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Editorials

The evaluation of gastrointestinal function in diabetic patients

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Nowadays, a number of options are available for the assessment of gastric motor function. Thus, a global evaluation of gastric motor function may be obtained by tests of gastric emptying while regional function of the antrum and fundus may be evaluated by such techniques as antral manometry and the barostat, respectively. Traditionally, given widespread access to a variety of tests of gastric emptying, gastric dysmotility has been classified according to the patient's gastric emptying status. Accordingly, a given patient will be defined as having either delayed (gastroparesis) or accelerated (the dumping syndrome) gastric emptying. The limitations of this approach must be appreciated. Thus, it is evident from a variety of recent studies that gastric emptying rate and symptoms may not correlate. Secondly, and this is particularly relevant to diabetes mellitus, the same disease process may at different times lead to accelerated, delayed or normal emptying, in the same patient. These caveats notwithstanding , the clinical approach to gastric dysmotility usually begins with a gastric emptying test. Recently, electrogastrography has been proposed as an alternative test of global gastric motor function.

TESTING GASTRIC EMPTYING

For most clinicians, the scintigraphic assessment of the emptying rate of a liquid, solid or liquid/solid meal represents the primary investigational tool for the detection of gastric motor dysfunction in the diabetic, or in other clinical situations[1]. Scintigraphy is widely available and should be within the capabilities of any nuclear medicine department. By using different isotopes to label liquid and solid, one can either separately or simultaneously measure the rate of emptying of the liquid and solid components of the meal. Apart from the radiation exposure involved, this is a relatively noninvasive test. Importantly, in an area of medicine where most data is qualitative, scintigraphy provides truly quantitative data. Of the various meals available, the emptying rate of indigestible solids is the most sensitive in detecting gastric motor dysfunction but, in practice, a semi-solid meal such as chicken liver or scrambled eggs is more practical and appears to yield clinically relevant results in the diabetic population. It is important to be aware, however, that several technical factors may significantly influence the results of gastric emptying studies. For this reason, it is recommended that each laboratory defines its own normal values, obtained using its particular meal and imaging technique. As mentioned already, one also needs to be aware of the limitations of gastric emptying tests in the evaluation of symptoms, given the often imperfect correlation between symptoms and gastric emptying rate.

In normal individuals, the emptying curve for a liquid meal follows a simple exponential pattern. Liquid emptying is thought to reflect the effects of a pressure gradient generated by an increase in fundic tone. Autonomic neuropathy, such as occurs in diabetes, leads to a loss of fundic accommodation and can lead to an acceleration of liquid emptying. The normal emptying curve for solid meals is quite different. Initially, following solid ingestion, no emptying takes place (the lag phase). This lag phase corresponds to the time it takes for high amplitude antral contractions to grind down, or triturate, the solid particles of the meal until they are small enough to empty, suspended in the liquid phase, through the pylorus. Once trituration has been accomplished, solid emptying now follows an exponential pattern similar to that of the liquid phase. In diabetes, impaired antral contractility will lead to a prolonged lag phase and a significant prolongation of the total time for gastric emptying of solids. From gastric emptying curves, a number of parameters can be obtained and used to describe the rate of gastric emptying. These include the time it takes for half of the meal to be emptied ($t_{1/2}$) and the percentage of the meal that has been emptied at a given time, such as at 30 minutes, 1 hour or 2 hours.

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Indigestible solids are emptied only on return of the fasting motor pattern, long after meal ingestion. Phase 3, a band of high amplitude contractions which periodically sweeps through the gastrointestinal tract while fasting, empties indigestible particles. Typically, antral Phase 3 activity is lost in those with advanced autonomic neuropathy; thus, their predilection for bezoar formation.

Several alternatives have recently become available for the assessment of gastric emptying. Of greatest potential for clinical relevance is the description of a breath test based on ^{13}C octanoic acid[2]. As this is a stable isotope, radiation exposure is not involved and this test has the potential to become an office-based assessment of gastric motor function. Preliminary studies demonstrate good intra-individual reproducibility, though correlations with scintigraphy have not been perfect. Ultrasonography can evaluate antral contractile activity and can provide an indirect assessment of gastric emptying rate. It is, however, highly dependent on the presence of a skilled ultrasonographer, and provides a relatively brief assessment of antral motor function. Magnetic resonance imaging can provide, not only a global assessment of gastric emptying, but also detailed information on regional gastric function. Given the costs of this methodology, it is unlikely, however, that it will achieve widespread use as a test of gastric function. Others have evaluated impedance-based techniques in the assessment of gastric emptying. Again, it seems unlikely that these will achieve widespread use in clinical practice, despite promise in clinical research.

ELECTROGASTROGRAPHY

Electrogastrography has been available since the turn of the century for the assessment of gastric electrical activity. Recent advances in electronics have considerably simplified this approach to the assessment of gastric motor function. ECG-type electrodes, placed on the abdominal wall over the surface markings of the stomach, are used to record gastric electrical activity. Direct comparisons with serosal electrodes have demonstrated that surface electrogastrography accurately records a representation of gastric slow wave activity. Typically, electrogastrographic recordings are performed, first in the fasting state and then following administration of a meal. Two parameters are of primary importance, namely, the prevalence of abnormal gastric rhythms (such as bradygastria and tachygastria) and secondly, the change in the amplitude (or "power") of the EGG following meal ingestion. In normal circumstances, the EGG power should increase significantly following a meal.

Electrogastrography is a relatively simple and noninvasive technique[3]. Several studies have clearly demonstrated that it can reproducibly record a representation of the gastric slow wave and that it can detect dysrhythmias in the fasting and post-prandial states. This technique is, however, highly susceptible to motion artifact and is therefore only appropriate for recordings in relatively still individuals. Signal amplification and processing are required to produce a meaningful trace but this is now readily provided by commercially available equipment. The greatest limitation to electrogastrography now lies in its clinical application. Despite the suggestion that it could serve as a screening test of gastric function, few studies have compared the relative value of electrogastrography to other modalities such as scintigraphy, in the assessment of gastric motor function. Available data has indeed provided somewhat conflicting results. Until truly prospective studies examine the role of electrogastrography in detecting gastric motor dysfunction among patients with a variety of gastrointestinal symptoms and provide direct comparisons, not only in terms of efficacy, but also in terms of cost and patient acceptability, with other commonly available modalities, the place of electrogastrography will remain uncertain.

MANOMETRY

Antral motility serves to grind down or triturate the meal. In assessing antral motor function, an important goal, therefore, is to record the frequency, amplitude and propagation of antral contractions. As gastric emptying also depends, in large part, on coordination between the antrum, pylorus and duodenum, an assessment of coordinated antral, pyloric and duodenal activity has become a further goal of tests applied to this area. Ultrasonography, by detecting dynamic changes in antral diameter over time, can also assess antral contractile activity. Recordings, are, however, usually short-lived and are most successful with a liquid meal. They are also highly-dependent on a high level of skill of the interpreter. For this reason, manometry remains the primary technique for the direct assessment of antral contractile activity[4]. Most commonly, this is performed using a multi-lumen perfused catheter assembly passed via the nares and positioned under fluoroscopy, so that sensors simultaneously record intraluminal pressure activity from the antrum, duodenum and jejunum. To accurately record antro-pyloric activity, multiple closely-spaced sensors must be employed. Otherwise, orad displacement of the assembly, on meal ingestion, will lead to loss of contact between sensors and the antrum and the pylorus in the post-

prandial period and lead to uninterpretable artifact. Some have recommended the inclusion of a "sleeve" device to accurately monitor pyloric activity.

In order to record normal variations in both fasting and postprandial motor activity, some have advocated the use of a solid-state assembly. Because they do not rely on perfusion, these assemblies permit prolonged ambulatory recordings in the patient's usual environment. During fasting, several cycles of the migrating motor complex can be evaluated and the response to a number of meals can also be assessed. Most importantly, recordings can be performed during sleep and diurnal variations in motor patterns thereby assessed.

Regardless of which technique is employed, the primary goals of antroduodenal manometry are to assess antral and duodenal intraluminal pressure changes during fasting and in response to the meal and also to provide an assessment of antro-duodenal coordination. During fasting, motor activity in the antrum and duodenum is organized into the migrating motor complex. Each cycle of this complex comprises three phases which occur in sequence and continue to recur as long as the individual remains fasted. Each cycle lasts between 90 and 120 minutes and begins with Phase 1, or motor quiescence. This is followed by sporadic or irregular activity, Phase 2, which increases in intensity over time and culminates in the most distinctive phase of the migrating motor complex, Phase 3 (or the activity function), a band of uninterrupted rhythmic contractions which migrates slowly in an aboral direction along the length of the intestine. The migrating motor complex is initiated in the proximal small intestine and is typically associated with the onset of related activity in the stomach. Thus, for example, Phase 3 in the duodenum is associated with intense rhythmic contractile activity in the antrum. Following meal ingestion, the migrating motor complex is abolished and is replaced in the duodenum, by irregular but intense contractile activity (the postprandial motor response) and in the antrum by intense and relatively rhythmic high amplitude contractions. The duration of this postprandial response depends on the volume and caloric content of the meal and can vary anywhere from 2 to 6 hours. If no further food is ingested, the migrating motor complex returns. At night, migrating motor complex activity is usually most prominent but differs in that Phase 2 activity is markedly suppressed or even may be absent. The migrating motor complex at night, therefore, features Phase 3 complexes in relative isolation.

Antroduodenal manometry provides a direct and simultaneous measure of intraluminal pressure changes in the antrum and duodenum. Normal patterns of motor activity in the antrum and duodenum have now been defined and the manometric features of several disease states, including intestinal neuropathy, autonomic neuropathy and intestinal myopathy, have been defined. This is, however, an invasive test and requires prolonged (at least 4 hours) recordings during fasting and following meal ingestion. Several recent studies have emphasized the importance of intrinsic variations in normal patterns of antral and duodenal motor activity. Furthermore, the clinical significance of some reported "abnormal" patterns has been disputed. What then is the role of antroduodenal manometry in the assessment of gastric motor function. My own belief is that its primary role lies in the definition of normal motility among those in whom there is some suggestion of dysmotility, yet, less invasive studies have proven either inconsistent, uninterpretable or unexpectedly normal[5]. More problematic is the definitive diagnosis of the underlying cause of dysmotility in an individual patient. The sensitivity and specificity for manometry in the detection of neuropathy and myopathy have been questioned and the range of normal variation continues to be extended. I am most happy therefore, when manometry is entirely normal, in this situation, I feel confident in reassuring the patients and their physicians that there is no evidence of a primary motor disorder of the upper gastrointestinal tract. In the diabetic patient, manometry should rarely prove necessary. If symptoms are appropriate and screening tests such as scintigraphy, ultrasonography, other tests of gastric emptying or electrogastrography prove abnormal, then there should be no need to proceed to manometry. It should be reserved for those patients with symptoms suggestive of dysmotility and in whom the less invasive tests have proven inconclusive.

TESTS OF FUNDIC TONE

In contrast to the antrum, where high amplitude contractile activity is the most important feature of normal motor function, the proximal stomach mediates its motor function primarily through the generation of, and fluctuations in tone. Following meal ingestion, the fundus and proximal corpus undergoes vagally-mediated relaxation (receptive relaxation) to accommodate the meal. Subsequent fluctuations in proximal gastric tone mediate emptying of liquids and solid particles suspended in the liquid phase. Manometry is not valuable in the assessment of proximal gastric function and, until recently, this was a relatively unexplored area of the gastrointestinal tract. The development of the barostat, a technique which can record fluctuations in pressure or volume within an organ while the

other parameter is varied, has provided tremendous insights into the function of the proximal stomach in health and in a variety of disease states, including diabetic gastropathy. A clinical role for the barostat, or other techniques to assess compliance and accommodation, has not, as yet, been established.

GASTROINTESTINAL FUNCTION IN DIABETES

Diabetes may be associated with several effects on gastrointestinal motor function. These include gastroparesis, accelerated emptying of liquids, esophageal dysmotility, small intestinal dysmotility (including the pseudo-obstruction syndrome), delayed colonic transit, megacolon and fecal incontinence. For this reason, the term diabetic gastroenteropathy is to be preferred over the more commonly used term diabetic gastroparesis[6]. The latter has become outmoded and is indeed misleading as it suggests, firstly, the limitation of diabetic dysmotility to the stomach and, secondly, a preponderance of delayed gastric emptying. As already mentioned, liquid emptying may, in fact, be accelerated in diabetes. Reflecting this spectrum of dysfunction, there is a similarly wide-range of symptomatology in diabetic gastroenteropathy. Thus, esophageal dysfunction may lead to dysphagia, gastroparesis to nausea, vamiting, post-prandial fullness and abdo minal pain, and accelerated emptying to the features of the "dumping syndrome". Delayed intestinal and colonic transit may contribute to constipation and abdominal pain, and rapid intestinal transit to diarrhea. Gall bladder dysfunction may contribute to the prevalence of gallstones among these patients and neuropathy of the anal sphincter to incontinence.

Diabetic gastropathy is common and has been reported in up to 50% of patients with long-standing Type I diabetes mellitus. While most prevalent among those with Type I diabetes, it is clear from recent studies that gastropathy may be equally prevalent among those with Type II disease. In the general population, therefore, Type II related gastropathy will be most common. Gastropathy is usually, but not invariably, associated with an autonomic neuropathy. Consequences of gastropathy may include delayed emptying of solids and indigestible particles, rapid emptying of liquids, bezoar formation, malnutrition and weight loss.

Gastric emptying rate may also influence blood sugar control. Delayed gastric emptying may lead to hypoglycemia. If a meal is not emptied and insulin continues to be administered timed to a meal, hypoglycemia will result indeed, unexplained hypoglycemia should always lead to a suspicion of gastric emptying delay. It has been suggested that accelerated emptying could contribute to hyperglycemia, but recent studies suggest a relatively minor role for gastric emptying rate in the pathogenesis of postprandial hyperglycemia, among those with Type II diabetes and accelerated gastric emptying. Recent studies have also emphasized the variability of gastric emptying rate within a given diabetic patient. Thus, longitudinal studies have demonstrated that even in the same individual, gastric emptying may be, at different times, normal, accelerated or delayed[7]. This observation is extremely important in the assessment of therapeutic interventions. Furthermore, symptoms and gastric emptying rate correlate poorly in diabetics as in other patients with gastric dysmotility. While severely delayed emptying is consistently associated with delayed postprandial vomiting of undigested material, more modest degrees of delay bear an inconsistent relationship to such symptoms as early satiety, postprandial fullness, bloating, nausea and vomiting.

While tests of gastric emptying will remain, for the foreseeable future, the cornerstone of the evaluation of the diabetic with suspected gastric dysmotility, the clinician needs to be aware of their limitations. Normal gastric emptying does not exclude the stomach as the origin of the patient's symptoms, neither does delayed emptying, implicating the stomach as the cause of their symptoms. It is to be hoped that future studies will serve to further define relationships between symptoms, motor function and therapeutic response in this population. Diabetic gastropathy has traditionally been ascribed to the affects of extrinsic autonomic denervation. Recently, a role for hyperglycemia has been emphasized[6]. Studies involving normal individuals, as well as patients with diabetes mellitus, have illustrated the potential of hyperglycemia to delay gastric emptying, suppress the gastric component of the migrating motor complex, induce antral hypomotility and provoke gastric dysrhythmias, such as tachygastria. Furthermore, some recent work in an animal model has suggested the direct involvement of the enteric nervous system and gastrointestinal smooth muscle in diabetes. Finally, the acid-base and electrolyte abnormalities associated with this complication may lead to the development of ileus and gastroparesis during the course of ket oacidosis.

MANAGEMENT OF DIABETIC GASTROENTEROPATHY

In the approach to a patient with gastrointestinal dysmotility, several factors need to be addressed. These include the patient's nutritional status, pain management, prokinetic therapy, symptom suppression and the consideration of endoscopic or surgical approaches. Attention to nutritional status is of paramount importance in the management of these patients. Specific deficiencies should be identified and appropriate replacement instituted. In patients with gastroparesis, a low fat, low

residue diet should be instituted, given the known effects of these dietary factors on gastric emptying rate and, in the diabetic patient, on bezoar formation. Several options are now available, in terms of the form and mode of delivery of nutrition, for the patient with gastroparesis and gastroenteropathy. In the first instance, every attempt should be made to institute an adequate nutritional intake via the oral route, by the use of diets of variable composition and consistency, and the addition of appropriate oral supplements. For the patient who cannot tolerate or achieve an adequate caloric intake by the oral route, either in the short or in the long-term, a number of alternatives are available. In the short-term, enteral nutrition can be delivered via a nasogastric or nasoenteric tube. If oral intake cannot be reinstituted in the long-term, access to the gastrointestinal tract may be achieved through a gastrostomy or jejunostomy. One approach is to commence enteral feeding via the nasogastric or nasoenteric route on a trial basis. If this is tolerated, a jejunostomy is placed and continued in the long-term. In patients with severe gastroparesis, gastrostomy feeding may, by definition, prove unsuccessful. A gastrostomy may, however, help by allowing the patient to periodically "vent" the stomach and relieve distressing distention and bloating. Indeed, one approach to the management of patients with severe intractable gastroparesis is the simultaneous placement of a gastrostomy for venting and a jejunostomy for enteral feeding.

Several pharmacological agents are available for the management of patients with diabetic gastropathy. These include prokinetic and antiemetic agents, analgesics for pain management, agents that modulate sensation and other symptomatic remedies. The first prokinetic agents were non-specific cholinergic agonists such as bethanechol. While these agents were capable of stimulating gastric emptying, there is little evidence for efficacy in gastrointestinal motor disorders and their use was complicated by a high prevalence of side effects outside of the gastrointestinal tract. Metoclopramide, a dopamine antagonist, represented, therefore, a significant advance in prokinetic therapy[8]. Through its central actions, metoclopramide is an effective antiemetic, its peripheral actions lead to an acceleration of gastric emptying and promote esophageal motor activity. While metoclopramide has been shown to be effective, in the short-term, in the symp tomatic therapy of diabetic gastroparesis, its long-term use has been complicated by tolerance and a relatively high prevalence of central nervous and hyperpro lactinemia-related side effects. One advantage of metoclopramide, however, is its availability in several formulations, not only in tablet form but also as a suspension and for subcutaneous injection. Domperidone, another dopamine antagonist, does not cross the blood-brain barrier and is therefore not associated with the central nervous system, extrapyramidal side effects which have complicated metoclopramide use. It is, however, both an antiemetic and prokinetic and has been shown to be valuable in the symptomatic management of patients with diabetic gastroparesis[9]. It may cause hyperprolactinemia, however, and is not, as yet, approved for use in the United States.

Cisapride facilitates acetylcholine release in the enteric nervous system through a 5HT-4-mediated affect and has been shown to promote motor activity along the length of the gastrointestinal tract. It has been shown to accelerate liquid and solid emptying both in the short-term (6weeks) and to sustain this effect beyond one year[10,11]. It has, therefore, become an important component of the management of patients with gastroparesis and other gastrointestinal motor disorders. It is available in tablet and suspension form. Concerns have recently been raised regarding its potential to induce cardiac conduction and rhythm disturbances, especially when employed in conjunction with agents which modify its metabolism. This agent should not, therefore, be used in conjunction with agents which are known to inhibit cytochrome P-450 3A4 metabolism in the liver or in individuals predisposed to cardiac conduction or rhythm abnormalities.

Erythromycin acts as a motilin agonist to stimulate motor activity, primarily in the upper gastrointestinal tract. When given intravenously, erythromycin in low doses (50mg - 100mg) is a potent gastro-prokinetic and will effectively correct gastroparesis even in patients with refractory symptoms. Intravenous erythromycin has become, therefore, an important component of the management of patients with intractable diabetic gastroparesis, particularly in those who require hospitalization[12]. Oral erythromycin, even when used in suspension form, has proven disappointing. Whether this reflects the relatively poor bioaviability of this agent, or the development of tolerance, remains unclear. The latter seems less likely given the recent demonstration of the long-term efficacy of intraven ous administration for up to 18 months in patients with refractory gastroparesis[13]. Several related compounds are currently under investigation. The goal is to produce an agent with minimal antibiotic activity but similar prokinetic properties to erythromycin and which is effective when administered orally.

Among patients with diabetic gastropathy, nausea is a prominent symptom. Many of these patients describe awaking each morning with nausea and, in fact, find nausea a much more distressing

symptom than vomiting. For this reason, antiemetic agents assume an important role in the symptomatic treatment of these patients. Some of the prokinetic agents, such as metoclopramide and domperidone, have antiemetic actions whereas others, such as cisapride and erythromycin do not. In these latter circumstances, an antiemetic such as a phenothiazine derivative or a 5HT-3 antagonist should therefore be used in conjunction, and can often be used successfully on a p.r.n. basis. In choosing a particular antiemetic, attention should be paid to whether they are available in the appropriate formulation, as well as to their duration of action and, of course, cost.

SURGERY IN THE MANAGEMENT OF DIABETIC GASTROPARESIS

In general, there is no role for gastrectomy, either partial or complete in the patient with diabetic gastroparesis. Limited experience suggests a poor response to this approach, which is no surprise, given the relatively diffuse involvement of the gastrointestinal tract in this disorder. The surgical approach which has achieved significant importance is the simultaneous placement of a gastrostomy and jejunostomy in patients with intractable gastroparesis who are unable to tolerate p.o. intake and who have significant distention. Nowadays this can be most efficiently and effectively achieved by the laparoscopic approach. An endoscopic approach which involves the simultaneous placement of a gastrostomy and jejunostomy has also been advocated but experience has been inconsistent. Most recently, electrical pacing of the stomach, through electrodes surgically implanted on the surface of the stomach, using a cardiac-type pacemaker, has been shown, in pilot studies, to produce a dramatic reduction in symptoms and a variable impro vement in gastric emptying rate in intractable gastroparesis[14-16]. Randomized, prospective controlled studies are currently in progress and results a re eagerly awaited.

THE APPROACH TO GASTRIC DYSMOTILITY IN DIABETIC PATIENTS

In this review, the status of currently available tests for the evaluation of gastric motor function has been discussed. Limitations have been highlighted and, in particular, the often-times poor correlation between symptoms and objective evidence of motor dysfunction emphasized. How should the clinician approach the evaluation and management of the patient with diabetes who has symptoms suggestive of dysmotility Firstly, mindful of the non-specificity of symptoms, the clinician should ensure that mucosal or mechanical causes have been ruled out. In particular, consideration should be given to peptic ulcer disease, gastro-esopha geal reflux disease and low-grade intestinal obstruction. Medications should be carefully reviewed for iatrogenic causes of nausea and vomiting and the possible contribution of psychological factors, and depression, in particular, borne in mind. If, at this stage, symptoms remain unexplained, two options are available. One begins with a screening test of gastric function such as gastric emptying scintigraphy (or electrogastrography) and then decides on further therapy based on its results. The second approach is to initiate empiric therapy with a prokinetic or prokinetic/anti-emetic combination. Testing, in this approach, is limited to those who fail to respond to therapy. More detailed and invasive tests of motor function such as manometry should be reserved for those with persisting and disabling symptoms who do not respond satisfactorily to empiric therapy.

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