleep restoration, and decreased tendencies toward symptom reporting ("antisomatization effect") [10]. The central benefits suggest that sensory neuromodulators may address mechanisms that are either downstream effects of the functional syndrome (symptomatic delayed gastric emptying in this instance), such as mood and sleep changes, or possibly more generally address a resultant global distress than the correction of a physiological abnormality within the stomach per se. To date, the degree to which each sensory neuromodulator alters each of these symptom pathways remains poorly understood. However, given the substantial differences in pharmacodynamics and mechanism of action among these various agents, it is likely that certain antidepressants may be better suited to address particular aspects of clinical symptomatology in patients with delayed gastric emptying as discussed later in this chapter.

Sensory Neuromodulators: Mechanism of Action

The exact mechanisms of effect of sensory neuromodulators in functional disorders in general, and in symptomatic delayed gastric emptying in particular, are not fully understood. At the neurotransmitter and receptor level, the mechanisms of action of the tricyclic antidepressants (TCAs) are multiple [11]. Importantly, they are believed to have influences on the serotonergic system through interference with presynaptic neuronal uptake of serotonin (5-HT), as well as through effects on 5-HT receptor binding. The TCAs also have an agonistic effect on α (alpha)2-adrenoreceptors, in turn invoking descending bulbospinal inhibition of spinal afferent nociception. Moreover, extended use of TCAs may result in increased opioid receptor densities, and indeed may augment endogenous opioid levels in certain brain regions, including the hypothalamus [12]. Other reported receptor-specific effects of TCAs relevant to their antinociceptive effects include binding of the *N*-methyl-D-aspartate (NMDA) receptor complex [13] and adenosine A1 receptor activation [14]. Further, inhibition of histaminergic receptors, and both muscarinic and nicotinic cholinergic receptors, may be responsible for some of the antiemetic and analgesic effects seen with these agents. The degree to which the chemical structure of each individual drug influences the neurotransmitter systems may vary, and this likely accounts for some of the observed differences in the efficacy and side effects between agents.

The advent of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants represented an advance for the practicing clinician treating affective disorders, as these agents offer similar serotonergic benefits on mood as the TCAs, but with better tolerability and a lesser propensity toward unwanted side effects. Considerable variability does exist among SSRIs in terms of their effects on nonserotonergic neurotransmitter systems (Table 26.1). Unfortunately, some of the nonserotonergic effects of TCAs that are seen to lesser degrees with SSRIs potentially contribute to sensory modulatory and antiemetic properties of the TCAs. Overall, in animal models and clinical studies of visceral and somatic pain, SSRI effects overall have not been consistently favorable [15–19].

The serotonin–noradrenaline reuptake inhibitors (SNRIs), as their name implies, block the presynaptic reuptake of both 5-HT and norepinephrine (NE). The monoaminergic reuptake potential of these agents varies: up to a 30-fold greater selectivity for 5-HT reuptake inhibition is seen with the SNRIs venlafaxine and duloxetine, whereas milnacipran is somewhat more selective toward NE over 5-HT reuptake inhibition. Similar limitations as with SSRIs may apply in terms of the analgesic and antiemetic properties of these agents. Nevertheless, the SNRIs all have demonstrated modest acute and chronic antinociceptive effects on animal models and clinical trials [17, 20].

Other antidepressants, such as the tetracyclic antidepressant mirtazapine and the dopamine reuptake inhibitor, bupropion, have been found to have analgesic effects on limited animal studies. Through its 5-HT_3 receptor antagonism, similar to other established antiemetics such as ondansetron, mitrazepine may exert additional benefits in the relief of nausea and emesis [21].

The limited experimental data currently available indirectly suggest that the utility of antidepressants in gastroparesis likely does not derive from meaningful changes in gastric emptying. A randomized, double-blind study of healthy controls failed to demonstrate any significant differences in objective measures of gastric emptying or maximal tolerated volume on a nutrient drink challenge with either low-dose nortriptyline or mirtazapine therapy [22]. Similarly, 30-min symptom scores after instillation of maximum tolerated gastric volume were not affected by antidepressant therapy in the same report. Another study suggested that while amitriptyline modestly slowed gastric emptying, it improved nausea following a high-calorie liquid load challenge and did not influence maximum gastric volumes of satiation [23]. Further, a study of desipramine and escitalopram in healthy volunteers also did not demonstrate changes in maximum tolerated volumes, but did result in significant improvement in symptom scores in the treatment group compared to placebo [24]. As these studies were all carried out in healthy volunteers, extrapolation of these findings to a clinical gastroparetic population must be done with caution. Nonetheless, the existing evidence suggests that antidepressants (SSRIs, tricyclics, and tetracyclics) have modest effects on normal gastric physiology, increasing the likelihood that these agents exert their benefit either from their modulation of visceral sensory function or from their central neuromodulatory effects.

Sensory Neuromodulators: Evidence for Clinical Use

Data supporting the use of sensory neuromodulators in symptomatic disorders associated with delayed gastric emptying exists mainly in the form of retrospective reports and open-label trials. The basis for use of antidepressants and sensory neuromodulators in this patient population has largely been derived from the experience in other functional disorders, particularly irritable bowel syndrome (IBS). Antidepressants have been used as sensory neuromodulators for several decades in IBS, and good-quality studies including randomized, controlled trials exist. Odds ratios of 2.6 (95% confidence interval 1.9–3.5) for global improvement of IBS symptoms have been reported in meta-analysis [25]. Cumulative benefit of at least a moderate degree has been rated as 80% in functional gastrointestinal disorders by treating physicians in open-label studies, with numbers needed to treat (NNT) of 3.2–4.3 for efficacy [26–29].

A recent retrospective cohort study evaluated the response of both diabetic and nondiabetic patients with either documented gastric emptying delay or symptoms compatible with gastroparesis [30]. While most patients presented with nausea and/or vomiting, this cohort did include patients with cyclic vomiting syndrome, generally considered a disorder with “migraine-like” tendencies rather than a true foregut functional disorder [31–34]. While the exact proportions of responders with each step in the treatment scheme are not reported, as many as 71% responded with an approach that started with nortriptyline, and included use of mirtazapine (along with domperidone, dronabinol, and aprepitant) when symptoms persisted.

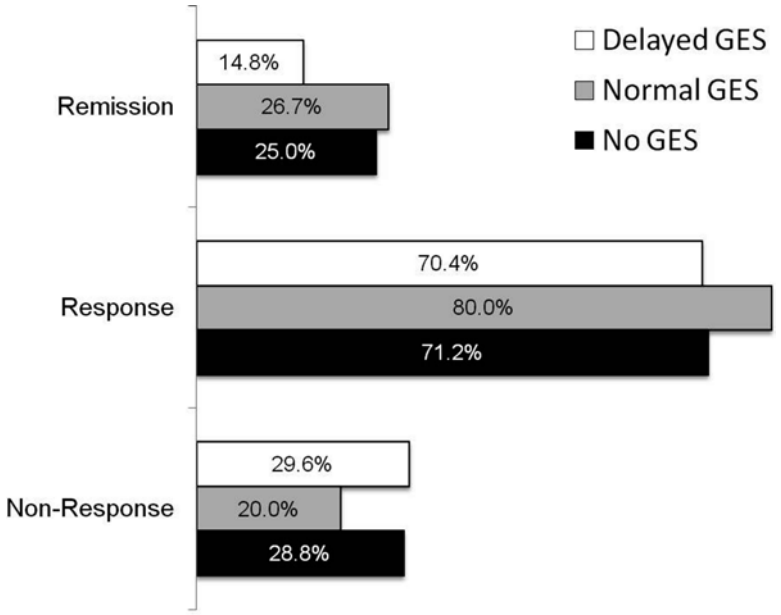

Fig. 26.2 Symptomatic outcome of patients with functional foregut symptoms with and without delayed gastric emptying from open-label sensory neuromodulator therapy [35]. Patients were categorized into three groups: those with documented delayed emptying on a gastric emptying study (GES); those with normal GES; and those with similar symptoms, where GES was not performed. A mean of 72% of patients achieved at least moderate symptomatic improvement as assessed from Likert scales, which was not influenced by gastric emptying status. Multiple neuromodulators were used

A similar proportion of patients with delayed gastric emptying (72%) responded symptomatically to a moderate degree in another open-label, retrospective study, where multiple antidepressants were used (mainly tricyclic antidepressants, SSRIs, SNRIs) [35]. This group compared responses to similarly symptomatic patients with normal gastric emptying and those who did not undergo gastric emptying studies, and found equivalent proportions of symptomatic remission and moderate symptom improvement (Fig. 26.2). Anecdotal response to mirtazapine has also been described in a case report [36].

While several sensory neuromodulators were used in the above studies, Sawhney et al. used TCAs in 24 diabetic outpatients with chronic vomiting [37]. A proportion of patients (42%) had cyclical symptoms consistent with cyclic vomiting syndrome, and delayed gastric emptying was only documented in 37.5%. Overall, moderate symptom improvement was seen in 88% of the cohort, and in 86% of the patients with gastric emptying delay; a cyclical symptom pattern predicted poor response ($p = 0.025$ on regression analysis), and the presence of peripheral neuropathy trended

toward a poor response ($p = 0.074$). A comparable degree of symptom improvement (84%) was noted in 37 patients with chronic functional nausea and vomiting treated with TCAs in uncontrolled, retrospective, open-label use [38]. The likelihood of remission was lowest when pain was a dominant symptom ($p = 0.03$ in multivariate logistic regression analysis). While most of these studies did not require delayed gastric emptying for study entry, the available data does suggest that foregut symptoms similar to that experienced by patients with gastric emptying delay may respond to significant degrees with sensory neuromodulator use.

Limited data exists on the use of newer antiepileptic agents (zonisamide, levetiracetam) in disorders associated with nausea and vomiting. These medications have been used as second-line agents in patients with cyclic vomiting syndrome intolerant of or failing TCA therapy [39]. Moderate clinical response in this patient population matched that seen in vomiting syndromes with the use of TCAs in open-label experiences (75%). Zonisamide is prescribed at 100–600 mg/d in a twice a day dosing schedule, and levetiracetam is used at 1,000–4,000 mg/d in divided doses. Despite the fact that the pathophysiology of cyclic vomiting syndrome is thought to be different from that of symptomatic delayed gastric emptying, there may be some overlap with centrally triggered vomiting syndromes such that these antiepileptic agents may have value in situations, where nausea and vomiting are out of proportion to the objective abnormality in gastric emptying.

Sensory neuromodulation has also been suggested as one of the mechanisms of benefit from the gastric stimulator (Enterra, Medtronics Inc, St. Paul, MN), an implantable device that improves nausea and vomiting associated with gastroparesis in 50–75% but does not necessarily accelerate gastric emptying [40–42]. Metoclopramide, a dopamine and serotonin receptor antagonist, has antiemetic properties from central receptor blockade in addition to its peripheral promotility actions on cholinergic neurons and dopamine and muscarinic receptors in the proximal gut [43]. Tachyphylaxis ensues at the peripheral level, but the central antiemetic properties may contribute to continuing symptom control with long-term use [44, 45]. However, use is limited by central nervous system side effects, including tremor, jitteriness, and extrapyramidal symptoms, seen in as many as 40% of patients [45].

Sensory Neuromodulators: Guidelines for Use

In general, sensory neuromodulators can be considered in patients with mainly perceptive upper gut symptoms (top end of symptomatic scale, Fig. 26.1), independent of gastric emptying delay. Obviously, appropriate exclusion of mechanical gastric outlet obstruction needs to be performed at the outset. The presence of weight loss may suggest advanced gastroparesis, and alternate feeding routes need to be addressed first to maintain nutrition; these patients are not good candidates for sensory neuromodulation. The presence or absence of comorbid-affective mood disorders (anxiety, depression) does not influence the decision for sensory neuromodulation.

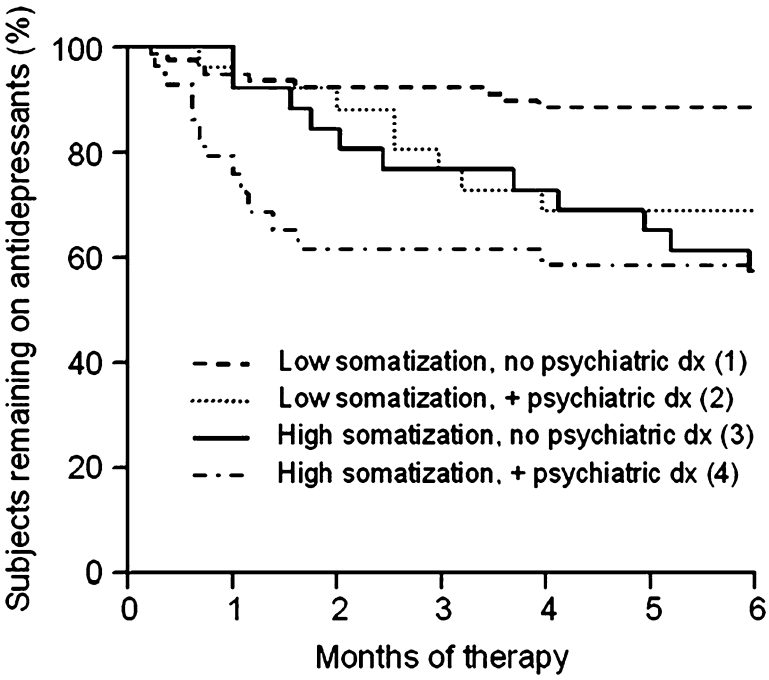

Fig. 26.3 The influence of somatization and psychiatric comorbidity on antidepressant discontinuation. In functional GI disorder populations, patients with higher degrees of non-GI somatic comorbidity (Group 3) are less likely to report satisfactory responses to neuromodulator use and are more likely to report side effects using these agents compared to those without additional somatic complaints (Group 1). The presence of overlapping psychiatric comorbidity (Groups 2 and 4) portends an even greater likelihood of antidepressant discontinuation. Low starting doses and implementation of nonpharmacologic therapies may be necessary in these patients. Adapted from Sayuk GS, et al. Psychosom Med. 2007; 69: 173–81. Used with permission

However, the likelihood of adherence to the prescribed sensory neuromodulator regimen in functional gastrointestinal disorders is influenced by the presence of psychiatric comorbidity [46]. The likelihood of adherence is highest in the absence of psychiatric comorbidity, and lowest with higher degrees of psychiatric comorbidity (Fig. 26.3). Patients with suspected somatization disorder may not tolerate antidepressant side effects, leading to premature discontinuation; a low starting dose is recommended in these patients [10, 46].

Evidence for benefit in functional gastrointestinal disease is best with TCAs [25, 26]. Therefore, most therapeutic trials start with a TCA, typically at 10–25 mg/d, taken at bedtime because of sedation as a side effect [37, 38]. The choice of the individual tricyclic agent depends on the degree of receptor blockade (i.e., "potency" and

side-effect profile). Amitriptyline is the most potent while desipramine is the weakest among the more commonly used tricyclic agents. Nortriptyline has intermediate potency, which in our experience makes it useful as the agent of first choice. Imipramine and doxepin are alternate agents of intermediate potency. If side effects are limiting, an agent of lower potency can be substituted; on the other hand, if no side effects result and therapeutic benefit is suboptimal, an agent with higher potency can be used. Doses are escalated by 10–25 mg every 2–3 weeks if response is inadequate. Therapeutic trials are typically 8–12 weeks in duration, up to a ceiling dose of 75 mg/d; higher doses are occasionally needed [38]. Once a patient is found to respond to a particular dose of TCA, it is typically advised that the patient remain on this medication for 6–12 months. If symptoms recur upon weaning from treatment, it is our practice to recommend continuation of this medication indefinitely.

Side effects can be limiting with the use of TCAs. Secondary amines (nortriptyline, desipramine) have fewer anticholinergic, antihistaminic, and alpha-adrenergic adverse effects, and therefore have a better side-effect profile compared to that of the parent tertiary amines (amitriptyline, imipramine, doxepin) [10]. Side effects generally fall into three main categories: sedation, anticholinergic (dryness of mouth, constipation), and other neuropsychiatric side effects (personality change, agitation). Weight gain and sexual side effects are also not uncommon. NNT of 3.7 is required to see significant differences in minor side effects compared to placebo, and NNT of 22 has been reported for major side effects [47]. Side effects are often the primary reason for a change in dose or a switch to an alternate agent within the TCA class; sometimes, an agent of a different class altogether is necessary (e.g., SSRI, SNRI, etc.).

Evidence for efficacy of alternate antidepressants, such as SSRIs, in functional gastrointestinal symptoms is limited; [19, 48, 49] no systematic reports exist for their use in symptomatic delayed gastric emptying. These agents are generally considered as second-line agents after TCA failure, but they have been used as a primary agent in patients with coexistent affective disorders, such as anxiety and depression. Given its effects on both NE and 5-HT neurotransmission, duloxetine more resembles TCAs and has been successfully used in functional gastrointestinal disorders in our practice [50]. Other antidepressants, such as bupropion, mirtazapine, venlafaxine, and trazodone, also have been used anecdotally in functional gastrointestinal disorders, and can be considered when other antidepressants fail [10, 36, 51]. Finally, antiepileptic agents (zonisamide, levetiracetam) can be considered when nausea and vomiting are out of proportion to the degree of gastric emptying delay, especially if a cyclical pattern of symptoms is encountered. There appears to be benefit in using an antidepressant medication of an alternate class when TCAs are not tolerated despite the paucity of good evidence suggesting their benefit in functional disorders. In a retrospective review, Patel et al report that approximately 72% of patients report benefit of at least moderate symptom relief, irrespective of class of antidepressant agent [35]. The medications and doses used in this retrospective series are presented in Table 26.2, along with potential side effects, advantages, and disadvantages of each class of agent used.

Table 26.2 Typical neuromodulators used in functional foregut disorders associated with delayed gastric emptying

Medication class	Agents	Typical dose	Advantages	Disadvantages
Tricyclic antidepressants (TCAs)	Amitriptyline (AMI)	10–150 mg at bedtime	May help with insomnia, concomitant diarrhea; weight gain; most studied antidepressant in the management of GI disorders	Anticholinergic and antihistaminergic side effects (orthostasis, urinary difficulties, dry mouth, sedation, confusion); sexual dysfunction; metabolic syndrome and worsening of glycemic control in diabetics; arrhythmia with QT prolongation; minimal effect on mood at this dose; 40–60% subjects do not tolerate due to side effects
	Nortriptyline (NT)	10–150 mg at bedtime	Less-anticholinergic effect as compared to AMI	Same as AMI
	Desipramine (DP)	10–150 mg at bedtime	Least-anticholinergic TCA, and minimal serotonin effect; good alterative in those not tolerating other TCAs	May be less effective in treating GI symptoms compared to AMI and NT
	Imipramine	10–150 mg at bedtime	Demethylated to DP; similar advantages	Same as DP
Serotonin–norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine	75–225 mg daily	Some mood effects, even at lower doses	Serotonin > norepinephrine effects at lower doses, with associated "SSRI-like" side effects (see below); sedation
	Duloxetine	30–90 mg daily	Good option with prominent "pain component" to symptoms	No generic option, expensive

Selective serotonin reuptake inhibitors (SSRIs)	Sertraline, paroxetine, fluoxetine, citalopram, escitalopram	Varies (used at low end of recommended dose range)	Significant mood benefits, weight neutral (especially fluoxetine), better tolerated from side-effect standpoint vs. TCAs	Nausea and diarrhea are common serotonergic side effects; insomnia; sexual dysfunction common; small risk of serotonin syndrome
Norepinephrine–dopamine reuptake inhibitors (NDRIs)	Bupropion	150–450 mg daily	Significant mood benefit, fewer sexual side effects, lowers seizure threshold	May induce anxiety, agitation, possible mild weight loss
Tetracyclic antidepressants	Mirtazapine	15–45 mg at bedtime	Antidepressant and anxiolytic effect; stimulates appetite and weight gain; useful with insomnia; less sexual dysfunction	Antihistamine side effects (sedation, dry mouth)
Anticonvulsants	Zonisamide	100–400 mg daily in divided doses	Useful adjunct to antidepressant regimen, few issues with drug interactions	Sulfonamide derivative (avoid with sulfa allergy); somnolence, confusion, dizziness, anorexia
	Levetiracetam	500–3,000 mg daily in divided doses	Rapid onset; neither metabolized by nor inducer of cytochrome p450 system; useful adjunct to other antidepressants; IV formulation available if not tolerating PO	Fatigue, somnolence, dizziness

Summary

Sensory neuromodulators have a definite role in the management of symptomatic patients with delayed gastric emptying. Over three quarters of patients with predominantly perceptive foregut symptoms (nausea, vomiting, abdominal pain, bloating) in the absence of significant weight loss may demonstrate moderate symptom improvement, as assessed by limited retrospective reports. However, there is overlap among functional dyspepsia with inherent delay in gastric emptying, vomiting syndromes, and true gastroparesis from neuromuscular dysfunction which manifests in patient selection for clinical trials as well. Further prospective study is needed to better define the role of sensory neuromodulators in the setting of delayed gastric emptying. In the meantime, since alternate options are less desirable or more invasive, a trial of an antidepressant, starting with a TCA, can be recommended for symptom control in symptomatic patients with delayed gastric emptying.

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Chapter 27
Alternative and Complementary Medicine for Gastroparesis

Jeanne A. Drisko

Keywords Gastroparesis • Gastroesophageal reflux disease • Complementary and alternative medicine • Integrative medicine

Background

Common gastrointestinal (GI) diseases, such as irritable bowel syndrome and gastroesophogeal reflux disease (GERD), and other less common GI diseases, like gastroparesis, are believed to result in 50 million visits per year to conventionally trained physicians [1–3]. It is estimated that these visits cost approximately $90 billion per year in the USA alone. As with many chronic medical disorders that are difficult to treat, patients turn to complementary and alternative medicine (CAM) therapies. Patients report reasons for the use of CAM therapies in GI disorders that range from dissatisfaction of conventional care, concern for side effects from drug therapies, or a desire to incorporate more natural therapies [1, 4, 5]. It is not the use of CAM therapies that should alarm conventional GI practitioners, but rather the idea that patients are not disclosing the use of CAM practices. While most CAM practices have a low-risk profile, the combination of medicinal plants with pharmaceutical medications, for example, could result in adverse outcomes [4]. It is incumbent on conventional practitioners to ask their patients about all of the therapies and supplements they are using and do so in such a way as to not alienate the patient.

Conventional GI providers may be uncertain what to do with the information when CAM use is elicited and the difficulty stems from a lack of familiarity with these therapies. As many conventional practitioners are aware when patients disclose the use of CAM and specifically identify a practice like acupuncture or the use of

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medicinal plants, it can often be frustrating to find the evidence base supporting the use of that particular practice. Even if there is some evidence supporting a CAM practice, the conventional practitioner often remains unclear about what is occurring during the CAM therapeutic encounter. One reliable source of information can be found at the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health [6]. There are four domains with admittedly much overlap and these domains include (1) mind body medicines encompassing everything from meditation and prayer to art therapy; (2) biologically based practices, such as medicinal plants, food, or vitamins; (3) manipulation and body-based practices, like massage or chiropractic manipulation; and (4) energy-based therapies, such as qi gong or magnetic fields. In addition, it describes whole medical systems, like traditional Chinese medicine or naturopathic medicine, which bridge most of the four domains.

Rather than using the terms complementary or alternative, there is a less pejorative term, integrative medicine, that may be used and has had a growing acceptance in academic institutions in the USA [7]. Integrative medicine experts may be called upon to bridge the gap between the conventional practitioner caring for the patient with gastroparesis and the alternative practitioner. Information may be supplied and as a result of the partnership, the patient benefits by more cohesive care and less risk of undisclosed practices that may result in complications. Currently, there are 45 academic institutions with the highest quality integrative medicine programs that have membership in the Consortium of Academic Health Centers for Integrative Medicine [7]. The Consortium defines integrative medicine as the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, health care professionals, and disciplines to obtain health and healing. Rather than the conventional practitioner either risking alienating the patient by discouraging the use of integrative therapies or accepting the use of these therapies that are unknown to them, it behooves the practitioner to find an integrative medicine doctor to partner with to provide understanding of the therapies being used and to act as a liaison for appropriate collaboration with a variety of CAM practitioners.

Evaluation

Conventional approaches in gastroparesis care, as well-described in this text, have expanded and there is growing understanding of how to best approach this complex and debilitating disorder. One area, where integrative medicine may best serve the gastroparesis patient, is in providing macronutrient dietary evaluation, laboratory assessment of the micronutrient environment, and prescribing the appropriate nutrient cocktail to support macronutrient and micronutrient deficiencies [8]. A typical integrative medicine evaluation begins with a 60–120-min initial clinic encounter that encompasses the history of present illness, past medical history, dietary history,

social history, review of pertinent systems, and the nutritionally focused physical examination. Based on this comprehensive evaluation, laboratory testing is ordered that assesses the micronutrient environment with expanded vitamin, mineral, essential fatty acid panels, and amino acid assessment. In addition, a detailed stool evaluation to assess beneficial microflora colonies, the potential presence of opportunistic bacteria, and secondary markers for digestive abnormalities may also be helpful.

The initial evaluation of the dietary recall diary may be turned over to an integrative medicine nutritionist who is well-versed in a whole foods diet and is able to guide the patient in selecting the correct meal plan that includes low-fat and low-fiber foods that are nutritionally dense. Sample recipes should be provided to the gastroparesis patient during this visit and the macronutrient intake reevaluated at follow-up visits. We are fortunate at the University of Kansas Medical Center Program in Integrative Medicine clinic to have an integrative medicine trained dietitian on staff and to have a demonstration kitchen, where food preparation can be modeled [9]. But if an integrative medicine dietitian is not available, many integrative practitioners have an understanding of whole foods diets and can give instruction. Food, of course, is the foundation of health.

Vitamin and Mineral Assessment

To capitalize on food as the foundation for health, it is well to remember biochemistry. Essential nutrients participate in fundamental roles in cellular metabolism, and as nutrient insufficiencies develop the effects are system wide and as these deficiencies continue over time organ systems are impacted [8]. Unfortunately, multiple nutrient deficiencies result in chronic degenerative disease and disease expression is compounded. Any and every aspect of body function may become compromised because of the patient's own unique biochemical fingerprint. Often, micronutrient insufficiencies are identified at the biochemical level without any specific symptoms of disease. As deficiencies progress, organ damage becomes evident. In conventional medicine, we have not been trained to assess micronutrient levels beyond a few well-known deficiencies, such as vitamin B_{12}, folate, and more recently, vitamin $D_{3.}$ However, micronutrients are critical at every level of cellular function and should be routinely assessed when there is chronic disease. Many factors influence nutrient status in individuals, but deranged digestion and absorption present in gastroparesis should lead to laboratory testing that uncovers important nutrient insufficiencies that guide replacement therapy.

Laboratory tests evaluate insufficiencies of basic building blocks of biochemical and enzymatic reactions and may be ordered from any conventional labs, such as Quest, Mayo, LabCorp, and others. Laboratory assessments are performed by using a variety of direct and indirect measurements, and concentrations may be measured in serum or red blood cells (RBCs) while metabolites are measured in blood or urine. It is by direct evaluation of vitamins, minerals, essential fats, and amino acids that informed recommendations for micronutrient supplementations can be made.

For clinical purposes in evaluating patients with gastroparesis, the most useful assay gives a clear answer to questions as to whether body pools are sufficient to meet metabolic demands. Rather than recommending a broad prescription of nutrients, the practitioner is able to tailor specific micronutrient prescriptions to target deficiencies. The most effective way of determining the need for supplementation is by discovering deficiency. Unfortunately, controlled clinical trial evidence supporting the use of micronutrients in gastroparesis is lacking [10].

Amino Acid Assessment

Twenty protein-forming essential and nonessential amino acids are required for the synthesis of tissue structures, transport proteins, and cell-signaling molecules [8]. Also amino acids are required for biochemical reactions of gluconeogenesis and essential fatty acid synthesis along with supplying building blocks for neurotransmitter biosynthesis. Neurotransmitters are formed from the pool of available amino acids and are critical for the activation and function of neurons not only in the central nervous system, but also the peripheral nervous system. The largest demand for neurotransmitters in the peripheral nervous system is by the gastrointestinal tract [11–14]. GI tract motility is modulated and regulated by serotonin, and serotonin production is dependent on a steady supply of tryptophan. Of note, the GI tract has a particularly high demand for production of serotonin for motility, but this process can be disrupted by inflammation.

Gastroparesis is associated with impaired digestion and assimilation of proteins, and this may result in an inadequate pool of amino acids for critical tissue and nervous system functions. If dietary proteins remain undigested in the stomach, amino acids are not released and the peptide residue may pass into the lower GI tract, where overgrowth of bacterial populations results [15].

In light of the potential for amino acid deficiency in gastroparesis patients, amino acid assessments are prudent and identify essential and conditional essential amino acids that need replacement. Testing methods include assessment of fasting plasma or whole blood level and when deficits are identified, this indicates gastroparesis patients who are unable to sustain adequate supplies for optimal cellular functions. Twenty-four-hour collections for urinary amino acid assessment may be the preferred test in determining when associated micronutrient deficiencies are present. However, 24-h urine collections outside of controlled medical settings may provide inaccurate data secondary to collection errors.

Essential Fatty Acids

There are 40 physiologically significant fatty acids with relatively simple molecular structures but with profound effects on inflammation, immune function, membrane stability, and nerve conduction [8]. These essential fatty acids are structural components

found in enormous quantities in every cellular and subcellular membrane throughout the body. Essential fatty acids are critical components of cell membranes and regulate the flow of energy and information for every cell and as a result for every organ system.

The nervous system with its high fatty acid content and associated nerve signal conduction transmission is particularly susceptible to essential fatty acid abnormalities. Membrane fatty acid composition affects the function of neurons by changing membrane fluidity, and when essential fatty acids are deficient nerve signaling is altered not only as the signal passes down along the nerve to the nerve ending, but also with resulting alteration and release of neurotransmitters.

Digestion, absorption, and assimilation of fats are well-described in any conventional physiology text and are not repeated here. The family of essential fatty acids, including omega-3, omega-6, omega-9, and medium-chained triglycerides, are well-known and well-defined in a large body of available peer-reviewed literature. However, what is discussed is the potential for gastroparesis patients to become deficient in the essential fatty acids because of the need for low-fat diets. The need to inhibit fat intake because of its action on gastric emptying, gastroparesis patients may be at risk for imbalances in critical fats.

Measurement is acceptable by either plasma or RBC samples and is analyzed by conventional laboratories, such as Mayo, Quest, or Kennedy-Krieger Institute Lab (Johns Hopkins). Plasma levels reflect dietary changes while RBC fatty acid levels reveal metabolic impact of drug therapy.

Treatment

After a thorough clinical and dietary intake and laboratory assessment, treatment regimens are tailored to patients with gastroparesis and monitoring of the macronutrient and micronutrient status is part of the follow-up evaluation. Treatment progress and outcomes are evaluated with a variety of instruments, including quality of life and symptom questionnaires. These instruments are usually administered at baseline and at the time of each follow-up clinic appointment and the instruments may be validated or not, but collected at each patient visit to provide internal control. Documentation of treatment outcomes is critical to give objective information about treatment progress and patient outcomes can advise when a change in therapeutic course is indicated. This is information shared with the conventional practitioner. The goal is shared information and partnership between the integrative medicine practitioner and the conventional provider with the gastroparesis patient at the center.

Food as Foundation

Unfortunately, there is a lack of controlled trials directly comparing nutrition intervention in gastroparesis [10]. Loss of gastric digestion, absorption efficiency,

and integrity may lead to cascading systemic dysfunction. A potential way to stave off systemic dysfunction is by supplying nutrient-dense whole foods to the gastroparetic patient yet tailored to their unique needs. By understanding the patient's physiology and the degree of gastric emptying dysfunction along with specific nutrient deficiencies, a nutritional regimen can be prescribed. After assessment of macronutrient status and micronutrient deficiencies, a dietary and supplement plan is developed for the individual patient. It is imperative to start with the best-tolerated diet, such as soft foods. However, as gastroparesis advances, the patient often requires more processed foods to satisfy nutrient needs. The patient may make their own processed foods (smoothies) made from whole foods to include fruits and vegetables. This diet is given to the patient with the caveat and caution to remove some of the food fiber. However, if tolerated, some fiber material should remain because of its known benefits in glycemic control and support of beneficial microbiota of the gut. There are a variety of juicing machines on the market that perform the function of fiber removal. It is important to remember that as food processing increases, the volume of the food needed to supply the micronutrient and macronutrient requirements increases. In this case, small amounts (8–10 ounces at a time) are tolerated, but frequent meals are needed to acquire the total calories and nutrients for the day.

Individual vitamins and minerals that are found to be deficient after laboratory testing can be added as well during the blending process, which reduces the need for gastric dissolution and makes the nutrient immediately available for absorption. Therapeutic supplementation of these micronutrients can be followed by periodic blood draws to determine if the plan is supplying targeted nutrients.

Free-form amino acid blends that include both essential and conditionally essential amino acids are commercially available and should include branched-chain amino acids in balanced blends. Amino acid testing illuminates amino acid abnormalities and guide amino acid supplementation and associated micronutrient needs. Free-form or nonpeptide-bound amino acids taken as a supplement in a small amount of liquid can be readily absorbed from the stomach and provide the essential and conditionally essential amino acids. These can be readily added as the food is processed.

If the gastroparesis patient is interested in preparing their own semiliquid, nutrient-rich smoothies, commercially available, prepackaged, calorie-rich food supplements high in sugar may be avoided. This is especially important for diabetic patients who need to avoid high-glycemic loads but also want to avoid synthetic sugar substitutes. Patients intolerant to dairy products or who are lactose intolerant may substitute alternative milks, such as rice or almond milk. These are readily available to most consumers and generally quite palatable (Table 27.1).

Because fats worsen the already impaired gastric emptying in gastroparesis, essential fatty acids, including medium-chain fats, may be given once per day several hours prior to a meal as needed and indicated by laboratory assessment of essential fat levels. The types of fats include Omega-6 family, such as borage oil, Omega-3 family well-known as fish oil, omega 9 essential fats or olive oil, and medium-chained fats, such as coconut oil. Only small amounts are needed over time to balance the essential fatty-acid profile in most deficient patients and can be assessed with periodic laboratory evaluation. When separated from food, these fats have a better

Table 27.1 Smoothie recipe

8 ounces liquid base with or without ice	1 cup frozen fruits and fresh veggies	1 serving protein	Healthy fats/oils
• Cow's milk • Goat's milk • Nut and seed milks, like almond, hazelnut, or hemp seed milk • Rice or oat milk • Coconut milk • 1/3 cup goat's milk yogurt • 1/3 cup coconut milk yogurt Use the milk or yogurt of choice to add creaminess. For thinner consistency, add more liquid For increased calorie needs, use canned coconut milk. You can also dilute coconut milk with other milk to decrease caloric content, yet still gain some of the nutritional benefits of coconut milk. So delicious is a brand of coconut milk that can be found in the dairy case that is diluted and lower in calories For fewer calories, use less milk and add ice	• Berries (strawberries, blueberries, raspberries, blackberries) • Mango • Pineapple • Banana • Peaches • Kiwi • Grapes • Oranges • Cherries • Cranberries • Apples (cored and peeled) • Pears (cored and peeled) • Avocado • Kale • Celery • Cucumber Colorful fruits add the vitamins, minerals, and phytochemical antioxidants that your body needs to fight off disease and illness. Adding a leaf of kale, some celery, or cucumber can increase the nutrient content of your smoothie without noticeably altering the taste	• Whey protein powder = 15 g vital whey by Well Wisdom • Rice protein = ~12 g of protein per tablespoon • *Xymogen* opticleanse GHI or oncoplex or fit food lite (vanilla) • CORE restore powdered supp. • Raw protein powder by *Garden of Life* (found at whole foods) • Hempseed protein powder = ~15 g protein per serving (4 tbsp) • 1/3 cup Greek yogurt = 15 g • 1/3 cup cultured cottage cheese (Nancy's brand) = 15 g Protein makes the smoothie more like a meal. It helps decrease the glycemic effect of fruit by reducing body's insulin response. Protein can also increase satiety and make the smoothie more satisfying for a longer time Whey protein is high in glutamine, an important amino acid that heals the gut by decreasing inflammation. Rice protein is a hypoallergenic, dairy-free option. Hempseed protein is a high-quality plant-based protein that also contains healthy omega 3 fats	• Fish oil to provide _____ mg total omega 3 s • Flaxseed oil to provide _____mg total omega 3 s • _____ tablespoons ground flaxseeds • _____ teaspoons coconut oil to provide medium-chain triglycerides • _____ teaspoons 3-6-9 balanced oil • _____ tablespoon(s) almond butter or organic peanut butter

Flavorings: Ginger, cocoa powder, grated coconut, lemon or lime juice, orange juice

opportunity for absorption. A balance of these essential fats is critical systemically for important immune, energetic, and neurologic functions and when delivered apart from the food bolus do not cause further delay in gastric emptying.

Antiemetics

Nausea is severe and debilitating in gastroparesis and is often underappreciated and undertreated by physicians [16]. It is recommended that aggressive use of conventional antiemetic therapies be used, but the array of integrative therapies may also be considered and are detailed below.

Ginger

Ginger (*Zingiber officinale*) is well-known and has been used for centuries around the world and found to aid digestive and stomach disorders [2]. In a small human study in healthy volunteers, ginger was found to accelerate gastric emptying and stimulate antral contractions [17]. Of interest, there was no effect on fundal activity. These findings need to be evaluated in a controlled trial of gastroparesis with a placebo arm.

Although specific clinical trials using ginger in the gastroparesis population are lacking, dosing regimens in other disorders associated with several nausea and vomiting recommend dosing from 1 to 4 g daily given in divided doses and can be given in capsular form containing dried, powdered ginger or prepared as a tea from the shavings from fresh ginger root [18]. Adverse events associated with the use of ginger are unusual [2, 18]. If patients have adverse events, they are usually minor complaints related to heartburn, flatulence, or bloating. No severe adverse events of a toxic nature have been reported. However, with any medicinal plant, caution must be exercised when using with pharmaceutical drugs with narrow therapeutic windows.

Acupuncture

Acupuncture use has been a mainstay for several millennia as part of traditional Chinese medicine healing paradigms. As a treatment modality, acupuncture has a growing acceptance in conventional Western medical practices, and the evidence base is expanding for use in nausea and vomiting and gastric motility disorders [19]. Acupuncture uses very small fine needles to pierce the skin at traditionally ascribed acupuncture points. Specific points have been associated with organ systems, and acupuncture effects on the GI tract have been shown in animal models [20, 21]. Conventional western medicine explanation for effects of acupuncture is thought to be related to local effects of substance-P and bradykinin or norepinephrine and serotonin [2]. Recent trials in both animal models of gastroparesis and in human

subjects use electroacupuncture, which modifies traditional techniques by using small electrical currents to stimulate appropriate acupuncture points [20–24]. Electroacupuncture has been proposed to provide a more constant and reproducible results in the research setting.

Acupuncture treatment effects on nausea and vomiting are thought to be by two proposed mechanisms. First, hyperirritability of the GI tract is calmed and second, the mid-brain chemoreceptor trigger zone is stimulated to release endogenous opioids and neurochemicals [2]. Stimulation of the acupuncture point P-6 site is traditionally identified as the desired location to treat nausea and vomiting and can be done by pressure applied to the point or by acupuncture needling [25, 26]. The P-6 site has not been specifically studied for nausea and vomiting of gastroparesis, but clinical trial evidence suggests that acupuncture and acupressure may be effective for nausea and vomiting. Although the preponderance of clinical trial results is mixed, a meta-analysis in 40 trials with almost 5,000 participants for treatment of nausea and vomiting concluded that acupuncture at P-6 site significantly reduced postoperative nausea and vomiting [27, 28]. No specific acupuncture trials have been conducted in nausea and vomiting associated with gastroparesis. Fortunately, acupuncture complications are rare and the practice is considered generally safe [27, 28].

Motility

Acupuncture

Acupuncture points PC-6 and ST-36 have been proposed to modulate gastric motility and increase levels of vasoactive intestinal peptide, somatostatin, and beta-endorphins while improving gastric emptying [2, 29].

Electroacupuncture has been studied in animal models of gastroparesis and patient populations with symptom complexes suggesting gastroparesis. Ouyang and colleagues developed an animal model of delayed gastric emptying of gastroparesis and found that gastric emptying was significantly improved with electroacupuncture [20]. A pair of acupuncture points were selected and corresponded to ST-36 located at the proximal aspect of the lower leg distal to the head of the tibias. These points are most frequently selected for the treatment of gastric disorders. The researchers attributed the improvements in gastric emptying to increased vagal activity with increased regulation of measured gastric slow waves in both the proximal and distal stomach, but only measured contractile spike bursts in the antrum which resulted in accelerated emptying of liquids in the animal. Subsequently, Ouyang and colleagues performed vagotomy in the same animal model of gastroparesis [21]. They provided electroacupuncture to the vagotomized animals and found impaired gastric relaxation when a meal was presented and gastric accommodation was restored. With electroacupuncture in the vagotomized animals, there was no change in gastric compliance or basal gastric tone. Of interest, a parallel evaluation in normal

animal controls that were not vagotomized found no effect on gastric compliance, basal gastric tone, or postprandial gastric accommodation. The animal study provides a basis for looking at acupuncture as a therapeutic tool in gastroparesis.

A small human trial enrolled 19 patients with reported nausea and vomiting, where only 10 of the total were reported to have associated delayed gastric emptying of solids [23]. The ten participants with delayed gastric emptying were compared to those without delayed gastric emptying and both received electroacupuncture at PC-6 and ST-36. There were significant improvements in dyspeptic symptoms in both groups and those participants with delayed gastric emptying were found to have significant improvements in emptying of solids as well.

Another clinic trial was conducted in subjects identified to have gastroparesis and 19 patients were randomized to either active-site electroacupuncture at PC-6 and ST-36 (9 subjects) or sham electroacupuncture at the corresponding sites [22]. The participants were blinded to assignment. The participants received four sessions over 2 weeks. In the treatment group, investigators reported significant reductions in nausea and vomiting with accelerated solid food bolus emptying with ongoing improvement 2 weeks beyond the intervention.

A more recent mechanistic study of the effects of electroacupuncture versus sham treatments was reported in a rat model of gastroparesis [24]. The investigators looked at gastric accommodation, gastric dysrhythmia, and gastric emptying after electroacupuncture at corresponding acupuncture point ST-36. They reported significant improvements in gastric dysrhythmia, and this effect was blocked by naloxone implicating opioid and autonomic pathways. Electroacupuncture appeared to restore gastric accommodation and gastric emptying with increased bowel transit through similar receptors and pathways and vagal activity was enhanced. Taken together, these data provide a mechanistic basis for electroacupuncture's role in gastroparesis.

The preponderance of evidence in small human trials and mechanistic animal studies points to the need for a large multicenter trial evaluating the role of electroacupuncture in gastroparesis. If relatively noninvasive adjunctive treatments with a low-risk profile can be offered to gastroparesis patients, a positive benefit may result.

Summary

Impaired gastrointestinal motility and severe nausea and vomiting associated with gastroparesis can be quite debilitating for patients, and this may lead some patients to seek out integrative medicine therapies. Currently, limited clinical trial evidence is available for the use of integrative therapies in gastroparesis. Compounding the lack of evidence, many conventional practitioners are unsure where they can find information about integrative therapies or how to evaluate practitioners of CAM. Trusted information resources have been provided, so conventional practitioners may explore therapies and it is suggested an integrative practitioner from one of the top academic integrative medicine programs be identified to act as a liaison.

Some promising integrative therapies have been highlighted that seem to have a potential role as adjunctive treatment options in gastroparesis and further clinical trials need to be encouraged.

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Chapter 28
Small Bowel Access for Jejunostomy Tube Feedings in Gastroparesis

Mark H. DeLegge

Keywords Gastroparesis • Weight loss • Enteral nutrition • Small bowel access • Jejunostomy tube

Introduction

The health care ramifications of gastroparesis (GP) can be significant. It has been estimated that patients with severe GP can have health-related costs of about US$7,000.00/month [1]. Although there are a variety of pharmacologic, surgical, and medical device interventions available for patients with gastroparesis, there is a group of "refractory" patients who do not respond to treatment or partially respond to current treatments [2]. It is in this group that we find patients who are at risk for fluid, electrolyte, and nutrient deficits. In addition, the erratic availability of macronutrients leads to the inability to effectively control blood sugars in patients with diabetes and gastroparesis. It is not unusual to see weight loss occur as there is a chronic inability to reliably consume calories over time.

Patients with symptomatic gastroparesis consume less calories than "normal patients" and are at risk for vitamin and mineral deficiencies. There has been much study of the effect of dietary intervention in order to reduce the symptoms of nausea, vomiting, and anorexia associated with gastroparesis. Unfortunately, all of these studies have evaluated the effect of diet on gastric function in volunteers without gastroparesis [3]. Because of this, there are few reported trials comparing specialized dietary inteventions as compared to standard diet in patients with severe, symptomatic gastroparesis [4]. Two very small studies did look at the use of a specialized diet in patients with symptomatic gastroparesis [5, 6]. Both of these studies did

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not report any improvement in symptoms with a specialized diet. They demonstrated that people using a specialized diet for symptomatic gastroparesis ingested fewer calories than those consuming a standard diet.

For patients who fail to stabilize their weight with diet, enteral nutrition (EN) is indicated. The delivery of EN into the patient with gastroparesis would require enteral access into the small bowel in order to bypass the gastroparetic stomach. Enteral access into the small bowel can be temporary (nasoenteric) or long-term (percutaneous). In general, temporary small bowel access is used to demonstrate small bowel feeding tolerance prior to putting in a more permanent jejunostomy tube. This chapter reviews the various techniques for small bowel access and reviews the use of small bowel feeding for patients with gastroparesis.

Nasoenteric Tube Access

Nasoenteric tube placement techniques have been developed for the bedside, for use with endoscopy, fluoroscopy, or to be placed during surgery. These techniques all have their indications, benefits, and risks. The final position of an enteral access tube is either the stomach, for gastric feedings, or the jejunum, for small bowel feedings. A patient who is intolerant of gastric feedings, such as a patient with gastroparesis, gastric outlet obstruction, or a patient who has had his or her stomach surgically removed, will receive small bowel feedings. Nasoenteric tubes have associated early complications (Table 28.1).

A number of techniques have been promoted for blind, bedside placement of an NJ tube. Thurlow et al. promoted the use of a stylet-filled tube and a corkscrew motion [7]. Zaloga confirmed the reliability of this technique with a greater than 90% success rate in J-tube passage [8]. In a separate technique by Ugo et al., the patient is placed in the right lateral decubitus position and the nasoenteric tube is tracked into proper position in the small bowel by auscultation. This technique resulted in an 83% successful bedside NJ tube placement [9]. More recently, there have been published reports of successful NJ-tube placement with a "self-propelled" NJ tube. These tubes have a spiral tip at the distal end. It is believed that the stomach can propel this type of tip through the pylorus easier as compared to a standard, straight distal tip. Berger reported on the use of the "self propelled" feeding tube in 105 critically ill patients [10]. The success rate of postpyloric passage of the NJ tube was 50%. The concurrent use of narcotics decreased the likelihood of successful tube placement. Newer technologies have been introduced into the market for NJ-tube placement. One group reported on the use of an external magnet to guide a nasoenteric tube with a metal tip into the small intestine. A small series reported a 95% success rate of tube placement within the duodenum with no complications [11]. Another group used bedside electromagnetic visualization and guidance for NJ-tube placement with an 87% success rate in critically ill patients with delayed gastric emptying [12].

Table 28.1 Complications of nasogastric or nasojejunal tube placement

Nasal mucosal ulceration
Otitis media
Pharyngitis
Pneumothorax
Sinusitis
Tracheoesophageal fistula
Tube migration
Aspiration pneumonia
Tube obstruction

Table 28.2 Endoscopic methods of nasoenteric tube placement

Methods	Technique
Drag and pull	Suture one end of a tube pulled with forceps into position
Over-the-guidewire	Tube pushed into position over a guidewire
Through-the-scope	Tube pushed through biopsy channel of endoscope into small bowel
Nasal endoscopy	Tube passed over guidewire placed through a nasal endoscope

There have been many attempts to blindly position a tube beyond the pylorus at the bedside with the use of pharmacologic agents. The results have been mixed. Seifert et al. and Kittinger et al. reported no benefit of successful NJ-tube placement with the use of metoclopramide [13, 14]. In contrast, Whatley et al. and Kalafarentzos et al. noted a benefit of successful J-tube passage with the use of metoclopramide, with a reported NJ-tube placement success rate of up to 90% [15, 16]. Silva et al. in a literature review, noted that metoclopramide given intravenously or intramuscularly was effective in promoting successful nasoenteric tube placement into the small bowel [17]. Griffith et al. confirmed the utility of another promotility agent, erythromycin, for promoting successful NJ-tube placement at the bedside in critically ill patients [18]. The use of promotility agents given prior to blind, bedside NJ-tube passage is gaining popularity. A recent meta-analysis of the literature concluded that there was a benefit associated with the use of intravenous promotility agents for improving bedside, nasojejunal tube passage success rates [19].

Failure to blindly pass an NJ tube at the bedside requires the use of fluoroscopic or endoscopic methods of passage. The preference of either technique is center dependent. Success of fluoroscopic guidance of NJ-tube passage can approach 100% [20]. However, in those institutions without fluoroscopic capabilities or expertise with nasoenteric tube passage, endoscopic passage of NJ tubes is preferred.

Endoscopic placement of NJ feeding tubes can be done at the bedside with conscious sedation. Table 28.2 lists the techniques for bedside, endoscopic nasoenteric tube passage. The drag and pull method is the method with the most history. In this technique, a suture or other material is attached to the end of an NJ tube. This suture is used to drag the NJ tube into position in the small intestine by the use of a grasping forceps. Difficulty usually occurs in releasing the suture from the grasping forceps resulting in inadvertent displacement of the NJ tube back into the stomach. A second common technique, the over-the-guidewire technique, requires the initial

placement of a guidewire into the small intestine. The patient is endoscoped into the distal duodenum or proximal jejunum and a guidewire is passed through the biopsy channel beyond the tip of the endoscope and well into the proximal jejunum. The endoscope is removed and the guidewire is left in place. A feeding tube is subsequently passed blindly or with fluoroscopic assistance into position in the small intestine. Patrick et al. reported a 94% success rate using this technique [21]. More recently, Fang et al. described the use of an ultrathin endoscope to perform nasal endoscopy. A guidewire is placed into the small bowel and the ultrathin endoscope removed. An NJ tube is passed over the guidewire into position [22]. This avoids the need to do an oral–nasal transfer of the feeding tube. Other methods of endoscopic NJ placement are used more infrequently.

Percutaneous Endoscopic Jejunal Access

Percutaneous Endoscopic Gastrojejunostomy

Percutaneous endoscopic gastrojejunostomy (PEG/J), places a jejunal feeding tube through an existing PEG into the small bowel using a vairety of methods. PEG/J allows both gastric decompression and jejunal feeding. One of the most common endoscopic techniques is an over-the-guidewire method. In this procedure, a pediatric colonoscope is used. After PEG placement, the patient is reendoscoped and an alligator forceps is passed up through the PEG to the outside of the patient. A guidewire is grasped and the colonoscope, forceps, and guidewire are advanced to the distal duodenum or proximal jejunum. A 9 or 12 fr J-tube is passed over the guidewire, through the existing PEG and into position in the small bowel (Fig. 28.1). The colonoscope, guidewire, and forceps are subsequently removed. DeLegge et al. reported a 100% success rate using this technique for PEG/J placement with a procedure time of approximately 26 min. There were no major complications [23]. This PEG/J system allowed for gastric decompression and small bowel feeding concurrently. The average longevity of this tube system was approximately 120 days when patients who died from comorbid diseases were excluded from the analysis of tube system longevity. Other methods have also been reported for PEG/J system placement. Taylor et al. described using an ultrathin endoscope passed through an existing PEG into the small intestine. A guidewire is passed through the endoscope into position in the small bowel and the ultrathin endoscope removed The J-tube is passed over the guidewire, through the PEG and into position [24]. Adler et al. described removing the existing PEG tube after the PEG tube tract had healed (generally 3–4 weeks). An endoscope is passed through the existing gastrostomy site into the small bowel. A guidewire is left in place and the endoscope is removed. A combination gastrostomy/jejunostomy (G/J) tube is passed over the guidewire and the jejunal portion of the tube is pushed into position in the small bowel [25]. The gastric portion of the tube remains in the stomach. A balloon internal bolster serves as the anchoring device for the system.

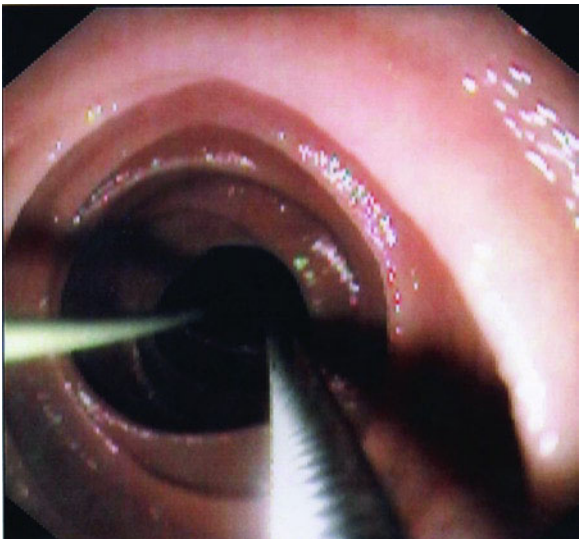

Fig. 28.1 Percutaneous endoscopic gastrojejunostomy (PEG/J) over-the-guidewire placement technique

PEG/J Management

Jejunal tubes in the PEG/J system are generally of small diameter size. The two most common sizes currently used are 9 fr and 12 fr. These sizes refer to the external diameter, thus the internal lumen is much smaller because of the wall thickness of the tube. These Jejunal tubes need to be flushed aggressively as to avoid clogging. Reported clogging rates of J-tubes have ranged from 3.5 to 35% [26, 27]. Semi-dissolved medications, bulking medications, such as Metamucil, and checking J-tube residuals all lead to an increased incidence for tube occlusion [28].

Complications of PEG/J

Complications of PEGJ tubes include those associated with percutaneous endoscopic gastrostomy (PEG) and includes wound infection, peritubular leakage, peritonitis, colocutaneous fistula, tube occlusion, tube migration, and bleeding as the most common. In addition, the jejunal tube may experience retrograde migration or luminal dysfunction secondary to kinking or clogging. Tube migration occurs most commonly in those patients who have persistent vomiting or in instances where the J-tube was not positioned properly through the PEG tube. The average longevity of the J-tube within the PEG/J system is 3–6 months [23, 29]. Because of this, the utility of the PEG/J system in the pateint with gastroparesis has been questioned. Although the G-port of the PEG/J system would allow intermittent gastric decompression to relieve nausea and vomiting, the J-tube would have to be intermittently replaced because of the migration and clogging issues.

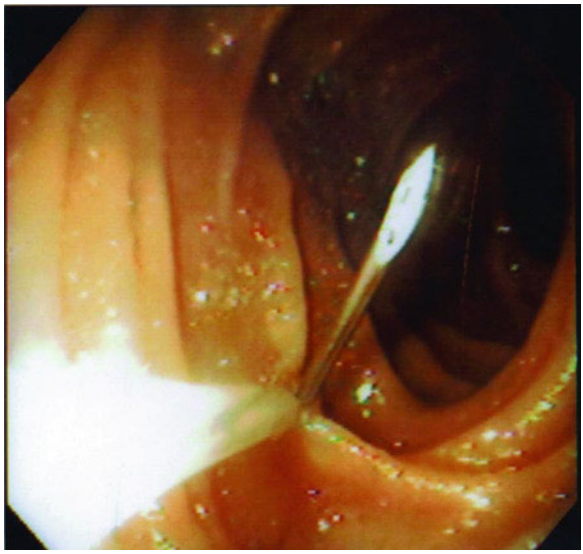

Fig. 28.2 Finder needle insertion and snare fixation in "2 Needle Stick Technique"

Direct Percutaneous Endoscopic Jejunostomy

Another method of endoscopic jejunal access, direct percutaneous jejunostomy (DPEJ), directly places a J-tube into the small bowel using an endoscope. This procedure requires the use of an enteroscope or a pediatric colonoscope to reach a puncture position beyond the ligament of Treitz. Good success with this procedure has been reported by both Mellert and Shike [30, 31]. There were some minor complications, including local site infection, but no reported cases of peritonitis nor bowel infarction. One of the difficulties with direct percutaneous endoscopic jejunostomy (DPEJ) placement is the frequent migration of the small bowel away from the introducer trochar needle once an adequate entry site on the abdominal wall was located. Varadarajula et al. resolved this problem with the use of a "2 needle stick" technique (Fig. 28.2). In this procedure, a smaller, sharper 19 gauge needle (finder needle) is first passed through an adequate abdominal wall site into the small intestine [32]. This needle is grasped by a snare, thus anchoring the small bowel against the abdominal wall. The larger introducer catheter is passed alongside the 19 gauge needle into the small bowel without pushing the small bowel into the abdominal cavity. The snare is removed from the 19 gauge needle and placed around the introducer catheter. A guidewire is passed through the introducer catheter into the small bowel, where it is grasped by the snare and pulled out of the oral cavity. A J-tube is attached to the guidewire and pulled into place in the small bowel similar to a PEG placement. Adequate positioning of the internal bolster of the J-tube is confirmed with endoscopic visualization.

DPEJ Tube Management

Immediately after DPEJ placement, it may be helpful to leave the tube unclamped so as to decompress the small bowel from the substantial amount of air that is insufflated during the procedure. Otherwise, the management is similar to that of PEG tubes.

DPEJ Complications

Complications and technical failures have been presented in three retrospective series on DPEJ outcomes. Technical failure rates ranged from 12 to 28%. Complications included bleeding, abdominal wall abscesses, colonic perforations, peristomal infections, enteric ulcers, and enteric leakage. Tube-related malfunctions similar to PEG tubes have also occurred [31–33].

Comparative DPEJ Versus PEG/J Studies

A retrospective study by Fan et al. compared physician reinterventions for J-tube complications in a group of patients who received PEG/J as compared to another group of patients who received DPEJ. The DPEJ patients had significantly fewer reinterventions [33]. DPEJ should be performed in patients who will require long-term jejunal feedings (>6 months) or in whom gastric access for decompression or medication instillation is not necessary. A prospective, randomized trial has been performed comparing PEG/J to DPEJ for long-term use [34]. The rates of successful tube placement were similar. However, the patients with the PEG/J systems required more endoscpic reintervions for jejunal tube migration and occlusion.

Surgical Jejunal Access

Surgical jejunal access has been the standard of care for many years. These procedures include gastrojejunostomy and jejunostomy. These procedures may be performed via a standard open technique or with laparoscopic guidance. In recent years, the advent of PEG/J and DPEJ has relegated the surgical access techniques to patients who are in the operating room for another surgical procedure or in patients where endoscopic or radiologic enteral access is technically impossible.

Jejunostomy is a surgical procedure in which a tube is placed into the lumen of the proximal jejunum. The first person to accomplish this procedure was Bush in 1858 in a patient with a nonoperable cancer [35]. In 1878, Surmay de Havre developed

an enterostomy technique in which a J-tube was introduced into the bowel through an enterostomy [36]. In 1891, Witzel first described the most well-known technique for jejunostomy which has subsequently undergone a number of modifications [37].

Surgical jejunostomy is also a common procedure in trauma patients who also have associated gastroparesis. In a review by Meyers et al. patients received surgical jejunostomies as an additional technique during major abdominal surgery in 95% of cases and as the sole surgical technique in 5% of cases [38]. Approximately 20% of the major abdominal surgical cases were trauma related.

In the standard jejunostomy, a transverse celiotomy is performed and a jejunal loop is identified. A purse string suture is placed in the jejunal loop and a small enterostomy is made. The serosal layer of the small bowel is sutured around the feeding tube creating a tunnel (Witzel jejunostomy) This enterostomy-purse string suture is subsequently attached to the abdominal wall and an 8 to 12 fr silicone or rubber catheter is inserted through the abdominal wall and into the jejunum. Complications with this standard technique include wound infection, wound breakdown, tube occlusion, and tube dislodgment. Holmes et al. reported a complication rate of 10% and a mortality rate of 1.4% in trauma patients receiving a surgical jejunostomy directly related to the procedure [39].

Needle catheter jejunostomy (NCJ) involves the placement of a 5 or 7 fr catheter into the jejunum, via a submucosal tunnel. It was hypothesized that this technique would have fewer complications compared with standard jejunostomy as the entrance to the jejunum was much smaller in comparison. Multiple studies have reported reduced infectious complications of NCJ when compared either historically or directly to the standard surgical jejunostomy. However, there is a significant percentage increase in tube occlusions secondary to its small size.

Laparoscopic placement of J-tubes developed in the early 1990s. Initially, it was proposed that these procedures were associated with less morbidity and operative stress than standard surgical jejunostomy. Shortly, it was experienced that these laparoscopic techniques did not significantly add any advantage compared with standard surgical jejunostomy with relation to operative time nor associated procedure morbidity. Gedaly et al. reported on the use of mini laparoscopic instrumentation (18 mm) for J-tube placement [40]. They reported an operative time of 44 min for the placement of J-tubes in nine patients. This is similar to the time required for standard, open jejunostomy. One patient developed postoperative, peritubular leakage. This is similar to the 10% complication rate noted with standard, open jejunostomy. Additional comparative trials of laparoscopic vs standard jejunostomy need to be performed to determine if laparoscopic J can offer a clear advantage over current, open operative techniques.

Fluoroscopic Jejunal Access

The placement of percutaneous gastrojejunostomies with fluoroscopic guidance has continued to gain acceptance since their introduction in the early 1980s [41, 42].

These procedures are usually performed by radiologists in the fluoroscopy suite. After topical anesthesia to the abdominal wall and occasional conscious sedation, the inferior margin of the liver is identified by ultrasound and marked on the patient's abdominal skin surface. A nasogastric tube is passed into the stomach for insufflation. After gastric insufflation, the stomach is punctured with an introducer catheter. Some radiologists attach the stomach to the anterior abdominal wall with T-fasteners, whereas others do not. A guidewire is placed into the small bowel through the introducer. The puncture site is serially dilated over a guidewire to a size of 10 to 16 fr. A gastrojejunostomy tube is passed over the guidewire through the stomach into the small intestine.

This fluoroscopic approach to enteral access has a reported technical success rate of >95% [43]. These procedures can be performed with minimal sedation. The major criticism of these procedures focuses on related complications. The majority of these complications involve either inadvertent puncture of contiguous abdominal organs or separation of the abdominal and gastric wall during gastrostomy tract dilation. This separation of the abdominal and gastric wall may lead to peritonitis, intraperitoneal leakage, and even death. Many radiologists support the use of T-fasteners to attach the gastric wall to the abdominal wall to prevent tract disruption during dilation of the gastric access tract. In addition, frequent occlusion of these feeding tubes, because of their smaller size, is common.

Jejunal Feeding in Patients with Gastroparesis

The clinical studies which have been reported detailing the results of jejunal feeding are extraordinarily limited. There are no prospective, randomized trials. Devendra et al. reported on two patients with severe gastroparesis as documented by a gastric emptying scan (GES). Both of the patients had difficult to control diabetes, persistent nausea and vomiting, and multiple hospital admissions [44]. A percutaneous endoscopic jejunostomy (PEJ) was placed for feeding. Over the next months, both patients had improvement in their symptoms with an improvement in gastric emptying as documented by GES. In a separate case report, Beaven reported on a 31-year-old woman with diabetes and gastroparesis who had failed pharmacological therapy and could not eat by mouth [45]. A PEG/J system was placed and the patient was followed for the next 5.5 months. She tolerated jejunal feedings and was again able to transition back to a diet completely by mouth. These cases would insulate that jejunal feeding can improve gastroparesis. The exact mechanism behind this is unclear. We know that lipid infusion into the jejunum and ileum reduces appetite and gastric emptying [46]. We also know that carbohydrate infusion into the small bowel slows gastric emptying [47].

The largest series of GP and feeding through a jejunostomy tube was reported by Fontana [48]. Twenty-six patients with refractory diabetic gastroparesis were identified over a 14-year period by chart review. The average duration of diabetes was 13 years. All patients had been admitted multiple times for gastroparesis.

All patients had failed acid-suppression therapy and prokinetic therapy. Most patients had NJ tubes placed that were not tolerated and were displaced secondary to vomiting. Surgical jejunostomy (Witzel) was performed. The average duration of J-tube use was 20 months and the average duration of follow-up was 47 months. Major complications did occur, including wound abscess around the tube, cellulitis, bowel obstruction, and an aspiration pneumonia with death. Minor complications included tube dislodgement tube obstruction, tube leakage, pain at the insertion site, and minor bleeding. A functioing J-tube was in place at the last time of follow-up or at death in 12/23 of the patients. A total of 10 deaths occurred in the 23 patients. Six patients had their J-tube removed because of returning GI function. The majority of patients reported an improvement in their nutritional status and a decrease in the frequency or duration of hospitalizations. Nineteen of twenty-three patients reported that their overall health improved.

Conclusion

Gastroparesis can be a costly and life-alternating disease. Although there are pharmacologic, surgical, and medical technology approaches to the disease, there is a percentage of refractory patients. These patients are frequently hospitalized for dehydration, weight loss, and metabolic and electrolyte abnormalities.

There is no data to suggest that dietary manipulation and education improve these patients' symptoms and outcomes. Often, jejunal feeding is necessary. The most common jejunal access tubes are combination of gastric/jejunal tubes (G/J tubes) or tubes placed directly into the small intestine (J-tubes). There are very few studies in the literature reporting on the outcomes of jejunal feeding in patients with gastroparesis. Case reports do note an improvement in gastric function following jejunal feeding although the explanation remains unclear. A retrospective analysis noted that although jejunal access and tube feeding are not without any complications, a patient's nutrition status and quality of life can be improved.

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Chapter 29
Gastric Electrical Stimulation for Gastroparesis

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Keywords Gastric electrical stimulation • Gastric pacing • Gastrointestinal motility • Gastric emptying

Introduction

The first report on electrical stimulation of the gut can be traced back to 1963; Bilgutay and colleagues applied gastric electrical stimulation (GES) via an intraluminal catheter placed in the stomach nasally and reported GES-induced peristalsis by fluoroscopy and a shortened recovery time from ileus after laparotomy in both humans and dogs [1]. These exciting findings were, however, not reproduced in a few subsequent controlled studies [2, 3]. In the late 1960s and early 1970s, a number of investigators began to study gastric myoelectrical activity and its correlation with gastric contractile activity, leading to a better understanding of gastric electrophysiology and further development of GES [4–6]. In early 1990s, Kelly and colleagues systematically investigated the effects of GES on intrinsic gastric myoelectrical activity or slow waves, gastric contractions, and gastric emptying mostly in dogs [7–10].

During the past decade, various methods of GES have been developed for the treatment of gastric motility disorders and applied in both patients with gastroparesis and canine models of gastroparesis. According to the stimulus, GES can be classified as short and long pulses [11]. The most commonly used method of short-pulse GES is the Enterra® therapy, attributed to the availability of an implantable pulse generator and FDA humanitarian approval of the therapy [12]. Clinical application of long-pulse GES has been very limited since none of commercially available implantable

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pulse generators is capable of delivering long pulses that are needed to alter gastric myoelectrical activity or motility. However, limited clinical studies [13] and extensive canine experiments have suggested therapeutic potential of long-pulse GES in treating gastric dysrhythmia and delayed gastric emptying [11, 14].

A number of novel methods have recently been developed for GES, including sequential multichannel GES, dual-pulse GES, and synchronized GES. While there is lack of clinical data due to the unavailability of implantable device, canine studies have demonstrated the viability of these new emerging GES methods in treating gastroparesis [11].

Short-Pulse GES and the Enterra® Therapy

Methods

Traditionally, electrical stimulation has been performed using short pulses – the pulse width is in the order of a few hundred microseconds (μs). This is because most commonly, electrical stimulation is performed on nerves or heart, and nerves and cardiac muscles respond to electrical stimulation quickly (a short time constant). For the same reason, all commercially available implantable pulse generators have been designed and developed for delivering short pulses. Short-pulse GES, also called low-energy, high-frequency stimulation, can be classified into two categories as follows.

Short-pulse stimulation. In this method, electrical stimuli are composed of continuous repetitive short pulses with a pulse width of <1 ms (ms), as shown in Fig. 29.1b. Besides the Enterra® therapy, few studies have been reported using continuous repetitive short pulses for GES. In one canine study, short-pulse GES (pulse width of 330 μs) was reported to improve gastric motility index when the stimulation frequency was about four times the intrinsic gastric slow waves [15].

Trains of short pulses. Different from the continuous delivery of repetitive short pulses, in this method, pulses are delivered intermittently with pulse train on for a certain time and off for a certain time as shown in Fig. 29.1c. It can also be considered to be derived from the combination of two signals: (a) continuous short pulses with a high frequency (in the order of 5–100 Hz); (b) a control signal to turn the pulse on and off, such as x seconds "on" and y seconds "off." The addition of x and y then determines the frequency of the pulse train. The pulse width in this method ranges from 0.1 to 10 ms. GES with pulse trains has been applied in sequential GES to improve gastric motility [16, 17]. It has also been used to treat patients with obesity [18].

The Enterra® therapy. The stimuli used in the Enterra® Therapy can be considered as continuous short pulses with each stimulus composed of two pulses or pulse trains in a more general sense: the train on time includes two pulses. The typical stimulation parameters used in the Enterra® therapy are as follows: pulse width

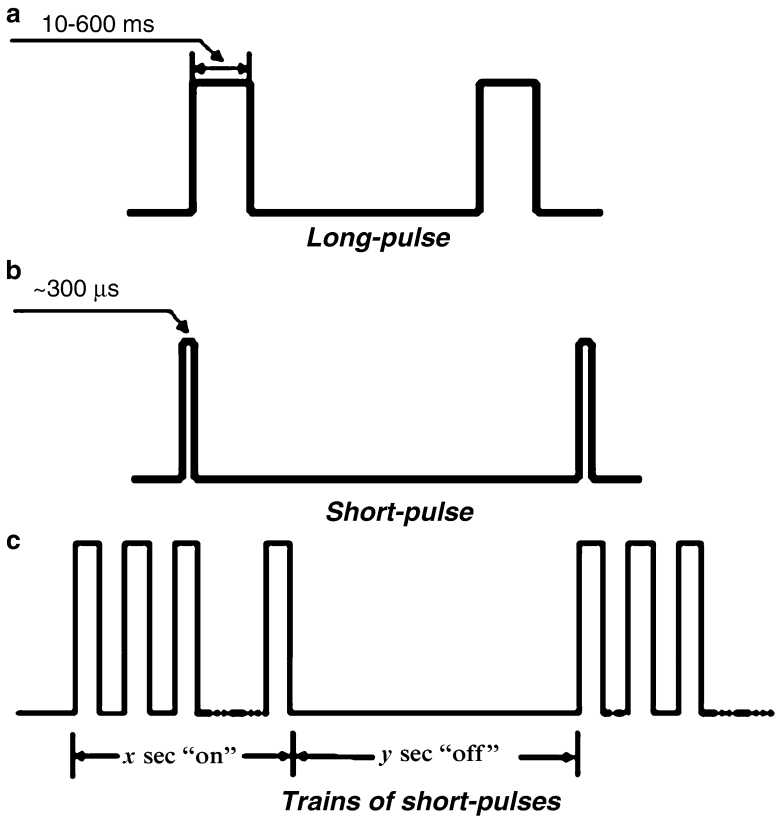

Fig. 29.1 Configurations of stimuli (**a**) Long pulse stimulation. (**b**) short pulse stimulation. (**c**) trains of short pulses

of 330 μs, frequency of 14 Hz, the interval between two consecutive stimuli (or train off time) of 5 s, and amplitude of 5 mA [12]. While most of clinical studies have used these parameters, it is unclear how these specific parameters were initially determined.

The Enterra® Therapy for Gastroparesis

Clinical studies have shown that the Enterra® therapy decreases upper gastrointestinal symptoms, reduces hospitalizations, the use of prokinetic agents, and medical costs, and improves nutritional status and quality of life in patients with drug-refractory diabetic, idiopathic, or postsurgical gastroparesis [12, 19–23]. The most interesting finding in these studies was the dramatic improvement in nausea and vomiting.

Depending on study centers, this improvement was noted in 50–70% of patients. There are differences in the response rate depending on the etiology of symptoms; patients with diabetic origins have a better response (60% or higher) than patients with idiopathic origin (about 50%). In a multicenter study with a controlled phase (1 month) followed with an open-label phase (12 months), a 50% reduction in nausea and vomiting was noted but the reduction in the total symptom score was not significant during the controlled period, whereas a substantial reduction in nausea and vomiting and a significant improvement in overall dyspeptic symptoms were observed in the open-label follow-up period [12].

Since the pulse width (about 300 μs) in the Enterra® therapy is shorter than the time constant of gastric smooth muscle (≥100 ms), the Enterra® therapy has been repetitively shown ineffective in altering or pacing gastric slow waves and therefore is not capable of normalizing gastric dysrhythmia [14]. No clinical data is available in the literature on the effects of the therapy on gastric contractions. Conflicting results have been reported on the effect of the therapy on gastric emptying [12, 21, 24]. The improvement in gastric emptying reported in some studies could be attributed to the improvement in overall clinical profiles of the patients and/or improvement in vagal activity [25].

Interestingly, improvement in diabetes reflected as a significant decrease in HbA1c has also been reported with the Enterra® Therapy in a few studies involving patients with diabetic gastroparesis [21, 26]. However, it is unclear whether GES has any direct effects on blood glucose. One recent study has compared the health-care costs between the GES therapy and the standard pharmacologic therapy and reported a significant and substantial reduction in the cost with the GES therapy during the second and third years of the implantation of the pulse generator [22].

Mechanisms of the Enterra® Therapy

The antiemetic effect of the Enterra® therapy has been reported in open-label clinical studies and in the WAVES controlled study. However, a possible placebo effect cannot be ruled out. Published mechanistic and animal studies support the antiemetic role of the Enterra® therapy. The Enterra® therapy was reported to improve gastric accommodation in dogs [27] and increase the perception threshold to gastric distention in patients [25]. Central mechanisms, although not well-understood, seem to be involved with the antiemetic effect of short-pulse GES. The Enterra® therapy or short-pulse GES has been consistently shown to reduce vasopressin-induced emesis that is mediated centrally [11] and improve vagal efferent activity assessed noninvasively by the spectral analysis of heart rate variability [25]. In a recent study with the scan of Fluoro-Deoxy Glucose positron emission tomography (PET), the Enterra® therapy was found to upregulate metabolic activity in the hypothalamus in patients with gastroparesis [25].

In summary, the ameliorating effects of the Enterra® therapy on gastroparesis are believed to be vagally mediated, speculated as follows: the Enterra® therapy or

short-pulse GES activates vagal afferent, resulting in increased vagal efferent activity. The increased vagal efferent activity improves gastric accommodation, resulting in an increased threshold to gastric volume distension, and in some cases accelerated gastric emptying as well. It remains to be studied whether short-pulse GES or the Enterra® therapy could also be used to treat nausea and vomiting due to chemotherapy-induced emesis [28].

Long-Pulse GES and Gastric Pacing

Methods

This method is most frequently reported in the literature because it is able to "pace" or entrain intrinsic gastric slow waves. However, most of the studies have been limited in animals since there are no commercially available implantable devices. It is also called gastric pacing or low-frequency, high-energy GES. In this method, the electrical stimulus is composed of repetitive single pulses with a pulse width in the order of milliseconds (10–600 ms), and a stimulation frequency in the vicinity of the physiological frequency of the gastric slow wave (see Fig. 29.1a).

Effects and Mechanisms of Long-Pulse GES on Gastric Motility

When GES of long pulses is performed with a pulse width in the order of a few hundred μs, it is capable of altering the functions of gastric smooth muscles that have a long time constant of about 100–300 ms [29] and therefore affecting gastric slow waves, contractions, and emptying.

Gastric pacing. Similar to cardiac pacing, GES with long pulses is able to pace the stomach: entrain the intrinsic gastric slow waves [9, 30, 31]. Typically, GES is performed at a frequency slightly higher than the intrinsic frequency of gastric slow waves. When entrainment or pacing occurs, the natural slow waves are phase locked with stimuli. It has been reported that the highest frequency that the gastric slow wave can be driven is about 50% higher than its normal frequency [30]. Gastric pacing can be achieved in various species, including mice, rats, dogs, pigs, and humans [32].

Normalization of gastric dysrhythmia. Due to its ability in pacing the stomach, long-pulse GES is capable of normalizing gastric slow wave dysrhythmia in both humans and dogs. It has been reported to normalize vasopressin- or glucagon-induced gastric dysrhythmia and slow wave uncoupling in dogs and dysrhythmia in a rodent model of diabetes [14], and to improve gastric slow waves in gastroparetic patients and postsurgical patients [13, 33]. While the exact mechanisms involved in the normalization of gastric dysrhythmia with long-pulse GES are unclear, it is known that it does not involve the vagal or cholinergic pathway [31] and is probably attributed to its direct effect on smooth muscles [34]. A recent study reported the

entrainment of slow waves in the absence of interstitial cells of cajal (ICC) in mice, suggesting that pacing can be achieved without ICC [35]. Similar findings were also reported in in vitro studies in ICC-knocked out mice [36].

Effects on gastric contractions. Although long-pulse GES is able to entrain gastric slow waves and improve gastric dysrhythmia, numerous efforts have failed to show that GES is able to enhance gastric contractions unless each stimulus is delivered in synchronization with the intrinsic slow wave, a method called synchronized GES [17]. On the contrary, GES with long pulses delivered at a tachygastrial frequency (a higher slow wave frequency known to be associated with gastric hypomotility) is able to inhibit gastric contractions [37] via the sympathetic mechanism. Accordingly, long-pulse GES at a tachygastrial frequency has been proposed to for the treatment of obesity since it inhibits gastric contractions and delays gastric emptying [11].

Effects on gastric tone and accommodation. Gastric accommodation is often impaired in patients with gastroparesis. With careful and appropriate selection of stimulation parameters, long-pulse GES may improve gastric tone and accommodation. Canine studies have demonstrated that long-pulse GES is capable of altering gastric (both fundic and antral) tone substantially in dogs [38]. With low stimulation energy, long-pulse GES may change gastric tone slightly, which is beneficial to patients with impaired gastric relaxation. With high stimulation energy, GES may substantially inhibit gastric tone and result in a substantial distention of the stomach, which may actually lead to early satiety, detrimental to gastroparesis. The inhibitory effect of long-pulse GES on gastric tone is mediated via the nitrergic pathway [38].

Gastric emptying. Long-pulse GES (single stimulation location) has been reported to have no effects on gastric emptying in healthy dogs but accelerate gastric emptying in a canine model of gastroparesis and patients with gastroparesis [11]. These findings are consistent with the effects of long-pulse GES on gastric slow waves and contractions. Since long-pulse GES does not enhance gastric contractions, it is understandable that it does not affect gastric emptying in healthy animals. The ameliorating effect of long-pulse GES on gastric emptying in diseased animal models and gastroparetic patients is believed to be attributed to its normalizing effect on gastric slow wave dysrhythmia. However, as it is discussed later in this chapter, two- or four-channel GES with long pulses is able to improve gastric emptying in both healthy and diseased models of canines [39, 40].

Gastric Pacing in Patients with Gastroparesis

Clinical studies have been scarce due to unavailability of implantable pulse generators capable of generating long pulses. In a single-center study using an external custom-made portable pulse generator, we investigated the effects of acute and chronic GES with long pulses on gastric slow waves, gastric emptying, and symptoms of gastroparesis. It was found that acute long-pulse GES normalized gastric dysrhythmia, and 4-week daily GES accelerated gastric emptying and improved gastroparetic symptoms [13]. In an earlier study in patients with postsurgical gastroparesis, acute

GES was able to entrain gastric dysrhythmia in most of 15 patients that were studied but unable to significantly improve gastric emptying in these patients [33]. These data seem to suggest that gastric dysrhythmia and delayed gastric emptying may be disassociated and that chronic GES is needed for the improvement in gastric emptying and symptoms of gastroparesis.

Emerging Innovative Methods of GES

In addition to the conventional GES methods described above, a number of innovative GES have been developed, including multichannel GES, dual-pulse GES, and synchronized GES. Although these novel methods have not yet been clinically tested due to lack of implantable device, animal research has demonstrated great therapeutic potentials for gastroparesis.

Multichannel GES

Conventionally, GES has been performed exclusively using single-channel stimulation via a pair of electrodes placed in the proximal stomach. However, pathophysiologically, it is known that gastric dysrhythmia or impaired gastric motility usually takes place in the distal antrum. That is, it could be more effective if the stimulation electrodes were placed in the distal antrum. On the other hand, however, it is well-known that GES via the distal electrodes is called retrograde GES, and retrograde GES has been reported to delay gastric emptying and impair gastric motility due to the retrograde dissemination of the stimulation effect [37].

The multichannel GES is designed such that the distal stomach is effectively stimulated while the retrograde dissemination or propagation of the stimulation is prevented or the stomach is sequentially stimulated from the proximal to distal location to generate peristalsis. In the multichannel GES, electrical stimulation is performed via stimulation electrodes at two or four locations along the longitudinal axis of the stomach [39, 40]. In another design, there are a few electrodes arranged circumferentially at each longitudinal location [16]. The stimuli along the longitudinal axis are sequentially programmed to match the distal propagation of normal gastric slow waves: there are phase shifts among different channels and the amplitude of the stimuli should be gradually reduced from the proximal stomach to the distal stomach to avoid retrograde propagation of the stimulation effect.

In a canine study, it was found that 4-channel sequential GES was more efficient in entraining gastric slow waves: the energy required for the 4-channel GES to completely entrain gastric slow waves was only 1% of that required by one-channel GES and more effective than one-channel in accelerating gastric emptying (see Fig. 29.2) [39]. The one-channel GES was not effective in accelerating gastric emptying, whereas the 4-channel GES was able to accelerate gastric emptying in healthy dogs. In another canine study, two-channel GES was also found to be

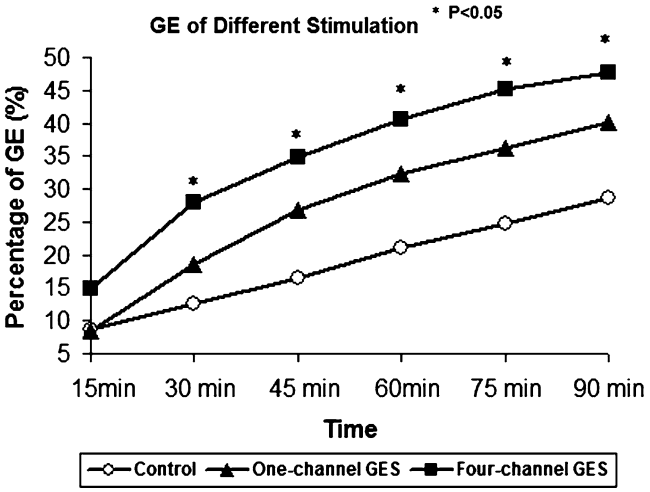

Fig. 29.2 Effects of single- and four-channel GES on gastric emptying

able to accelerate gastric emptying delayed by vasopressin and improve gastric dysrhythmia [40]. In a few other studies, multichannel GES with circumferential arrays of electrodes was reported to induce antral peristalsis and accelerate emptying of the stomach in anesthetized dogs [16]. In a recent clinical study in patients with diabetic gastroparesis, we found that two-channel GES was effective in reducing symptoms and improving gastric emptying and gastric slow waves.

As discussed above, multichannel GES is more effective and potent in accelerating gastric emptying than the conventional single-channel GES, apparently attributed to the improved propagation of slow waves and more coordinated contractions along the longitudinal axis of the stomach. Accordingly, this innovative method of GES has a great potential in treating gastroparesis.

Dual-Pulse GES

Findings in the literature and our own experience seem to suggest that long-pulse GES is able to entrain gastric slow waves, normalize gastric dysrhythmia, and possibly improve gastric emptying, but has little effects on symptoms of nausea and vomiting. On the other hand, short-pulse GES improves gastroparetic symptoms of nausea and vomiting, but exerts little effects on gastric dysrhythmia [14]. In patients with gastroparesis, symptoms and dysmotility (delayed gastric emptying) are often disassociated; that is, improvement in gastric motility does not necessarily leads to improvement in symptoms of gastroparesis. Accordingly, an effective GES therapy may have to consider independent improvement in both symptoms and dysmotility. A novel dual-pulse GES method was proposed based on this concept.

In the method of dual-pulse GES, stimulus of GES is composed of a short pulse (in the order of a few hundred μs) followed with a long pulse (in the order of a few hundred ms). A canine study has shown that dual-pulse GES is capable of both normalizing gastric dysrhythmia and improving symptoms suggestive of nausea and vomiting induced by infusion of vasopressin [41]. In another canine study with dual-pulse GES performed using two channels, gastric dysrhythmia and symptoms as well as gastric emptying were improved with this combinational method of two-channel, dual-pulse GES [42]. In addition, it was found that dual-pulse GES with five short pulses followed with one long pulse enhanced vagal activity via the short pulse component and reduced gastric tone via the long pulse component; gastric compliance was significantly improved [43]. Dual-pulse GES has the advantages of both long-pulse GES (improving motility) and short-pulse GES (improving nausea and vomiting) and is therefore attractive for treating gastroparesis. Technically, it is fairly easy to generate dual pulses.

Synchronized GES

From above discussion, we have learnt that GES with various configurations is able to improve gastric slow waves, accelerate gastric emptying, and ameliorate nausea and vomiting. However, none of the above-mentioned GES method is able to induce or enhance gastric contractions. In searching for this, we noticed that in all GES methods discussed above, electrical stimuli are delivered at a fixed frequency at random without synchronization with the intrinsic gastric slow waves.

Recently, a novel method has recently been proposed: synchronized GES [17]. Synchronized GES requires the implantation of two pairs of electrodes, one for the detection of gastric slow waves and the other for stimulation. In this proposed method, each electrical stimulus is delivered upon the detection of an intrinsic slow wave peak, that is, GES is performed at the occurrence of cyclic physiological electrical events of the stomach. It is hypothesized that synchronized GES is capable of inducing or enhancing gastric contractions by synchronizing each electrical stimulus with the intrinsic physiological electrical activity.

In a canine study, we have successfully demonstrated that synchronized GES is able to induce/enhance gastric contractions in the fasting state and improve impaired postprandial antral contractions induced by glucagons, resulting in acceleration in gastric emptying [17]. Similar prokinetic effect of synchronized GES was also reported in diabetic mice with gastroparesis [44]. In addition to delayed gastric emptying, impaired antral contractions, and gastric dysrhythmia, impaired gastric accommodation is also common in gastroparesis. Prokinetic agents have failed to produce expected relief in symptoms since they accelerate gastric emptying but often impair gastric accommodation. In a recent canine study, however, synchronized GES has been found to improve gastric accommodation and compliance impaired by vagotomy [45]. These findings suggest that the synchronized GES method is well-suited for treating gastroparesis with accompanied impairment in gastric accommodation.

The limitations of the synchronized GES method include the following: (1) it requires an additional pair of electrodes for sensing; (2) the method is not well-suited for patients with substantial gastric dysrhythmia. In this case, synchronization would be difficult if normal slow-wave rhythmicity is not present. Alternatively, GES would have to be performed at a fixed frequency to normalize dysrhythmia.

Conclusion

Among various methods of GES that have been developed, the GES with short pulses or the Enterra® therapy has been most intensively studied clinically and shown to be effective in reducing nausea and vomiting in patients with gastroparesis. There is a lack of controlled data; so far, a few controlled studies have all failed to show a difference between sham and actual stimulation. However, animal studies and recent mechanistic human studies do support the antiemetic role of the Enterra® therapy. More basic and clinical studies are needed to improve the therapy by optimizing stimulation parameters and locations, to investigate whether the therapy is also applicable to nausea and vomiting unrelated to gastroparesis, and to further understand possible mechanisms involved in the antiemetic effect of the therapy.

Long-pulse GES seems more attractive in a sense that it is able to able smooth muscle functions and therefore regular gastric motility. However, there is a lack of clinical studies since none of currently available implantable device is capable of generating pulses that are needed for this method of GES. However, the conventional single-channel GES is also limited in its ability in improving motility. For example, multichannels are needed for long-pulse GES to be effective in accelerating gastric emptying; synchronization of stimuli with gastric slow waves is required for GES to induce or enhance gastric contractions; and an addition of short pulses (and thus dual-pulse stimulation) is necessary for GES to be acutely effective in improving nausea and vomiting. The emerging methods of GES introduced in this chapter may represent the future of GES for treating gastric motility disorders; however, the unavailability of implantable device for these methods hinders the progress and development of GES in these directions. Alternatively, less-invasive or noninvasive methods need to be developed for the placement of stimulation electrodes, such as endoscopical placement of stimulation electrodes [46, 47]. This would greatly facilitate research and future clinical applications of GES.

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Chapter 30
The GI Surgeon and Gastroparesis

Sean P. Harbison

Keywords Gastroparesis • Gastric emptying • Gastroeophageal reflux disease • Nutritional support • Diabetes

Introduction

Gastroparesis, delayed or impaired passage of gastric contents in the absence of mechanical obstruction, is a clinical disorder with varying presentation and multiple etiologic factors which encompasses a wide spectrum of clinical symptoms, including nausea, vomiting, bloating, early satiety, dyspepsia, abdominal pain, and frequently weight loss. The symptoms and clinical presentation of gastroparesis vary significantly and is reflective of its pathogenesis, severity, and association with predisposing or associated conditions.

Gastroparesis is currently understood to result from several possible causes: the most common being diabetes, connective tissue disorders, renal failure, central nervous system events, idiopathic, and postsurgical, commonly foregut and/or biliary surgery [1]. The true prevalence of gastroparesis is unknown but is thought to occur in 20–40% of patients with type I diabetes mellitus and about 20% of patients with type II diabetes. Delayed gastric emptying occurs in about 25% of patients with functional dyspepsia, a related disorder which includes a constellation of abdominal complaints that affects up to 20% of the US population [2]. Patients may develop gastroparesis after undergoing foregut surgery with or without vagotomy or even uncomplicated biliary surgery. One study noted that up to 8% of patients with postsurgical gastroparesis had developed symptoms after cholecystectomy [3]. An increasing awareness is being paid to postfundoplication gastric emptying in

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patients surgically treated for GERD. Originally understood to overall accelerate gastric emptying, fundoplication may in addition result in early satiety and dyspepsia in up to 40% of patients due to loss of the fundic gastric reservoir. Finally, the third most common cause of gastroparesis is characterized as idiopathic and has been postulated in some patients to occur after a viral infection [4, 5].

The general principles for treating symptomatic gastroparesis are: (1) to correct and prevent fluid, electrolyte, and nutritional deficiencies; (2) to reduce symptoms; and (3) to identify and rectify the underlying cause of gastroparesis, if possible. Care of patients generally relies on dietary modification, medications that stimulate gastric motor activity, antiemetic drug therapy and pain control. Our rudimentary understanding has not yet allowed widespread effective treatment of the underlying cause in the majority of cases [6]. Patients suffering with gastroparesis are best treated in a multidisciplinary center staffed by experienced clinicians able to provide appropriate social/psychological, dietary/nutritional, medical, gastroenterologic, and surgical support.

Gastroparesis is perhaps one of the most crippling of the disorders of gastrointestinal (GI) motility. Its multifactorial pathogenesis and lack of definitive, effective treatments render patients with refractory gastroparetic symptoms clinically challenging. Patients with gastroparesis are frequently debilitated nutritionally, physically, and emotionally. Many patients may be subject to potential complications, such as severe malnutrition, dehydration, electrolyte imbalance, incapacitating pain, and in the diabetic patient, poor glycemic control and its sequelae. Not only do patients with gastroparesis have difficulty leading "normal" functional lives, but they also consume a significant amount of resources. Treatment costs of patients with gastroparesis can be high economically and emotionally [7].

The GI Surgeon and Patients with Gastroparesis

Invasive surgery is often avoided in patients with gastroparesis; however, the gastrointestinal surgeon may play an important role in the ongoing care of patients with medically refractory symptoms. Surgical treatment is contemplated when other treatment options have not been successful or when clinical indications mandate intervention for ongoing patient care, for example gastric decompression or enteral access for nutritional support. It should be recognized that the current armamentarium of surgical treatment options for gastroparesis has not been well understood or systematically studied.

The experienced GI surgeon should be an integral part of the multidisciplinary team in the group of gastroparetic patients requiring surgical intervention. Better outcomes may result when open lines of communication are maintained with the surgeon, gastroenterologist, nutritionist, and the patient. In addition to the inherent risks/benefits and limitations of the planned surgical procedure, physicians must be aware of the significant surgical comorbidities many gastroparetic patient posses. Up to one third of patients are diabetic and many may be malnourished. Both of these conditions contribute to generalized immunosuppression, impaired wound

Table 30.1 Overview of surgical treatment modalities: "supportive" therapy

Treatment	Indication	Morbidity	Studies	Outcomes
Venous access	Fluids/medications Short term (<6 wks) Nutritional support	6–60% Infection DVT Compl of TPN	Multiple Prospective Randomized	Complic 33–54% Infectious, DVT PICC *LESS* cost-effective
Gastrostomy	Venting/ decompression	22.4% Infectious Tube related	2 nonrandomized *N*=8, 18	Subjective relief of Sx, in 18/18 Weight gain, DC meds in 8/8
Jejunostomy	Enteral feeding access, Nutritional support	>50% Infectious Tube-related Obstruction	2 nonrandomized *N*=2, 4 Retrospective *N*=26	All subjective: Improved nutrition Decreased Sx Improved Glycemic control

Table 30.2 Overview of surgical treatment modalities: "definitive" therapy

Treatment	Indication	Morbidity	Studies	Outcomes
Drainage: Pyloroplasty Pyloromyotomy Gastrojejunostomy	Eliminate Pylorospasm, Gastric continence	<10% (risk of procedure)	Case series (1) Retrospective (2) *N*=2, 2, 4	Subjective improvement No change N/V
Resectional Therapy Completion Gastrectomy	Remove end organ Near total Gastrectomy	Up to 40% Frequent subsequent Surgeries 194adm/33pts	2 retrospective *N*=52, 60	78% subjective Improvement 43% improve Visick grade
Gastric electrical stimulation	Refractory gastroparesis	<5% (risk of procedure)	Prospective, Randomized *N*=33	~60% symptom Reduction: Diabetic group Greatest effect

healing, and increased risk of postoperative infection. Furthermore, patients with gastroparesis may be prone to gastroesophageal reflux, retained gastric contents, and even bezoars which increase the risk of perioperative aspiration.

Surgical intervention is often aimed at support or symptom control. Soykan et al. found that 21% of patients seen at a tertiary medical center received nutritional support via enteral or parenteral feeding and 26% were considered "nonresponders" to prokinetic therapy and eventually underwent surgical intervention [3]. Surgical intervention is often considered for refractory patients to provide "supportive" therapy, including intravenous or enteral access, for nutritional support and decompression (Table 30.1). In several centers, surgeons place the Enterra™ gastric electric stimulator for electrical stimulation treatment. Occasionally, patients may be evaluated for either palliative therapy aimed at ameliorating symptoms, such as gastric decompression, and/or surgical drainage procedures, or "definitive" procedures, such as resective surgery (Table 30.2).

Supportive Intervention for Gastroparesis

Intravenous Access: PICC Lines, CVC, Hickman Catheters, Infusaports

There are numerous methods of establishing central venous access if total parenteral alimentation is needed (Table 30.3). Central venous catheters (CVCs) may be placed in the operating room, at the bedside or in an appropriate ambulatory setting. Central catheters can be divided into two types: short and long term, depending upon patient needs and (contra)indications (Table 30.3).

Nontunneled or subcutaneously tunneled short-term catheters intended time frame for use is for a week to month. Nontunneled CVCs are placed in the subclavian or internal jugular veins while tunneled CVCs are peripherally inserted central venous catheters (PICCs) placed in the basilic, cephalic, or brachial veins. Short term CVCs may be placed at the bedside: complications, such as pneumothorax and hematoma are unusual, occur in 0.5–1% of cases and can be minimized by the use of ultrasound or fluoroscopy to image the vein. Nontunneled CVCs have a slightly higher infection rate because of the proximity of the skin insertion site to the vein; catheter associated bacteremia and infection occurs in 0.1–0.3% of cases [8]. Peripheral CVCs because of their ability to be placed in a smaller vein with a subcutaneous tunnel have increased longevity and lowers the rate of infection.

Long-term catheters are used for outpatients requiring central venous access for periods up to several months and include PICCs, tunneled CVCs (Hickman), and totally implantable intravascular devices (Ports). Implantable and tunneled CVCs have the lowest rate of infection because the portal of entry for bacteria is minimized but not eliminated: a subcutaneous or "pocket" infection may still occur. Placement of long-term CVCs requires either an operative or interventional procedure; complications of which are hematoma and pneumothorax and less than 1% [9].

Both short- and long-term CVCs may be associated with the most troublesome and potentially dangerous complication: infection. Catheter-related infection, site infection, or line sepsis should be considered in the presence of signs of local infection, or bacteremia. Uncomplicated site infections or even bacteremia may be treated without removing the CVC depending upon severity and causative organism; however,

Table 30.3 Intravenous and central venous catheters

Catheter type	Site	Expected duration of use
Peripheral catheter, short	Forearm, hand	Days
Nontunneled polyurethane CVC	Subclavian, internal jugular, femoral vein	Days to week(s)
Nontunneled silicone CVC	Subclavian, internal jugular veins	Weeks to month
Peripherally inserted CVC (PICC)	Basilic, cephalic, or brachial veins	Weeks to month(s)
Tunneled CVC (Hickman)	Subclavian, internal jugular veins	Months
Totally implantable port	Subclavian, internal jugular	Months

elective replacement is advised if ongoing central access is needed. More serious catheter site infection, clinical signs of line sepsis or identification of resistant organisms mandate removal of the catheter and replacement to a new site.

Another frequent venous access complication is catheter-related thrombosis that may occur in 6–60% of patients based upon comorbid risk factors. Venous thrombosis presents as a swollen painful arm and should be treated by catheter removal and consideration of thrombolytic therapy or anticoagulation.

Many options are available for gastroparetic patients requiring intravascular access. Judicious consideration of patient needs, including the indications and possible complications of CVCs along with the deleterious long-term effects of hyperalimentation are essential when choosing the type of device and placement site.

Gastrostomy

Decompressing gastrostomy tubes have been utilized to provide relief of nausea, vomiting, and bloating by venting or suctioning retained gastric liquid or gas. Generally, gastrostomy tubes should not be used for nutritional feedings, as patients have delayed gastric emptying. In the gastroparetic patient population, gastrostomy tubes may be paired with a separate feeding jejunostomy tube to provide simultaneous enteral alimentation. Occasionally, combination gastrostomy/jejunosotomy or transgastric jejunostomy tubes are used. These are multilumen tubes designed to consolidate both decompression and enteral feeding into a single tube placed into the gastric lumen and fed through the pylorus well into the proximal small intestine. A drawback to this type of tube is the frequent migration of the jejunal tube back into the stomach and a tendency to increased tube dysfunction and consistently higher incidence of perioperative and short-term tube-related complications. In a prospective comparative study of PEG and combination gastrojejunostomy tubes with 7- year follow-up, the tubes had an equivalent lifetime. Early and late complications occurred in 6.2% of PEG treated versus 22.4% of gastrojejunal tube treated patients [10]. The advantage of two separate tubes is provision of decompression of the stomach and simultaneous maintenance of enteral feeding as an adjunct to oral intake or even as a primary source of nutrition with a lower incidence of tube-related complications.

Gastrostomy tubes may be placed by various methods – endoscopically, fluoroscopically, or surgically utilizing either open or laparoscopic technique. The most widely used technique of gastrostomy placement is the various modifications of the “PEG” method originally introduced by Gauderer and Ponsky in 1980 [11]. For patients with contraindications to the percutaneous endoscopic approach, such as previous upper abdominal surgery or morbid obesity, surgical gastrostomy, either open or laparoscopic is an alternative. This method is also used for those who require simultaneous placement of feeding jejunostomy tubes. Both percutaneous and surgical techniques have been established as safe and effective means of accessing the gastric lumen.

Decompressing or venting gastrostomy has been utilized effectively in postsurgical and malignant mechanical obstruction [12]. Less well studied in the gastroparetic population, the technique has nevertheless been identified as a safe and effective procedure although little prospective data exist for effective use for patients with gastroparesis [13]. Nonprospective data from one study over a follow-up period of up to 41 months suggest venting gastrostomy qualitatively reduces symptoms of nausea, vomiting, and bloating and allows for improved nutrition via both the oral and the alimentary (jejunal) route [14]. Patients experienced symptom improvement, weight gain, and were able to return to work or school.

Gastrostomy tubes, while easily placed, are not innocuous. Procedure-related mortality is essentially the anesthetic risk of 0.3–1%. Overall, gastrostomy complication rates for the life of the gastrostomy tube for both percutaneous and surgical techniques are similar and have been cited as 17–24%, with 3–5% regarded as being serious or life threatening [15]. These tube-related complications are often infectious; wound infection, fasciitis, peritonitis, and stomatitis from leakage, bowel perforation, or fistula. The other common category of complication is tube dysfunction; occlusion, fracture, dislodgement, and irritation/erosion into an adjacent organ or abdominal wall. Conversely, gastrostomy has been shown to be a durable: tube lifetime in one series is cited as a median of 363 days with a range from 1 to 1,732 days (4.7 years) [13]. It is notable that in several series, overall mortality rate of patients with gastrostomy tubes during the study period of up to 4 years was substantial, cited from 38 to 53% and was related to complications of underlying disease, most often diabetes [13, 16]. Patients who require this type of supportive therapy often are preselected to have significant comorbid disease. Gastrostomy tubes are a useful adjunct in the care of gastroparetic patients. Once safely placed, tubes should be followed closely and maintained by the operating surgeon, gastroenterologist, or experienced allied health professional as approximately one in five patients experience tube-related difficulties during the lifetime of the tube. A properly maintained gastrostomy can provide symptomatic relief for years.

Feeding Jejunostomy

Patients with gastroparesis often are unable to tolerate oral intake or meet their nutritional needs. Patients who need nutritional supplementation greater than 4–6 weeks may benefit from the placement of an enteral feeding tube. Enteral alimentation usually denotes jejunal feeding in gastroparetic patients, as gastric feeding is frequently not feasible. Alimentary nutrition obviates the cost, complications, and adverse nutritional sequelae of total parenteral nutrition (TPN) while providing trophic benefits and better glycemic control all of which have been well described [17]. Feeding jejunostomy tubes may be placed by several methods: endoscopically or surgically utilizing open or laparoscopic technique. Endoscopic placement requires either conversion of a preexisting gastrostomy or primary placement of percutaneous

endoscopic jejunostomy tube. Fraught with technical difficulty for placement and prone to tube-related dysfunction, endoscopically placed tubes are less often used in this patient population [18].

Surgically placed jejunostomy using either open or laparoscopic technique is the more common method. Needle catheter jejunostomy has been described and may be placed fluoroscopically; however, the small bore tube required for this procedure renders it prone to occlusion and less useful for long-term enteral alimentation.

Patients' ability to tolerate jejunostomy feedings may be predicted clinically using a trial of nasojejunal feedings preceding definitive surgical placement of a permanent jejunostomy. Surgical feeding jejunostomy can be accomplished using either open or laparoscopic technique with equivalent perioperative morbidity [19]. Care must be taken by the operating surgeon to ensure that the accessed jejunal limb or tube is not unduly twisted or angulated and that the tube itself does not narrow the bowel lumen. Such technical errors cause early tube dysfunction, occlusion, or proximal mechanical bowel obstruction.

Within 24 h after tube placement, formula infusion may be safely initiated at low infusion rates (approximately 20 ml per hour) with dextrose/water or dilute nutrient and advanced slowly until caloric goal is reached. If tolerable, nocturnal cycling of feeding permits freedom from an infusion pump and somewhat more normal daytime work and function. Similar to decompressing gastrostomy, jejunostomy feeding tubes are frequently used for nutritional support in the gastroparetic patient but have not been well systematically studied. It is clear that jejunostomy tubes and feeding are associated with a high incidence of both major and minor morbidity. In studies of patients not able to tolerate oral feeding but not restricted to gastroparesis, authors reported overall complication rates for patients greater than 50% throughout the life of the tube. Adams et al. reported 53 complications in 34 patients with neurologic disease, including seven deaths: Cogan et al. noted 62 complications in 36 nursing home patients [20, 21]. In his study of gastroparetic patients, Fontana described 70 overall complications in 26 patients with a 4-year mortality of 38% [19]. Common complications include infectious; either tract or wound infection, or tube dysfunction, such as occlusion or dislodgement. Clearly, patients who require jejunal feeding have severe gastrointestinal dysfunction associated with multiple other risk factors.

Despite significant complications associated with the use of feeding jejunostomy, it has been shown to improve overall nutrition reduce hospitalizations and symptoms, such as nausea and vomiting [19]. Over 83% of the patients in Fontana's group experienced improved overall health. For patients who can continue some oral intake the tube acts as a good back-up system for nutrition, hydration, and medications. Although often needed by patients with severe gastroparesis and multiple other comorbidities and prone to frequent tube-related complications, feeding jejunostomy is an excellent adjunct for nutritional support. Placed equally effectively by several methods jejunostomy tubes should be followed closely by the treating physician or experienced allied health professional.

Definitive Therapy

Drainage Procedures: Pyloromyotomy, Pyloroplasty, and Gastrojejunostomy

Antral hypomotility, pyloric dysfunction or pylorospasm have all been implicated in gastroparesis as a whole although primarily that of diabetic origin. It has been hypothesized that eliminating relative gastric outlet resistance might accelerate emptying and improve symptoms of nausea and vomiting. A less invasive "medical pyloroplasty" is feasible: botulinum toxin, a potent inhibitor of cholinergic neuromuscular transmission has been used successfully albeit temporarily to treat spastic disorders of striated and smooth muscle and has been injected locally into the pyloric sphincter. In several studies, 43% of diabetic gastroparetic patients receiving botulinum toxin experienced symptom reduction lasting up to 5 months [22, 23].

Surgical drainage procedures, pyloromyotomy, pyloroplasty, or gastrojejunostomy, may theoretically provide permanent relief of symptoms by alleviating or bypassing the same contributory factors (Table 30.2). Drainage procedures alter gastric emptying primarily through passive maintenance of gastric continence. Both types of drainage procedures result in decreased resistance to outflow and have little to no effect upon the change in gastric contractile force. Studies in normal patients have shown drainage procedures that result in normal to increased emptying of both solids and liquids. Larger solid particles and indigestible food tend to empty prematurely due to reduced outflow resistance. Pyloroplasty or pyloromyotomy thus minimally alters emptying of solids while liquid emptying is only mildly accelerated most likely due to passive decrease in outflow resistance [24].

Gastrojejunostomy, depending upon its location, may provide more profound gastric emptying simply due to the effects of gravity; the functional and/or mechanical gastric outlet obstruction is bypassed. More extensive drainage procedures, such as those involving a Roux-en-Y limb, may actually impede gastric emptying further due to antiperistaltic activity and enterogastric reflux from the jejunal Roux limb. The role of surgical drainage procedures in the treatment of gastroparesis is ill-defined and has been poorly studied; there are no systematic-controlled prospective studies. The benefits of surgical drainage procedures for the gastroparetic patient must be mitigated against the risk of surgery and known limitations of the procedure and then utilized with the utmost care.

Resectional Therapy for Gastroparesis

Resectional therapy for severe gastroparesis entails near complete removal of the offending organ, in this case the stomach. The intuitive nature of the treatment: removal of the dysfunctional organ belies a complex set of clinical and surgical issues which

render the decision to proceed with resectional therapy for gastroparesis difficult. Completion gastrectomy has been proposed and performed for all types of gastroparesis but studied in a systematic way only in the postsurgical, postvagotomy patient population. In the diabetic group, completion gastrectomy has been applied successfully but studied only in case report or small retrospective reviews with few patients [25, 26]. It has been hypothesized that multiple factors cause gastric stasis in the postsurgical patient: foregut and gastric surgical procedures may inherently result in dysmotility; from 10 to 30% of patients experience chronic gastric stasis following vagotomy or distal gastric resection [27]. Gastric dysmotility may be worsened if a Roux-en-Y gastrojejunostomy was used for reconstruction of the gastric remnant. Ill-defined motor abnormalities in the Roux limb itself have been implicated as an additional source of impaired gastric emptying [28]. The proposed surgical procedure for patients with refractory postsurgical gastroparesis is thus extensive subtotal or near completion gastrectomy (approximately 70–80% gastrectomy) leaving a small, approximately 1 cm remnant of proximal stomach coupled with reconstruction using a long (approximately 60 cm) Roux-en-Y limb to prevent enterogastric reflux.

Two studies, reviewing 81 and 62 patients, respectively, have examined surgical therapy using this treatment modality. Eckhauser et al. were able to follow up 52 of 81 patients who underwent completion gastrectomy over 56-month period. They used questionnaire-based outcome data and determined that 78% of patients' symptoms had improved since surgery but 15% (8 pts.) were symptomatically worse [29]. It is also notable that this group of patients tended to have multiple operations; 89 surgical procedures were performed in 52 patients. Forstner-Bartbell et al. studied 62 patients who had undergone completion gastrectomy over an 11-year period. Their study group had a median of four prior operations and objective evidence of gastric stasis. Patient outcomes were rigidly determined using the Visick-grading scale pre- and postoperatively (*see* Table 30.2) [30]. Postoperatively, nausea, vomiting, and postprandial pain were all reduced but only 43% experienced symptom relief while 57% remained as Visick grade 3 or 4 without symptomatic relief. Patients were found to have no change in chronic abdominal pain, diarrhea, and dumping. Objective measures, such as nutritional status and gastric emptying, were not studied and although nutritional status was reported as stabilized, 16 patients remained on TPN after the procedure [31].

Completion gastrectomy is a significant undertaking with substantial surgical risk, and good chance patients will not experience improvement as a result. Patients often have severe underlying nutritional and medical comorbid factors. Surgical intervention for resectional therapy carries with it a high rate of reoperation either for ongoing surgical issues or complications both with increased risk of perioperative morbidity and mortality. Based upon the small amount of existing data, this radical approach can be carried out in well-selected patients with an expectation for symptom improvement in 43–78% of cases. The moderate success of the procedure must be weighed against the magnitude of the intervention and offered to well-selected, well-informed patients.

Gastric Electrical Stimulation

A substantial group of patients with gastroparesis, up to 40%, experience adverse side effects from prokinetic therapy or are refractory to treatment [32]. In an effort to treat the underlying cause of gastroparesis, electrical stimulation of the stomach has been investigated and is now utilized with some success. Studies in dogs and subsequently in humans have shown that it is possible to utilize high-energy, low frequency electrical stimulation that entrains and eventually paces gastric myoelectric activity [33, 34]. Unfortunately, the effects of gastric pacing tend to be short-lived. Currently, gastric electric stimulation (rather than pacing) with Enterra™ gastric stimulator has been used to treat gastroparesis with high frequency, low energy stimulation with some success. Gastric electrical stimulation (GES) has been shown to improve symptoms, such as nausea, vomiting, and abdominal pain, and modestly accelerate gastric emptying [35–37].

The gastric electric stimulator apparatus is placed surgically utilizing either open or laparoscopic technique. Two electrical stimulator leads are placed in the muscularis of the anterior greater curvature of the stomach 1 cm apart and 10 cm proximal to the pylorus. The pair of electrodes is connected to a neurostimulator generator positioned subcutaneously in the abdominal wall. Intraoperatively, the electrodes are tested for acceptable electrical impedance and the neurostimulator programmed to preset parameters. Intraoperative upper endoscopy is routinely performed to confirm correct placement of stimulator electrodes as acceptable electrical impedance between the two leads is essential. Controlled prospective data from several single-institution studies with smaller patient populations has met with promising results. Success with this technique led to a multi-institutional prospective randomized study investigating the efficacy, symptom reduction, and the quality of life for patients treated with GES. The study, entitled the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS) led to FDA approval of GES as a Humanitarian Use Device (HUD) [38]. Shortcomings of the study included a small sample size ($N=33$) and the fact that Medtronic Inc., a manufacturer of neurostimulators, cosponsored the study. Nevertheless, the clinical success of this study has been borne out; patients undergoing GES placement report significant improvement in symptomatology as well as reduction in abdominal pain. Gastric emptying, however as measured by scintigraphic methods, was moderately improved after GES placement. Symptom reduction occurs in approximately 60% of patients with diabetic gastroparesis but was somewhat less effective for patients with idiopathic or postsurgical etiology [39]. Advantages for surgical placement of GES are that it is a procedure of significantly less magnitude and morbidity than completion gastrectomy; and gastrostomy and/or jejunostomy tubes may be used in parallel with GES for concomitant support if needed. Adverse events relate mainly to surgical placement of GES and include subcutaneous pocket infection, erosion of leads or generator, and less often, incisional hernia. Bowel obstruction caused by the leads is possible but has rarely occurred. Complications resulting in device removal have been necessary in approximately 5% of cases [40]. GES has been promising in a

well-selected group of patients with refractory gastroparesis and has afforded encouraging success with minimal surgical morbidity. Continued controlled investigation is warranted and ongoing.

Conclusion

Continued basic science and clinical studies have expanded the understanding of gastric motility and its disorders. Gastroparesis has been found to be associated with a variety of nonsurgical and postoperative etiologies. Patients who suffer with this complex disorder frequently require surgical intervention at some time during the course of their disease. The variety of possible surgical interventions for gastroparesis spans the entire continuum of magnitude and risk. This review has provided an overview of current surgical treatment modalities for gastroparesis. Since the role of surgery and its optimal use remain ill-defined, the gastroenterologist and GI surgeon must thoughtfully weigh the risks and limitations of surgery against its potential benefits.

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Chapter 31
Endoscopic Full-Thickness Gastric Biopsy for Evaluation of Patients

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Keywords Gastroparesis • Full-thickness resection • Gastric electric stimulation • Interstitial cells of Cajal • Electrogastrogram • Natural orifice translumenal endoscopic surgery • Submucosal endoscopy

Introduction

Gastroparesis is characterized by recurrent episodes of postprandial nausea, vomiting, epigastric pain and fullness, early satiety, and bloating in the absence of mechanical obstruction of the gastric outlet or the proximal small bowel [1]. The common etiologies for delayed gastric emptying include diabetes mellitus, postsurgical, often as a result of damage of the vagus nerve, and idiopathic (including delayed gastric emptying as a result of a viral illness) [2, 3]. Other less frequent causes include collagen vascular diseases, neurologic problems, such as Parkinson's disease and multiple sclerosis, intestinal pseudoobstruction, endocrinopathies, medication-related, and as a manifestation of a paraneoplastic syndrome [2].

Normal gastric function is regulated by a composite interaction between the neurohormonal, myoelectric, and contractile properties of the stomach. Gastric contractility is controlled by the gastric slow waves that originate from the interstitial cells of Cajal (ICCs) [4, 5]. The electric activity generated by the ICCs begins at the junction of the fundus and the body of the stomach at a rate of approximately 3 cycles per minute and is conducted circumferentially and distally toward the pylorus. ICCs are located in the myenteric plexus that is tucked in the gastric smooth muscle cells, which also are innervated through the enteric nervous system [4, 5].

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Whenever there is postprandial stimulation of the stomach, smooth muscle cells can achieve the level of depolarization for electromechanical coupling to occur and generate an action potential leading to gastric contractility up to a rate of three times per minute, which eventually results in gastric emptying of nutrients. This response also is modulated by intestinal peptides and the vagus nerve.

Up to one third of patients with gastroparesis do not respond adequately to standard medical treatment, which includes dietary modifications, and a trial of antiemetics, prokinetics, and/or antidepressants [3]. Gastric electric stimulation (GES) has an important role in managing this difficult-to-treat group of patients [6, 7]. However, one third of patients will be nonresponders to GES [2]. Serious loss of ICCs on full-thickness gastric biopsies has been shown to be a predictor of poor response to GES [8].

Recently, there has been growing interest in studying gastric wall histopathology in patients with gastroparesis [9]. Understanding the histologic abnormalities in these patients not only helps recognize the pathophysiology of the disease, but may also aid in improving treatment and individualizing therapy. The advent of interventional endoscopic accessories and techniques has made it possible to obtain full-thickness gastric biopsies using a translumenal approach [10, 11]. This advance allows a less invasive means (as compared to surgical biopsies) to obtain deep gastric biopsies. This chapter discusses gastric histopathology in gastroparesis, endoscopic techniques to obtain full-thickness gastric biopsies, and the potential of using biopsies to guide individualized therapy.

Gastric Histopathology in Gastroparesis

Several studies have assessed the neuromuscular pathology in gastroparesis using full-thickness antral biopsies. Harberson et al. obtained full-thickness antral biopsies from 28 patients with refractory gastroparesis (14 with diabetic gastroparesis and 14 with idiopathic gastroparesis) undergoing surgical laparotomy with placement of a GES [9]. These biopsy samples were compared to control samples obtained from eight patients undergoing gastric resection for other reasons. Hematoxylin and eosin (H & E) and immunohistochemical staining were used to detect the presence of inflammation, ganglion cells, and ICCs. Lymphocytic infiltration was found in the myenteric plexus of nerves and ganglia in 7 of the 28 patients, 6 of whom were diabetic, but none of the eight controls. There was a 27% reduction in the number of ganglia per high power field (hpf) in gastroparetic patients compared to controls. In addition, there was a reduction in the number of total nerve cell bodies in the patients with gastroparesis compared to the controls (2.2 ± 0.3 vs. 3.2 ± 0.12, respectively, $p = 0.0002$). C-kit staining was used to identify ICCs. There were significant reductions in the c-kit staining ICCs in the myenteric plexus in both diabetic patients (4.4 ± 0.4) and idiopathic gastroparesis patients (4.4 ± 0.4) compared to controls (5.7 ± 0.6). Thus, histologic abnormalities in gastroparesis were heterogeneous and included myenteric inflammation, decreased innervation, and reduction of ICCs.

Harberson and colleagues proposed that the inflammation or loss of innervation may result in injury to the ICCs, with subsequent reduction in the number of ICCs and loss of pacemaker activity [9]. Full-thickness gastric biopsies are, thus, crucial for the full understanding of pathophysiology of gastroparesis.

Correlation Between Gastric Histopathology and Gastroparetic Symptoms

The loss or absence of ICCs in patients with gastroparesis appears to correlate with clinical findings and myoelectric activity. Forster et al. studied 14 gastroparetic patients (9 diabetic, 4 idiopathic, and 1 postsurgical) for whom standard medical therapy had failed and who had been treated with GES [8]. Patients underwent full-thickness antral gastric wall biopsy at the time of surgery. The biopsy samples were stained with c-kit and scored for the presence of ICCs. Baseline electrogastrogram (EGG) recordings were obtained in the fasting state and after a test meal. Total symptom score was calculated at baseline and at 3 months after GES placement. Five patients had almost no ICCs and were compared with nine patients with 20% to normal cell numbers. Both groups did respond symptomatically to gastric electrical stimulation. However, patients with severely depleted ICCs had less reduction in their symptoms as compared to the other group (39 vs. 66%, respectively). In addition, patients with severely depleted ICCs had significantly more tachygastria and had significantly greater total symptom scores at baseline and after 3 months of GES. The authors of this study concluded that ICCs were absent in up to a third of patients with diabetic or idiopathic gastroparesis, and the absence of these cells was associated with abnormalities of gastric slow waves, worse symptoms, and less improvement with GES.

Lin et al. studied the associations between the status of ICCs and EGG parameters, gastric emptying and symptoms in 41 patients with refractory gastroparesis who were scheduled to undergo surgical placement of GES (34 diabetic, 5 idiopathic, and 2 postsurgical) [12]. All patients underwent EGG recordings, assessment of total symptom scores, and a 4-h gastric emptying study prior to surgery. Full-thickness antral biopsies obtained during surgery were stained with c-kit to assess the number of ICCs. Fifteen patients (36%) had severely depleted (or no) ICCs (ICC− group) and 26 patients had normal (or adequate) ICCs (ICC+ group). EGG recordings in the ICC – group exhibited significantly less normal slow waves than in the ICC+ group, both in the fasting and fed states. Tachygastria occurred more often in the ICC – group compared to the ICC+ group (32% vs. 11%, respectively, $p = 0.01$). There was no statistical difference in gastric emptying and symptom severity between both groups. However, severely depleted ICCs did result in significantly poorer response to GES. While 75% of patients in the ICC+ group had ≥50% symptom improvement 1 year after GES, only 33% of patients in the ICC− group experienced similar improvement.

Endoscopic Gastric Full-Thickness Biopsy Techniques

Natural orifice translumenal endoscopic surgery (NOTES) has gained a great deal of attention from gastroenterologists and surgeons all over the world since its introduction in 2000 [13]. Breaching the gastrointestinal boundary opened the realm for new endoscopic techniques, innovative endoscopic instruments, and pioneering diagnostic and treatment modalities. Numerous methods have been described for translumenal (e.g., transgastric, transcolonic, and transvaginal) access site closure after NOTES procedures [14–17]. Most published reports describe the use of clips, endoscopic staplers, threaded tags, and suturing devices. Other available methods include the use of plugs or adhesives. The advent of these closure devices and methods has made it possible to perform endoscopic full-thickness biopsies.

Rajan et al. in a preclinical porcine study evaluated different endoscopic techniques for obtaining deep gastric-muscle-wall biopsy specimens and determined if myenteric ganglia were present in the tissue samples [18]. The five studied techniques were (1) EUS-guided tru-cut biopsy, (2) jumbo biopsy of the postendoscopic mucosal resection (EMR) site, (3) jumbo biopsy of the gastrostomy margin, (4) serosal-side biopsy through a gastrostomy and (5) double EMR resection. EUS-guided tru-cut biopsy was performed using a 19-gauge Tru-cut biopsy needle (Quick-Core; Cook Endoscopy, Winston Salem, NC). The second technique entailed performing EMR followed by biopsy of the exposed muscle layer using a Jumbo forceps (Olympus America, Center Valley, PA). The third technique was performed using a fistulotome to create a gastrostomy through the anterior gastric wall. A guidewire was passed through the track which was then dilated using an 8 mm balloon. Biopsy specimens were then obtained from the margin of the gastrostomy by using a jumbo forceps. The fourth technique entailed obtaining biopsies from the serosal side of a gastrostomy. The gastrostomy was created as described above. It was further dilated to 15 mm using a balloon followed by passage of an endoscope into the peritoneal cavity. Biopsies were then obtained using a jumbo forceps in a retroflexed position. The double EMR technique involved a second EMR that was performed on the muscle layer that was exposed by a first EMR. The double EMR technique was the only technique that yielded gastric tissue which included the muscular layers and myenteric ganglia. This technique may be performed easily by experienced endoscopists. However, its main shortcoming is the creation of an immediate perforation after the second EMR. Although multiple studies have described various closure devices (mainly in the setting of NOTES), a 100% reliable means of closure must be developed before the widespread use of the double EMR technique to obtain deep gastric-muscle-wall biopsies.

Rajan and colleagues proposed that the optimal deep gastric-muscle-wall biopsy procedure would seal the gastric wall defect before tissue resection, eliminating the risk of peritonitis [19]. This group studied a technique they called “no hole” full-thickness biopsy of the stomach [19]. This technique involved the performance of two cap-assisted EMRs. An EMR cap-assisted resection was performed first. Subsequently, a smaller cap was attached to the tip of the endoscope and an endoloop

was positioned around the endoscope outer sheath. The muscular layer was then suctioned into the cap and the endoloop was opened and released from the cap and then tightened while suction was still being applied. This resulted in formation of a pseudopolyp of the exposed gastric muscular layer. A second endoloop was placed to tighten the base of the polyp. T-tag tissue anchors (Olympus America) were placed on either side of the pseudopolyp. The pseudopolyp was subsequently resected with snare electrocautery. The T-tags were then pulled close together to decrease the risk of perforation (Fig. 31.1). Full-thickness biopsies were obtained from six pigs without any immediate complications. Two animals were killed within 6 days of the procedure because of peritonitis resulting from delayed perforations; both animals were found to have displaced T-tags and endoloops.

Ikeda et al. proposed two methods of full-thickness gastric biopsy: endoscopic full-thickness resection with sutured closure [20] and the circumferential cutting method [21]. The first method entailed performing EMR using a ligating device [20]. Before resection, two or three stitches were placed in the deep muscular layer 2–3 mm out of the resection area. The polypoid lesion, including the muscularis propria, was resected with conventional hot snare technique by placing the snare below the rubber band. The stitches placed around the resected site were then tied

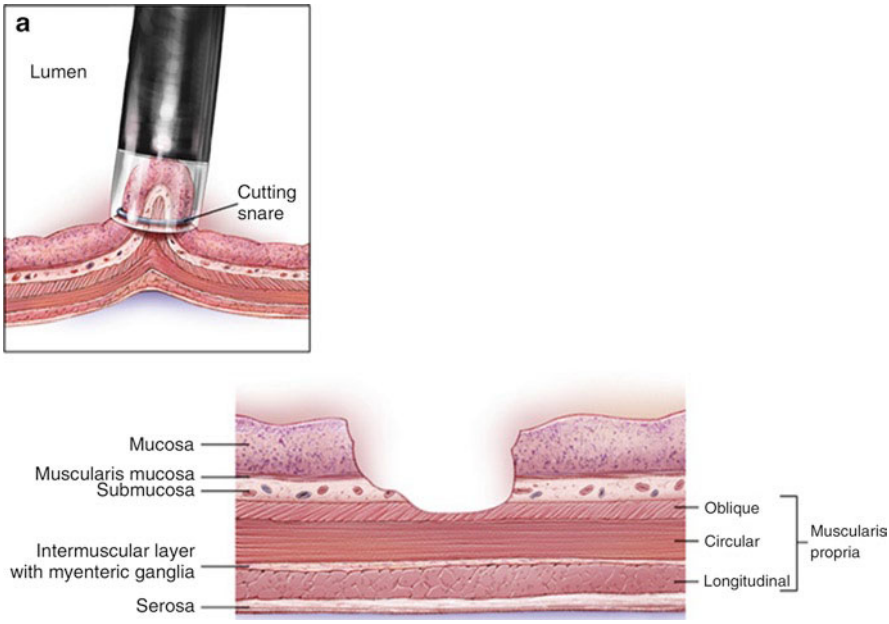

Fig. 31.1 (**a**) Cap-assisted endoscopic mucosal resection performed without a protective submucosal cushion. (**b**) Exposed muscle layer suctioned into the cap while the endoloop was gently released and tightened around the pseudopolyp. (**c**) Second endoloop and prototype T-tag tissue anchors are positioned around the base and adjacent to the pseudopolyp, respectively. (**d**) Pseudopolyp resected by snare electrocautery. (**e**) Resection site further closed by tightening (opposing) prototype T-tag tissue anchors

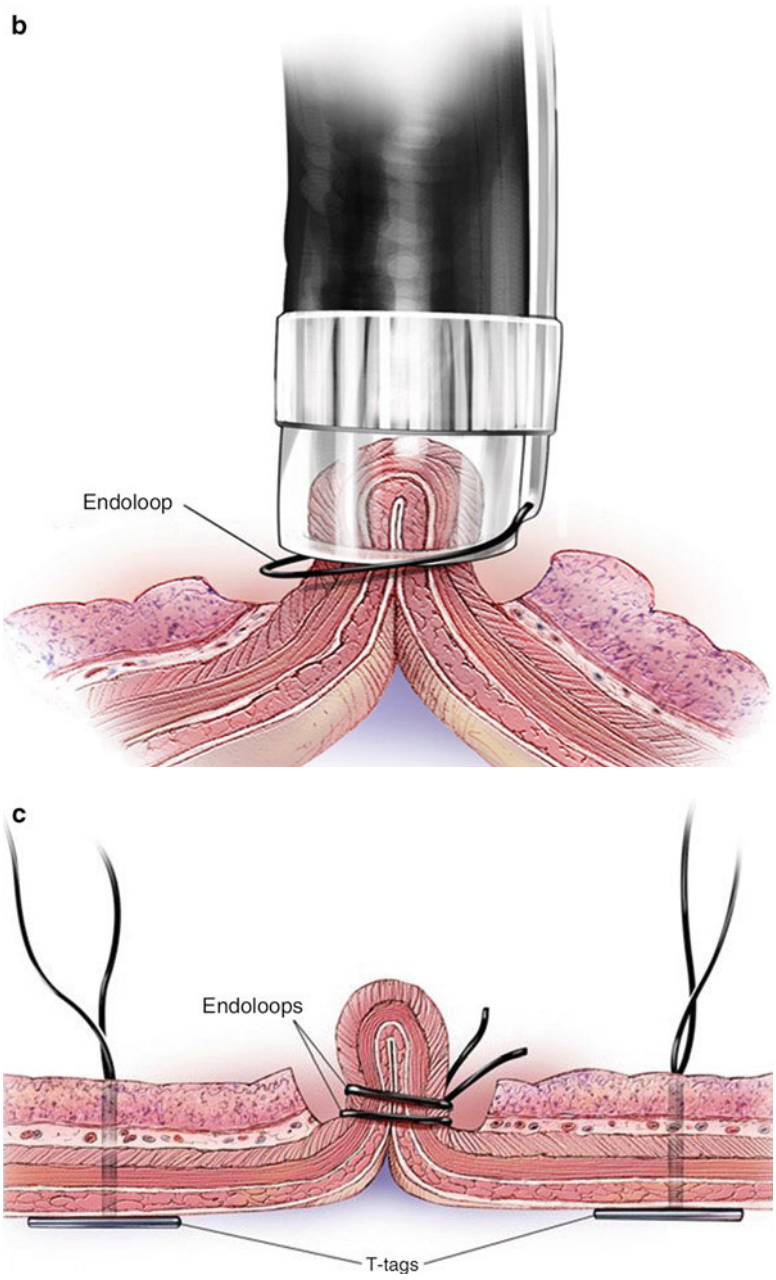

Fig. 31.1 (continued)

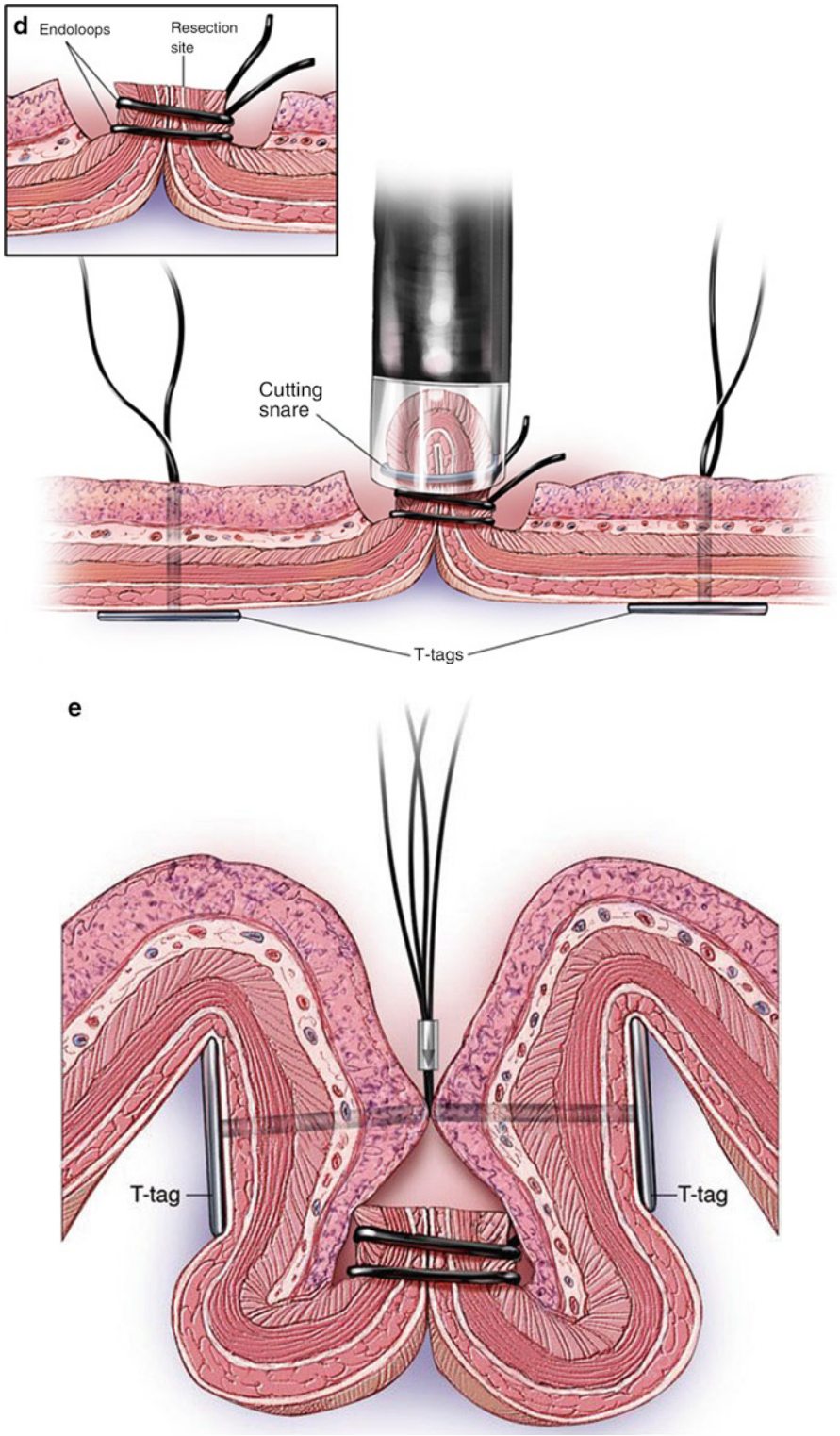

Fig. 31.1 (continued)

together using a prototype thread-locking device. Full-thickness resections were performed successfully in eight pigs without complications. Healing of the suture site was evident at follow-up endoscopy. The second technique described by Ikeda and colleagues was the circumferential cutting method [21]. A circumferential excision was made using a needle knife, a sphincterotome and a snare with forceps. First, two stitches were placed on the sides of the targeted area. A needle knife was then used to puncture the stomach and a guidewire was passed into the peritoneal cavity. A prototype sphincterotome (bidirectional cutter) was passed through the wall into the peritoneum, bowed and pulled back. The target area was cut halfway around, the sphincterotome removed, and a snare was passed through one working channel and a forceps passed through the other working channel of a double channel endoscope. The forceps was used to pull the tissue into the snare. Then, the snare was closed, and the tissue was fully cut and retrieved. The sutures were subsequently used to close the opening. Twelve domestic pigs were used in survival and nonsurvival studies. Full-thickness gastric biopsies were successfully obtained in all pigs, and all defects were successfully closed without complications.

Elmunzer et al. evaluated the feasibility of a grasp-and-snare endoscopic full-thickness resection technique using a novel tissue lifting device that provided a secure tissue anchoring and manipulation [22]. A double-channel therapeutic endoscope was used with a prototype tissue-lifting device through one channel and a snare through the other channel. The lifting device was advanced through the open snare and was anchored to the gastric mucosa. It was then pulled back toward the endoscope everting the mucosa into the gastric lumen and the snare was closed around the everted tissue. A blended electrosurgical current was subsequently applied resulting in a full-thickness biopsy. In total, 23 of 24 resections resulted in full-thickness gastric biopsies. This study did not, however, address closure of the lumenal defects that were caused by the biopsy.

Sumiyama et al. studied a novel technique of submucosal endoscopy with mucosal flap safety valve to obtain full-thickness gastric-muscle-wall resection and access the peritoneal cavity [23]. A dual channel endoscope with an EMR cap was used. High-pressure short bursts of carbon dioxide (CO_2) were injected into the submucosal layer through an injection needle to create a submucosal gas cushion. A mucosal incision was made at one margin of the cushion with a bipolar needle knife (B-Knife; Zeon Medical Inc, Tokyo, Japan). A biliary retrieval balloon (Olympus America) was later inserted into the submucosal layer from the mucosal incision and was inflated to dissect the connective tissue to create a space to easily insert the endoscope with the attached EMR cap. The muscular layer opposite to the mucosal entry point was resected by cap EMR. The mucosal incision was closed by mucosal apposition with clips or, if that failed, by fixation of the mucosal flap onto the muscular layer using tissue anchors (Olympus Optical Co, Ltd, Tokyo, Japan) or medical acrylate glue (Indermil; Tyco Healthcare, Norwalk, Conn). By using the above novel technique, the authors successfully performed submucosal space endoscopy and deep-layer gastric-wall resection in four pigs. The mucosa overlying the dissected submucosal space served as a safe flap valve, preventing peritoneal leakage.

More recently, Fraser and colleagues described a simple technique to obtain gastric full-thickness biopsies in three dogs via a percutaneous, endoscopically assisted approach [24]. Dogs underwent gastroscopy and abdominal skin areas were marked based on appropriate antral indentation by external finger pressure. A 14-gauge biopsy needle was then introduced through a 3 mm incision in the abdominal skin, and biopsies were obtained from each dog, with no subsequent closure interventions and without any complications. Histologic analysis of the biopsies revealed all layers of the stomach, including enteric nervous system elements.

Use of Endoscopic Biopsies to Guide Therapy

As discussed above, the loss of ICCs correlates with dysrhythmias of the stomach and a poorer response to GES. Thus, knowledge of the histopathology of gastric musculature and status of ICCs may be of importance in selecting appropriate patients for GES. There is growing evidence that neuromuscular histologic abnormalities in the stomach (and other parts of the digestive tract) are responsible for the pathophysiologic disturbances of the gastrointestinal tract [25–28]. Full-thickness biopsies will help diagnose specific abnormalities in the digestive tract, which hopefully will guide diagnosis and specific targeted therapies. Our understanding of severe motor diseases of the gastrointestinal tract, such as refractory gastroparesis and intestinal pseudoobstruction, is limited. This is part of the reasons why the current therapy of these diseases is suboptimal. Obtaining full-thickness biopsies for pathologic diagnosis will hopefully improve our understanding and therapy of refractory gastrointestinal motility disorders, including gastroparesis.

Conclusion

GES has an important role to improve gastroparetic symptoms and the quality of life in patients with severe gastroparesis refractory to medical therapy. Patient selection is key to obtaining a good response to gastric stimulation. Patients with severely depleted ICCs respond poorly to gastric stimulation. Full-thickness biopsies may help diagnose severe depletion of ICCs and/or other specific gastric abnormalities, which hopefully will guide diagnosis and specific individualized therapies. Recent advances in endoscopic techniques have allowed development of novel endoscopic methods to obtain full-thickness gastric biopsies. Most of these techniques are still experimental with risks of complications, including leakage. More recently, submucosal endoscopy with mucosal flap safety valve to obtain full-thickness gastric-muscle-wall resection and access the peritoneal cavity was described. Further studies are needed to explore the safety and efficacy of this and other promising techniques.

Conflicts of Interest: Rukshana Cader has no conflicts of interest to disclose. Mouen Khashab has no conflicts of interest to disclose. Anthony Kalloo is a founding Member, equity Holder and consultant for Apollo Endosurgery.

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Chapter 32
A Brief History and Future Directions for Permanent, Temporary, and Endoscopic GES

Sumanth Daram and Thomas L. Abell

Keywords Gastric electrical stimulation • Gastroparesis • Gastric electrical activity • Enteric nervous system • Autonomic nervous system • Electrogastrography • Cajal cells

Introduction

Gastric electrical stimulation (GES) currently relies on devices that are endoscopically or surgically implanted, and which function much as do cardiac pacemakers, by utilizing exogenous electrical stimulus to help regulate the wave activity necessary to healthier gastric motility. GES can mitigate the gastrointestinal symptoms associated with drug refractory gastroparesis, particularly nausea and vomiting, and so can improve significantly the quality of life for patients with this disorder. The present chapter begins with a brief history of the therapy's development and moves to a discussion of topics now under investigation in gastric motility laboratories worldwide.

Background

In 1963, electrical stimulation of the stomach was first reported as a therapy for postoperative ileus [1]. The possibility of using electrical energy to treat disordered gastrointestinal function had tantalized researchers for decades, but technical obstacles

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delayed any real progress until the 1960s. Early work focused on surgical approaches that measured the gut electrical activity, as well as the application of electrical current to the gastrointestinal tract. Concurrent with the postoperative ileus report, the first commercially available gastric electrical stimulator, the "Peri-Start," began to be marketed by *Medtronic*. Clinically tested by a young Texas surgeon, Michael deBakey, this device eventually fell out of favor, largely owing to an absence of clear evidence that it could improve postoperative ileus [2].

Despite the setback, researchers interested in GES began to work over the following decade on what would eventually become known as "pacing" of the gut. Most of these investigators traced their origin to one or two centers, and particularly to the Mayo group, led in the 1970s by surgeon Keith Kelly. These researchers owed much of their inspiration to such physiologists as Charlie Code, whose cineradiography of the alimentary tract significantly influenced the direction of subsequent research. Code's time at the Mayo Clinic overlapped with that of gastroenterologist Walter Alvarez, who, prior to arriving at the Mayo in the late 1920s, described the electrogastrogram (EGG). Alvarez worked at Harvard in the early twentieth century with noted physiologist and father of gastrointestinal motility studies, Walter Cannon, whose experimental radiographic studies, performed alongside his work in homeostasis and the popularized "fight or flight" response, provided a foundation for the twentieth century gastrointestinal motility studies [3–5].

By the 1980s, GES investigators sought to influence gut electrical activity directly, with the aim of improving physiological function. Custom devices permitting the delivery of energy at a wide variety of settings were constructed, and relatively high-energy stimulation applied to the small bowel so as to effect, for example, changes in absorption. A canine model, with implanted electrodes and strain gauges, was commonly employed for these studies.

Experimental Studies

By 1988, an animal lab had been readied at the University of Tennessee, Memphis to study the capacity of electrical stimulation to "correct" disordered gastrointestinal function, as measured by electrogastrography (EGG). Memphis had become the site to which 200–300 new patients with severe disorders of nausea and vomiting were referred each year. The need for effective treatments for their symptoms was the impetus for flourishing research. Using a canine model and a custom device from *Empi*, a multiyear study by Familoni, Abell, and Voeller was undertaken to examine varied stimulation parameters and their effects on gastrointestinal motility, especially gastric motility. The principal finding was that the combination of much higher than physiologic frequencies with very low energies produced the best motility response. This approach would become the basis for GES. As *Medtronic's* Enterra® has been the only commercially available device for GES to date, the technique is also referred to as Enterra® therapy.

Over the same period, other investigators in the USA, notably in Florida and Virginia, were using much higher energies and closer to normal frequencies for trials addressing similar indications, such as the nausea and vomiting associated with disordered gastric emptying. Studies from all these groups would be published throughout the 1990s.

Investigational Work

In the 1990s, the group at Memphis demonstrated the efficacy of high-frequency GES over low-frequency (physiologic) stimulation in the canine stomach [6]. Based on a successful, but experimental, use of this high-frequency/low-energy approach in a patient in 1997 [7], a proposal for an investigational device exemption (IDE) was submitted to the FDA. Its approval permitted a formal US trial of the new protocol and the then-available Itrel II device from *Medtronic*. At the same time, *Medtronic* arranged for a number of sites outside the USA to conduct a study that employed an essentially identical protocol, but without standardizing such measures as gastric emptying. This international investigation became the GEMS study, which was eventually published in *Digestion* [8].

The GEMS study made use of temporary stimulation, with placement of temporary devices either via endoscopy or laparoscopy, prior to permanent device implantation. However, as more than 80% of the patients who participated had an immediate, anti-emetic response to the technique, another study was designed in which permanent stimulators were implanted directly.

This new study, a randomized, double-masked protocol, limited to patients with delayed gastric emptying, was performed at a number of sites on three continents. In order to determine and standardize appropriate gastric emptying parameters, an initial study on normal volunteers was conducted. This preliminary investigation was later published as the low-fat meal, gastric-emptying protocol that is now used by most gastroenterologists. The study was called WAVESS, and would eventually be published in *Gastroenterology* [9]. In the spring of 2000, based on the results of the GEMS and WAVESS studies, the US FDA approved the use of Enterra® under the humanitarian use device designation for patients with medication refractory gastroparesis of the diabetic and idiopathic types [10].

Clinical Investigation and Application

Over the past 10 years, several thousand patients worldwide have been implanted with Enterra®. The majority of these patients have been provided with this device in the USA, where it still has HDE designation, despite attempts to obtain the full approval that would permit widespread use. A recent review of 32 published trials

found that all of these studies were positive in at least one parameter; however, most were open label trials. Thus, much recent focus has been on randomized blinded (or masked) trials, registered with the US clinicaltrials.gov site, which can be classified as evidence-based medicine (EBM).

Such a recent, clinical trial involving permanent GES, the *Enterra® Therapy Clinical Study*, has been completed and uploaded on the clinicaltrials.gov Web site. A multicenter, interventional, randomized, crossover safety/efficacy study, this trial included subjects with either diabetic or idiopathic gastroparesis. Participants were surgically implanted with an Enterra® device, and afterward subjected to an initial 4-month period with the device "ON." Subsequently, participants were crossed-over to a 4-month period with the device "OFF." The study did not show a significant difference in the primary outcome measure, percent reduction in frequency of weekly vomiting episodes, with the device ON as compared to OFF. However, a statistically significant improvement in the percent reduction for frequency of weekly vomiting episodes at 12 months was noted in both diabetic and idiopathic gastroparesis patients [11]. The apparent lack of benefit in terms of the primary outcome measure may well have been due to the carryover effects from the initial period of stimulation during the common ON phase before randomization.

Future Applications of GES

Among the many questions about GES that await a definitive answer, at least three are foremost. The first requires a determination of how best to deliver a specific type of stimulus. The second involves identification of optimal stimulus delivery site(s). The third concerns the stimulation parameters to be used. We address these primary points, and then discuss subsequent, related questions.

What Is the Best Way to Deliver Electrical Stimuli?

Gastrointestinal electrical stimulation can be delivered in one of the following ways.

Continuous stimulation. A continuous delivery of electrical stimulation while theoretically attractive, requires the delivery of a higher/greater volume of energy, posing practical, technological challenges.

Cyclical Stimulation. Electrical stimulation is delivered in cycles. This method is currently used for GES.

Intermittent stimulation. Electrical stimulation could be controlled by the patient or a feedback mechanism that senses food. Although both approaches are currently under exploration and development, neither has yet been used in any formal, published FDA trial.

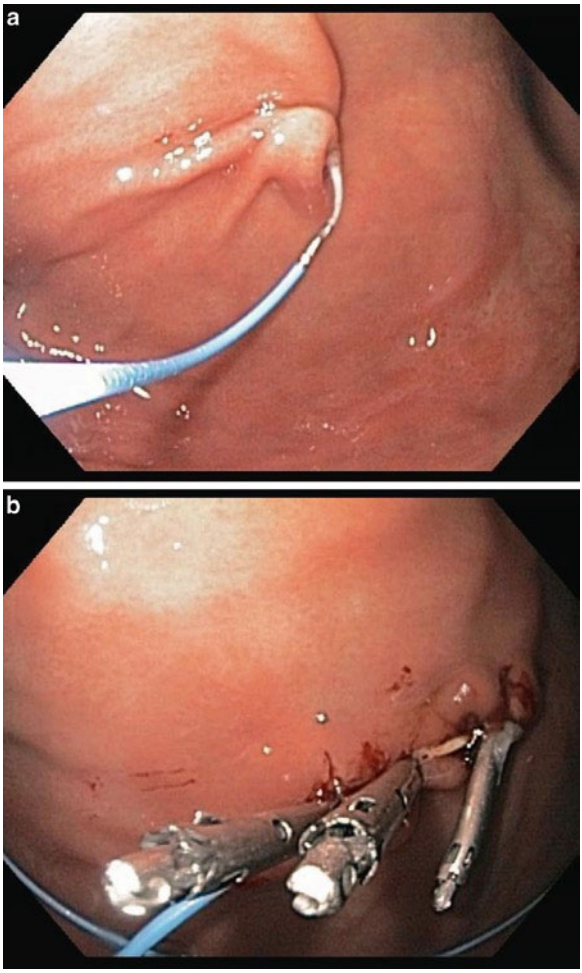

Fig. 32.1 (**a**) Endoscopic view of temporary gastric stimulator electrode inserted through endoscope and screwed into gastric mucosa. (**b**) Endoscopic view showing anchoring of electrode with clips

Where Should Stimulation Be Delivered?

GES could be delivered to one of the following sites.

Mucosa. The gastric mucosa provides the most easily accessible site for electrode placement, but it has so far only been used for temporary stimulation. Electrodes can be situated either through a percutaneous enterogastrostomy (PEG) site, or endoscopically, Fig. 32.1 [12, 13].

Serosa. At present, most GES is delivered via the gastric serosa, with electrodes placed by laparatomy or laparoscopy.

Cutis. True external stimulation, akin to external cardiac stimulation, is an attractive idea. Cutaneous stimulation has been demonstrated in animals, but not in human subjects.

What Stimulation Parameters Should Be Used?

This question is crucial to the application of electrical stimulation in the GI tract.

Low Energy. Enterra® is designed to deliver low energy while utilizing higher than physiologic frequencies.

High Energy. This GES approach makes use of near-physiologic frequencies. It has been advocated for use in at least two trials, but has yet to undergo formal FDA approval.

How Many Electrodes Are Needed to Deliver the Electrical Stimulus?

One set of electrodes. Currently, GES makes use of a single set of electrodes.

Multiple electrodes. The use of multiple electrodes has been tested in animal models, but not in humans.

Combination of multiple electrodes. Sequential (and/or intermittent) stimulation makes use of a combination of electrodes. Multichannel pacing requires a fraction of the energy of single-electrode pacing, and has improved gastric emptying and symptoms in experimental models of gastroparesis, as well as in patients with diabetic gastroparesis [14, 15].

How Can We Predict Which Stimulation Parameters May Work Best in an Individual Patient?

Low-energy electrical stimulation has been shown to produce the best clinical results; however, our experience has suggested that a significant number of patients benefit by having their stimulation parameters changed to higher energies over a period of time. This clinical experience led us to suggest an energy algorithm (see Fig. 32.2) for use with patients who either did not improve, or who experienced recurring symptoms at low-energy stimulation settings [16]. It also led us to examine effects of an intra-operative variation of energy settings, based on EGG parameters. (Below we discuss the use of EGG data in predicting favorable outcomes with GES).

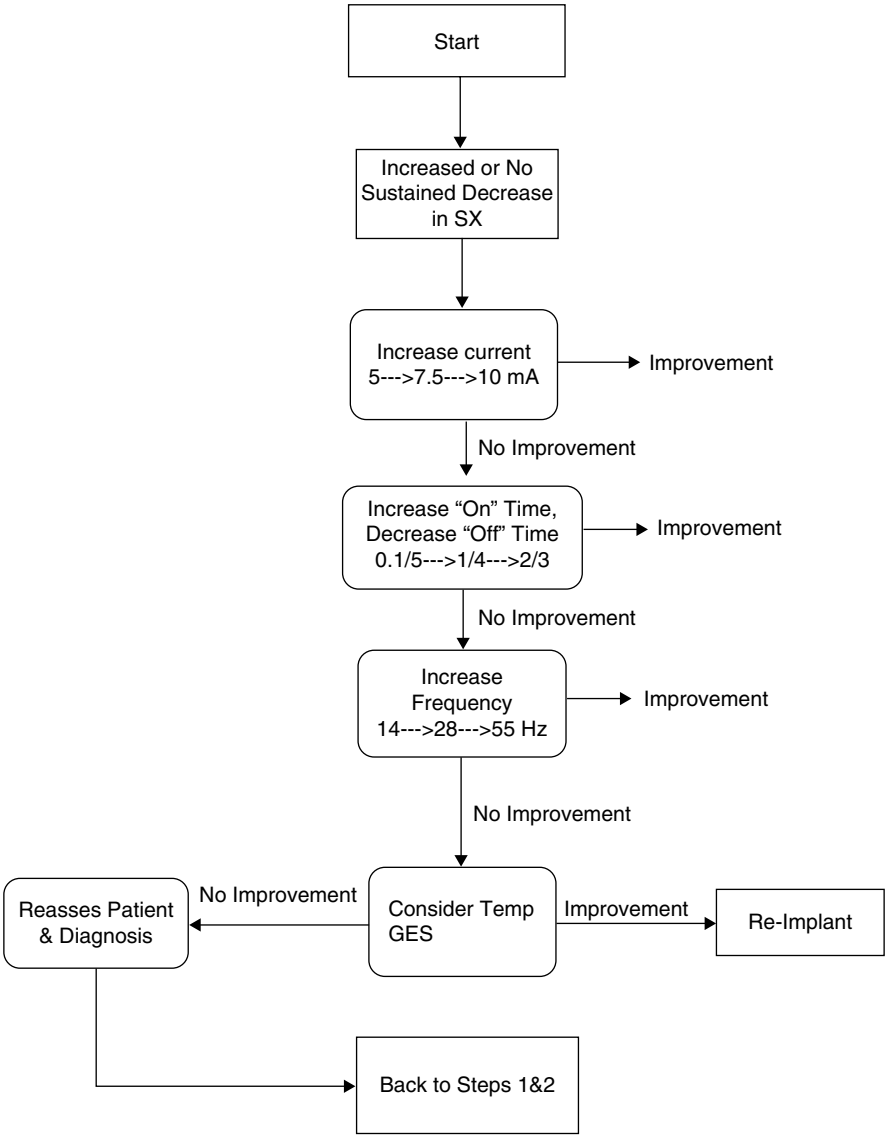

Fig. 32.2 Algorithm for GES-associated symptom improvement. SX = symptoms, mA = milli-Amps, HZ = Hertz, GES = gastric electrical stimulation. (Adapted from: Abidi N, Starkebaum WL, Abell TL. An energy algorithm improves symptoms in some patients with gastroparesis and treated with gastric electrical stimulation. Neurogastroenterol Motil 2006; 18:334–8). A typographical error in the original algorithm has been corrected in this adaptation

Early results from an ongoing study in our group appear to suggest that individual patients vary significantly in the stimulation parameters required to generate optimal EGG results. We are studying the effects of such varied stimulation parameters on clinical outcomes [17].

Can Less Invasive Methods Be Used to Predict Response to GES in an Individual Patient?

The placement of a permanent GES device involves considerable cost and patient risks. It is therefore important to define preoperative characteristics that may predict outcomes for individual patients, whether these predictors are related to symptoms or derived through additional testing.

Symptom related. The decision to implant a GES device may be based solely on patient symptoms. Among the usual symptoms of gastroparesis (nausea, vomiting, early satiety, bloating, and abdominal pain), pain has been shown to be the least likely to respond to GES. Patients whose predominant symptom is vomiting are more likely to benefit from GES [18].

GET based. Results recently obtained by investigators in France indicate that patients with initial delays in gastric emptying parameters (21 of 33 patients) displayed improvements comparable to those seen in patients with normal GET. These researchers concluded that indications for GES should be determined clinically, and that the technique may be useful for patients with normal gastric emptying [19].

EGG based. EGG abnormalities are used as a basis for implantation of the GES device [20].

Full thickness gastric biopsy based. Abnormalities at pathologic examination of biopsy specimens may help determine the appropriateness of GES device placement. Patients with decreased counts for interstitial cells of Cajal in full thickness antral biopsies are less likely to respond to GES [21].

ANS testing based. The decision to implant a GES device is made on the basis of abnormalities seen with ANS testing.

Other neurologic testing based. The decision to try a GES device may be based on the presence of a known neurologic abnormality, such as abnormal findings on full thickness biopsies.

Can We Determine Optimal Stimulation Parameters for Individual Patients?

Mucosal EGG. We have previously demonstrated that a low-frequency amplitude ratio after temporary GES correlates with greater likelihood for symptom improvement after permanent GES device placement [20].

Other parameters, in combination. Autonomic and enteric parameters may be employed to predict the type of GES needed.

Intra-operative testing. As discussed earlier, low-energy electrical stimulation typically results in the most favorable GES clinical outcome. However, a significant

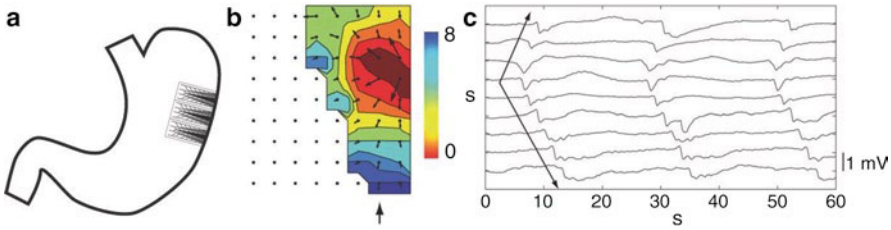

Fig. 32.3 From left to right: (**a**) Multi-electrode arrays are placed on the gastric serosa in the position indicated; (**b**) Activation map of a typical normal wave. Each point represents an electrode, and each color band (isochronal band) shows the area of slow wave propagation per 1 s of time. Activity is shown to arise near the greater curvature and to propagate initially in all directions. The arrows represent the velocity magnitude, with a higher velocity shown in association with the pacemaker origin. (**c**) Example human gastric electrograms (corresponding to the column of electrodes second from right in map (**b**)), showing slow wave activity spreading proximally and distally from the pacemaker site

number of patients require modulation of their energy settings to higher energies either shortly after GES placement or over a period of time. We have therefore endeavored to study the effects of varying energy settings on EGG parameters intra-operatively, at the time of GES device placement. To learn whether or not these study results translate into meaningful clinical outcomes is the objective of our current investigations [17].

High-resolution Mapping. Slow waves coordinate gastric motility; thus, abnormal slow wave activity may contribute to motility disorders. O'Grady et al. have recently used high-resolution mapping to provide an accurate demonstration of human gastric slow wave activity. The gastric pacemaker region is associated with high-amplitude, high-velocity activity, and multiple wave fronts propagate simultaneously. This information serves as a baseline for high-resolution mapping studies in gastroparesis (see Fig. 32.3). In the future, patient-specific results from such studies may help to aid optimization of stimulation parameters [22, 23].

How Is the Currently Available, Permanent GES Device (Enterra®) Implanted?

During surgery to initiate GES, two electrodes are implanted in the seromuscular layer of the wall of the stomach at the gastric antrum/body junction. Previous animal and human studies provide evidence for placing the electrodes at 10-cm proximal to the pylorus on the greater curvature of the stomach. The leads are typically placed 1-cm apart and parallel. Electrodes must not penetrate the gastric mucosa upon final placement; their proper placement should be confirmed by intra-operative endoscopy. Placement can be achieved either laparascopically or through laparatomy. Given the requirement for correct placement of leads, laparoscopy can be technically challenging.

New Technological Developments in GES

Cutaneous placement of temporary GES electrodes (Percutaneous electrode system). Researchers from Sweden have developed a novel method for permanent implantation of electrodes without the need for laparatomy or laparoscopy. A plastic cannula with an internal needle is percutaneously introduced through the abdominal wall, gastric serosa, and muscularis to the sub-mucosal portion of the stomach. A similar approach has been proposed by other groups [13]. Care is taken to avoid luminal perforation. After using a saline injection to create a fluid filled space, a self-anchoring electrode is left in the antral sub-mucosal space [24, 25].

Mucosal placement of temporary GES electrodes. Placement of temporary GES electrodes endoscopically (ENDOstim) or through PEG (PEGstim) has been shown to be feasible and effective [12, 26].

Wireless EGG. Signal acquisition can now be achieved by means of an ambulatory system carried by the patient, to whom it is connected through skin electrodes. The acquired signal is transmitted via Bluetooth to a mobile phone, where data are stored in the memory until transfer via the GSM network to a remote processing and diagnostic unit [27].

Robotic Placement of permanent GES Electrodes. Gould et al. have recently demonstrated that robotic placement of the GES electrodes is safe and effective. Compared with standard laparoscopic techniques, the accurate insertion and anchoring of leads has been shown to be more efficiently and comfortably accomplished with robotic techniques. To determine whether or not robotic GES electrode placement will result in significant clinical advantages for patients will require long-term follow-up [28].

Miniature Wireless GES Devices. Deb et al. have developed two new miniature gastric stimulators. One has a wirelessly rechargeable battery; the other is wirelessly powered, and thus requires no battery. Preliminary tests of these models have been performed in a porcine model. If experimental results can be duplicated in humans, endoscopic implantation of permanent GES devices may become feasible [29].

What Is the Future for GES?

In spite of the technological advances for GES that have been achieved to date, no consensus on the mechanism of action of GES in gastroparesis has emerged. Theories currently proposed include the effects of stimulation on: gastric tone, gastric emptying, fundal relaxation, and accommodation; enteric nervous system function; and central neuronal pathways [30]. A better understanding of the mechanism of action can lead to improved GES efficacy.

In the meantime, researchers have successfully used GES to treat medically refractory nausea and vomiting for patients with normal gastric emptying studies,

as well as postsurgical gastroparesis. Abrahamsson et al. have reported that, for patients with chronic intestinal pseudo-obstruction and medically refractory vomiting, GES seems to have an antivomiting effect similar to that seen in patients with severe diabetic gastroparesis [31]. Furthermore, a number of GES protocols have proved efficacious for weight reduction in obesity.

Clinical dilemmas and outcomes, alongside increasing evidence of the complex interactions and pathways that may be addressed by GES, have led to an increase in questions and concerns about the technique's mechanisms and utility. These inquiries, in turn, have led to intensified research efforts. Efforts to develop both wired and wireless temporary devices that can serve as trial stimulators are underway, though not yet commercially available, and interest in the area of multichannel pacing devices is growing. The delivery of GES only at detection of intrinsic slow waves is also under investigation [32].

Of great interest, Lammers et al. have recently used high-resolution mapping to define the origin and propagation of gastric arrhythmias, and O'Grady et al. to track slow wave propagation [23, 33]. The role of arrhythmias in the pathogenesis of gastroparesis, as well as the effect of GES on them, needs to be studied. Over the coming years, it is hoped that gastric contractility and factors affecting it will be better understood, and so help us to devise novel GES parameters and devices [33]. In addition, the increasing refinement of battery technologies, the development of minimally invasive means of electrode implantation and improvements in the size of stimulators will increase the potential utility and feasibility of GES.

Future Studies in GES

Investigations into gastric electric stimulation are increasing. The clinical response to Enterra® remains acceptable: about 80% of patients have at least a 50% reduction in symptoms, and about half of these patients have a much greater reduction in symptoms. However, GES is a significantly expensive modality and, owing to the surgery required for implantation, carries measureable risk. To mitigate adverse events and cost, it is imperative that we identify preoperative characteristics able to predict improved patient outcomes. Much work thus remains to be accomplished in this arena. Nonresponders to standard high-frequency/low-energy GES should be evaluated with an incremental energy algorithm, as previously reported [16]. We are now investigating the effects of such incremental energy on intra-operative EGG parameters to help develop methods for determining optimal energy parameters for individual patients [17].

A number of centers have focused on other ways for identifying the likelihood of optimal patient response to GES. Proposed approaches for these determinations include clinical patient related factors, as well as noninvasive autonomic nervous system measures, EGG, mucosal EGG, and full thickness gastrointestinal biopsies. We and other researchers have found temporary GES, whether placed endoscopically or via PEG electrodes, helpful in predicting a patient's outcome with permanent GES.

Additionally, we have found that a younger age, a higher baseline vomiting score, and a low frequency-to-amplitude ratio on EGG at baseline are independently associated with greater chances for success [20]. Other researchers have reported that diabetic gastroparesis and the absence of preoperative opioid dependence can also help predict better outcomes with GES [18].

The establishment of the NIH Gastroparesis Clinical Research Consortium (GPCRC) almost 5 years ago has resulted in a large registry of data on patients with gastroparesis. It is hoped that this data may eventually help in determining useful criteria through which to predict patient response to Enterra or other GES therapies. The technologies described above require continued assessment, whether by the FDA, the NIH or other agencies; for example, the American Gastroenterological Association has proposed an Office of Technology Evaluation to help facilitate the assessment of new GES technologies and to assist with their proper use.

Summary

Gastrointestinal stimulation, a promising technology for over a century now, has over the past two decades seen a great increase in its capacity to be of benefit to patients with drug-refractory gastrointestinal motility disorders. GES will continue to evolve over the coming years, as questions regarding its best use are answered, and as new technologies are developed. GES may emerge as an important clinical tool for patient care, and one that is more universally available for appropriate patients.

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Chapter 33
Cell Transplantation for Gastroparesis

Laren Becker and Pankaj J. Pasricha

Keywords Embryonic stem cells • Induced pluripotent stem cells • Neural stem cells • Enteric neural progenitors • Progenitors of interstitial cells of Cajal

Introduction

Normal gastric motor function requires coordinated interaction among central nervous system (CNS), enteric nervous system (ENS), interstitial cells of Cajal (ICC), and smooth muscle cells (SMCs). Neuromuscular disorders resulting in gastroparesis are multifactorial in origin involving dysfunction at various levels of this complex interaction. For example, the pathogenesis of diabetic gastroparesis may involve vagal dysfunction, reduced neuronal nitric oxide synthase (nNOS) expression in the myenteric plexus, smooth muscle abnormalities, and deficits in ICC networks [1–8]. Given this complexity, it is perhaps not surprising that our current therapies, whether pharmacologic or device-based (electrical stimulation), fail to repair this functional interaction. An ideal approach would be to replace or replenish permanently impaired cells while maintaining the spatial and temporal function of the network. With our recent insights in stem cell biology, such therapies seem promising.

In this chapter, we discuss the progress that has been made discovering various stem cell populations and exploring which population may be most suitable for cell-based therapies. We focus on embryonic stem cells (ESCs) and induced-pluripotent stem (iPS) cells, CNS-derived neural stem cells (CNS-NSCs), enteric neural progenitors (ENPs) derived from the gut, and progenitors of ICCs.

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Embryonic Stem Cells and Induced Pluripotent Stem Cells

ESCs represent a pluripotent stem cell population capable of differentiating into all three germ layers. A major advantage of this stem cell population is their abundance due to ease of propagation and expansion. However, there are both ethical and scientific concerns associated with the use of ESC. Thus, a drawback of pluripotency is an increased potential to form teratomas and difficulty of differentiating to a desired cell fate [9]. Fortunately, "nudging" ESCs toward the desired lineage prior to transplantation appears to decrease tumorigenicity and improve engraftment [10]. There has been significant progress in defining techniques and protocols to induce ESCs toward a neural lineage [11–15]. More recently, several investigators have identified methods of inducing ESCs toward a neural crest (NC) phenotype from which the ENS is derived [16–19]. These ESC-derived NC cells are capable of colonizing explanted gut and differentiating into neuronal and glial cell types [17, 18]. Whether these ESC-derived NC cells would develop functionally relevant neuromuscular connections in vivo remains to be seen.

Recent discoveries that reprogramming differentiated cells with a minimal set of genes can generate pluripotent stem cells, termed iPS cells, offer an exciting new ESC-like population for cell-based therapies [20, 21]. This iPS cell technology avoids the ethical controversy surrounding ESCs and provides an accessible source of immunologically compatible stem cells for autologous transplantation. An initial concern of increased cancer risk due to transfection of the oncogene, *c-myc*, and genomic integration of retroviral vectors [22] has lessened with exclusion of *c-myc* from the gene cocktail and use of alternative transfection methods that avoid viral vectors [23–25]. Like ESCs, iPS cells will likely require "nudging" toward the desired lineage prior to transplantation. To this end, investigators have found protocols similar to those used for ESCs to differentiate iPS cells to neural lineage [26, 27]. Techniques to induce iPS cells into NC cells have also been identified [28]. iPS cells have been successfully transplanted into a rat model for Parkinson's disease and lead to functional improvement [29] suggesting that a similar approach may be applicable for ENS disorders. Recently, investigators have been able to directly convert fibroblasts to neurons by the addition of three genes [30]. It remains unclear whether a similar approach can be used to directly generate enteric neurons.

Neural Stem Cells and Enteric Neural Progenitors

Neural stem cells are a multipotent "adult" stem cell population that hold promise for cell-based therapies of the ENS. Unlike ESCs, NSCs are poised for a neural lineage and thus do not require "neural induction" prior to transplantation. They also hold lower potential for tumor formation. While adult stem cells may be propagated in vitro, they do not demonstrate similar long-term self-renewal as ESCs and eventually undergo senescence and crisis due to lack of telomerase activity [31].

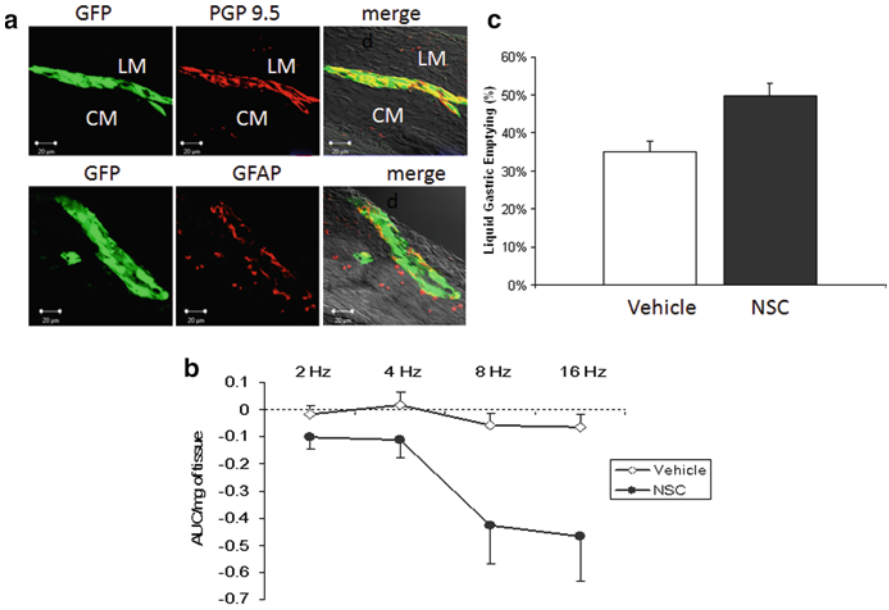

Fig. 33.1 Transplantation of CNS-NSCs in pylorus of nNOS-deficient mice restores gastric function. (**a**) 1 week post transplantation, GFP-expressing NSCs have engrafted into the host stomach and can be seen expressing both neuronal (*top*) and glial (*bottom*) markers. (**b**) NANC-induced relaxation of pyloric muscle in response to EFS was significantly increased in *nNOS−/−* mice 1 week post transplantation of CNS-NSCs compared to vehicle controls. (C) *nNOS−/−* mice transplanted with CNS-NSCs demonstrated increased gastric emptying of liquids compared with those transplanted with vehicle (Figure adapted from Micci, MA, et al. *Gastroenterology*, 2005). Used with permission

Thus, unlike ESCs or iPS, NSCs require an accessible source tissue to replenish their stocks.

CNS-NSCs have been identified and isolated from sites in the rodent brains, particularly the hippocampus and subventricular zone [32]. Although derived from the brain, CNS-NSCs have remarkable plasticity when transplanted to other tissues including the gut. They are capable of differentiating into nNOS-expressing neurons, a key neuronal subtype in the ENS, in vitro and after injection into rodent stomach [33]. We have also demonstrated that CNS-NSC can be nudged toward an enteric phenotype by coculturing in vitro with dissected longitudinal muscle and myenteric plexus (LM-MP) gut tissue [34]. Finally, when CNS-NSCs were transplanted into the stomach of nNOS-deficient (gastroparetic) mice [35], they partially restored gastric function after 1 week (Fig. 33.1) [36]. However, for unclear reasons, there was not sustained engraftment with significant cell loss 2–4 weeks after transplantation.

Despite the plasticity of CNS-NSCs, there is evidence that intrinsic differences between NSC populations may influence phenotypic fate following transplantation [37, 38]. Recently, NSCs have been isolated directly from the gut [37–47].

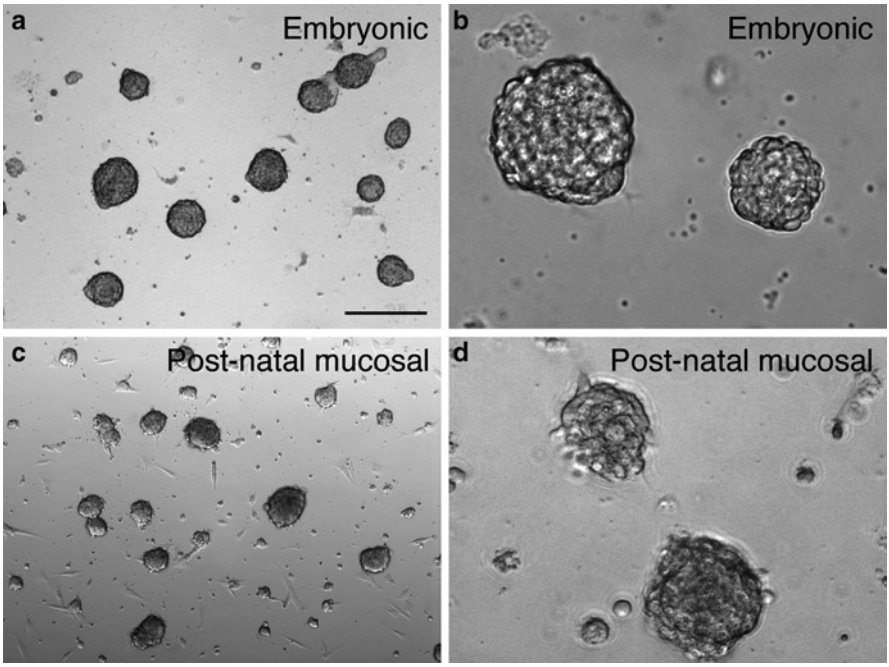

Fig. 33.2 Neurosphere-containing ENPs can be generated from biopsy specimens of postnatal human gut mucosa similar to those generated from human embryonic gut tissue. (**a**, low power, and **b**, high power) Phase-contrast images of embryonic gut tissue after 10 days in culture show characteristic neurospheres. (**c**, low power, and **d**, high power) Although smaller in size and less numerous, similar neurospheres were generated from biopsy specimens of postnatal gut tissue after 10 days in culture (Figure adapted from Metzger M et al. *Gastroenterology*, 2009) Used with permission

Thus, this population of stem cells, termed ENPs, may be more appropriate for regenerating the ENS than CNS-NSCs. ENPs isolated from embryonic and postnatal guts in rodents and humans are capable of colonizing explanted gut tissue and differentiating into ENS-appropriate neuronal and glial subtypes [37–47]. While these graft-derived neurons and glial cells have been shown to increase coordinated contractions and coordinated calcium waves in vitro [41], whether they form functionally significant networks in vivo has yet to be demonstrated. A recent study by Metzger et al. demonstrated that ENPs could be derived from mucosal biopsies taken during endoscopy [43], which provides a readily accessible source should this population of stem cells prove clinically useful (Fig. 33.2). It remains unclear whether there are behavioral differences in ENPs depending on where in the gut they come from and where they are transplanted. These questions need to be explored to help characterize the optimal subset of ENPs for transplantation into the stomach.

Progenitors of Interstitial Cells of Cajal

Loss of ICC has been implicated in the pathogenesis of gastroparesis [2, 5, 48–50]. While the exact mechanism remains unclear, in the case of diabetic gastroparesis, reduced insulin/insulin growth factor-1 signaling leads to decreased stem cell factor (SCF), a factor necessary for maintenance of ICCs [3, 51]. While restoration of these signaling pathways may serve as one approach for treating gastroparesis, regeneration of ICC networks by transplantation of ICC progenitors may be another. Kit^+ mesodermal precursors of ICCs have been characterized in embryos and in the immediate postnatal period [52–55]. More recently, progenitors of ICCs have been found in adult guts of rodents that are Kit^+ and express the adhesion marker CD34+ [56, 57]. Whether these progenitors can be isolated in human and represent a population amenable for transplantation remains to be seen.

Conclusion

Given the number of clinical trials using stem cells in various organs, physicians will likely start seeing cell-based therapies as part of their arsenal in the near future. It is likely only a matter of time before we find stem cell populations that are suitable candidates for treating neuromuscular disorders of the stomach. However, several obstacles remain with regard to clinical application [58]. What is the best method for delivering stem cells to the diseased tissue? Will they require endoscopic or surgical transplantation or can they reach the appropriate site following intravenous infusion? Do they require imbedding in a polymer or other matrix prior to transplantation? Will immunosuppressive therapies be required? Is prolonged engraftment possible or will repeat transplantations be required? Over time, will these stem cells be predisposed to tumor formation? Despite these hurdles, novel cell-based therapies for treating debilitating disorders, like gastroparesis, will hopefully be realized in the near future.

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