Wireless Motility Capsule Test in Children with Upper Gastrointestinal Symptoms

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Objective To compare scintigraphic gastric emptying and antroduodenal manometry (ADM) studies with the wireless motility capsule test in symptomatic pediatric patients.

Study design Patients aged 8-17 years with severe upper gastrointestinal symptoms (ie, nausea, vomiting, retching, abdominal pain) referred for ADM were recruited. A standardized protocol for ADM was used. On a different day, participants were given a standardized meal and then swallowed the wireless motility capsule. A wireless receiver unit worn during the study recorded transmitted data. If not performed previously, a 2-hour scintigraphic gastric emptying study was completed at the time of ADM testing.

Results A total of 22 patients were recruited, of whom 21 had complete scintigraphic gastric emptying study data and 20 had complete ADM data. The wireless motility capsule test had 100% sensitivity and 50% specificity in detecting gastroparesis compared with the 2-hour scintigraphic gastric emptying study. The wireless motility capsule test detected motor abnormalities in 17 patients, compared with 10 detected by ADM. Dichotomous comparison yielded a diagnostic difference between ADM and the wireless motility capsule test ($P < .01$). Migrating motor complexes were recognized in all patients by both ADM and the wireless motility capsule test. The wireless motility capsule test was well tolerated in all patients, and there were no side effects.

Conclusion In symptomatic pediatric patients, the wireless motility capsule test is highly sensitive compared with scintigraphic gastric emptying studies in detecting gastroparesis, and seems to be more sensitive than ADM in detecting motor abnormalities. *(J Pediatr 2013;162:1181-7)*.

Children with chronic, severe gastrointestinal (GI) symptoms, such as vomiting, early satiety, abdominal distension, and nausea, represent a diagnostic challenge. Diagnosis of the pathophysiological abnormality underpinning these symptoms is often attempted through various methods, including scintigraphic gastric emptying studies and antroduodenal manometry (ADM). A new approach, using a wireless motility capsule, offers the opportunity to evaluate patients in the pediatric age using a relatively noninvasive and inexpensive technology.

Only a few studies are available for diagnosing stomach and small bowel motility disorders. The scintigraphic gastric emptying study is considered the standard test for measuring gastric emptying time (GET). Gastric emptying of solids is tested using one of several protocols in which a radiolabeled standardized meal is given and measurements of the percentage of gastric retention of the meal are obtained at different time intervals. The radiation exposure is equivalent to 1-2 chest radiographs, and the studies can take up to 4 hours. ADM is used to evaluate suspected upper GI motility disorders. Using a catheter with serial pressure sensors inserted intranasally, this test can measure contraction amplitude and propagation, evaluating distal gastric and proximal small bowel motility. Based on the pattern of pressure measurements, ADM may clarify whether a subset of gastric emptying disorders is myopathic-predominant or neuropathic-predominant. At present, ADM remains restricted to few specialized pediatric centers, however.

The wireless motility capsule test measures intraluminal pressure, temperature, and pH, and allows calculation of transit times in the different segments of the GI tract, including GET. Similar to manometric studies, it can record pressure profiles within defined segments of the GI tract. To date, experience in the use of the wireless motility capsule test in pediatrics is very limited; however, the wireless motility capsule has been studied extensively in adults and has received US Food and Drug Administration approval for use in the diagnosis of gastroparesis and constipation.[1-5] The aims of the present study were to evaluate the information obtained by the wireless motility capsule test and the information provided by a clinically indicated scintigraphic gastric emptying study, and to compare the results of ADM and wireless motility capsule

ADM	Antroduodenal manometry
GET	Gastric emptying time
GI	Gastrointestinal
MMC	Migrating motor complex
SBTT	Small bowel transit time

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testing performed in pediatric patients presenting to a specialty motility center with symptoms suggestive of an upper GI tract motility disorder.

Methods

In a single-center study, children aged 8-17 years with severe upper GI symptoms (ie, nausea, vomiting, retching, abdominal pain) referred for ADM studies underwent a wireless motility capsule test. The scintigraphic gastric emptying study was done when clinically indicated either at the time of the ADM or at a different time within 1 year of the wireless motility capsule test. Any medications that affected GI motility and gastric pH were discontinued at least 3 days before each study. The patient had to be able to swallow the wireless motility capsule. Exclusion criteria included parenteral nutrition because of the inability to tolerate enteral feedings (owing to a high likelihood that the capsule could not be emptied to the stomach); evidence of strictures, including inflammatory bowel disease; a history of esophageal or gastric surgeries, such as transesophageal fistula, fundoplication, or gastrojejunostomy; and a history of gastric bezoar. The study protocol was approved by the Institutional Review Board at Nationwide Children's Hospital.

ADM

ADM was performed using was a water-perfusion system (Medical Measurement Systems, Enschede, The Netherlands). The catheter had 8 pressure sensors located 3 cm apart. The catheter was placed transnasally by interventional radiology. There were 2-3 measuring sites in the stomach and 5-6 sites in the small intestine. The test consisted of a 4-hour fast and a 1-hour postprandial period. The meal given during the test varied based on patient preference.

Scintigraphic Gastric Emptying Study

The scintigraphic gastric emptying study was performed after an overnight fast. The patient was given a standardized meal (2 eggs, toast, jelly), with the eggs labeled with 0.5-1 mCi of Tc-99m. The study protocol at our institution included an initial 3-minute scan and a 2-hour follow-up scan. The scintigraphic gastric emptying study definition of gastroparesis used was >50% of the ingested radioactive material remaining in the stomach at 120 minutes.

Wireless Motility Capsule Test

The wireless motility capsule test was performed according to published guidelines with a standard meal of eggs, toast, and jellyl or a SmartBar (SmartPill Corp, Buffalo, New York) immediately after ingestion of the capsule.[1] The wireless motility capsule test and ADM were performed on consecutive days.

Total transit time was measured as the time between ingestion of the capsule and either a drop in temperature or an abrupt loss of signal, and was confirmed by the patient's diary. GET was calculated from the time of wireless motility capsule ingestion to pyloric passage, as determined by an abrupt ≥2 pH unit increase from the lowest postprandial value to at least 4 that did not decrease to <4 for >10 minutes at any subsequent time. Small bowel transit time (SBTT) was defined as the time between the passage of the capsule into

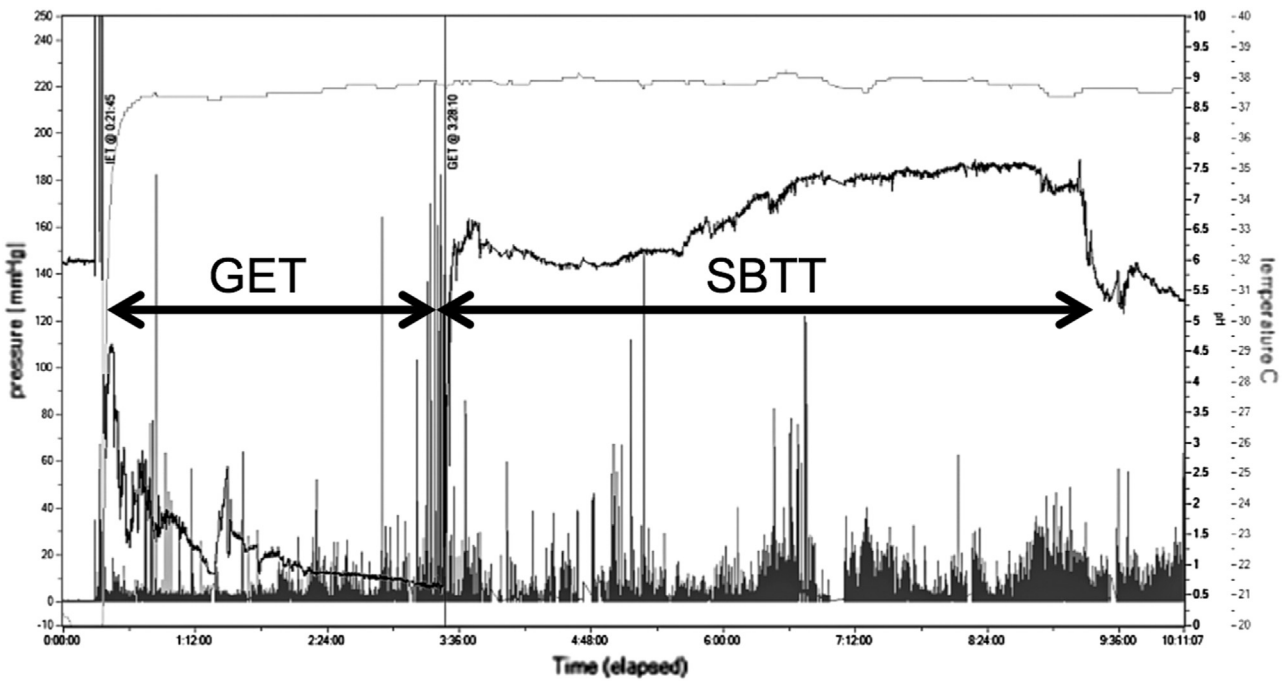

Figure. Example wireless motility capsule test tracing measuring GET and SBTT. The GET is measured by subtracting the time from the first sharp rise in pH from the initial ingestion time. The SBTT is measured by subtracting the time from first drop in pH after entering the small bowel from the GET.

the small bowel to when the capsule entered the cecum (Figure).[6] The definition of gastroparesis used in the wireless motility capsule test was persistence of the capsule in the stomach at 300 minutes after ingestion.[5] Prolonged SBTT was defined as persistence of the capsule in the small bowel for >6 hours after entering the small bowel.[2]

The ranges for GET and contractility parameters have not been established in the pediatric population; however, because our patients were predominantly teenagers, adult standards were used. A GET of ≤5 hours was considered normal, 5-12 hours as indicative of mild gastroparesis, and >12 hours as severe gastroparesis.[5,7] Contraction frequency, area under the receiver operating characteristic curve, and motility index parameters were calculated 1 hour before (gastric contractility) and 1 hour after (small bowel contractility) gastric emptying. Windows with >20% data loss were not included in the analysis. Data corruption occurred when the receiver was out of range of the patient for extended periods.

The contractility parameters obtained by the wireless motility capsule test were compared against normal ranges reported in an adult cohort to identify the percentage of subjects diagnosed as normal, with mild gastroparesis, or with severe gastroparesis had gastric contractility and/or small bowel contractility abnormalities. Ranges for abnormal contraction frequency, area under the receiver operating characteristic curve, and motility index were <29 ct/hour, <1358, and <9.82, respectively, in the gastric region and <36 ct/hour, <1456, and <10.57, respectively, in the small bowel region.[5]

Wireless motility capsule test pressure data were also analyzed for the presence of high-amplitude contractions suggestive of migrating motor complex (MMC) activity using methods described in a previous adult cohort study.[8] Pressure was analyzed during the fasting period, defined as 2 hours after ingestion of the standard wireless motility capsule test meal until the resumption of a normal diet routine at 6 hours postingestion, providing up to 4 hours of analysis. The entire analysis period was subsequently divided into gastric and small bowel windows based on GET. Pressure peaks were compared against amplitude thresholds of 27.9 mmHg in the gastric region and 26.7 mmHg in the small bowel region. Windows that did not have at least 1 contraction that met the respective threshold were considered to possibly not have an MMC.

Statistical Analyses

Calculations for scintigraphic gastric emptying study and wireless motility capsule test transit time results were done with Spearman rank correlation and Fisher exact test analysis of the variables. The diagnostic results for wireless motility capsule test and ADM contractility parameters were compared using a dichotomous χ^2 test.

Results

Twenty-two patients were enrolled in the study. Complete scintigraphic gastric emptying study data and wireless motility capsule test GETs were obtained in 21 of these patients. One patient had missing wireless motility capsule test data at the time of gastric emptying.

Twenty patients completed both the ADM and wireless motility capsule studies. One patient had missing wireless motility capsule test data at the time of gastric emptying, and 1 patient had missing ADM data. The 20 patients who completed both studies included 17 females and 3 males, aged 9-17 years (mean age, 14.3 years). Predominant symptoms were nausea, vomiting, early satiation, abdominal pain, and constipation (Table I). The ADM studies identified 10 patients with normal motility, 8 patients with evidence of rumination, 2 patients (1 with rumination as well) with neuropathic changes in either the antrum or duodenum (hyperactivity and nonpropagated clusters), and 1 patient with antral hypomotility (Table II).

Comparison of Wireless Motility Capsule and Scintigraphic Gastric Emptying Studies

Twelve patients completed the scintigraphic study at the same time as the wireless motility capsule test. The remaining 9 underwent scintigraphic studies at a different time than the wireless motility capsule test, with a range of 256 days before to 33 days after the study (mean, 110 days before). Nine patients had delayed gastric emptying identified by scintigraphy, and 15 patients had delayed gastric emptying identified by the wireless motility capsule test (Table II). Among the patients with complete wireless motility capsule test data, 6 had a prolonged SBTT,

Table I. Patient demographics and presenting symptoms by final wireless motility capsule test GET diagnosis

Patient	Sex	Age, years	Symptoms
Normal			
1	M	13	**Abdominal pain**, constipation, abdominal distention
2	F	17	**Nausea**, abdominal pain, headache
3	F	12	**Nausea**, constipation, abdominal distention, vomiting
4	F	15	**Abdominal distention**, anxiety
5	M	9	**Nausea**, vomiting, abdominal pain, diarrhea
6	F	10	**Vomiting**, abdominal pain, constipation, nausea
Mild gastroparesis			
7	F	14	**Vomiting**, abdominal pain, diarrhea
8	F	16	**Nausea**, vomiting, abdominal pain, constipation
9	F	17	**Abdominal pain**, nausea, postprandial vomiting
10	F	14	**Nausea**, abdominal pain, diarrhea, abdominal distention
Severe gastroparesis			
11	M	15	**Nausea**, vomiting, abdominal pain, constipation, abdominal distention
12	F	13	**Postprandial nausea and vomiting**, abdominal pain, headache
13	F	14	**Abdominal pain**, vomiting
14	F	15	**Vomiting**, fatigue
15	F	13	**Nausea**, vomiting
16	F	17	**Abdominal pain**, abdominal distention
17	F	16	**Nausea**, vomiting, constipation, headache
18	F	16	**Nausea**, vomiting, abdominal pain, diarrhea
19	M	17	**Nausea**, vomiting, abdominal pain, diarrhea
20	F	14	**Nausea**, abdominal pain, constipation, headache
21	F	14	**Vomiting**

Predominant symptoms are in bold type.

Table II. Contractility parameters by the wireless motility capsule test for normal, mild gastroparetic, and severe gastroparetic patients and their ADM final diagnoses, scintigraphic gastric emptying percentages at 2 hours, and SBTT

Patient	Gastric contractility	SB contractility	ADM	Scintigraphic gastric emptying at 2 hours, %	SBTT (hours: minutes)
21	Missing data	Missing data	Rumination	67	1:03
Normal GET					
1	No abnormalities	No abnormalities	Normal ADM	79	5:45
2	Abnormalities	Abnormalities	Normal ADM	97	3:41
3	No abnormalities	Abnormalities	Normal ADM	68	5:22
4	Abnormalities	Abnormalities	Normal ADM	57	5:01
5	No abnormalities	No abnormalities	Normal ADM	97	3:24
6	No abnormalities	No abnormalities	Rumination	84	2:37
Mild prolonged GET					
7	No abnormalities	No abnormalities	Hyperactivity/rumination	89	3:54
8	No abnormalities	No abnormalities	Rumination	43	15:45
9	No abnormalities	No abnormalities	Neuropathic dysmotility	43	5:20
10	No abnormalities	No abnormalities	Normal ADM	43	6:15
Severely prolonged GET					
11	Abnormalities	Abnormalities	Rumination	34	5:31
12	Abnormalities	No abnormalities	Rumination	62	5:44
13	No abnormalities	No abnormalities	Rumination	22	0:47
14	Abnormalities	No abnormalities	Rumination	74	8:40
15	Missing data	Missing data	Normal ADM	72	5:32
16	Abnormalities	No abnormalities	Antral hypomotility disorder	42	7:00
17	Abnormalities	Missing data	Normal motility	30	8:04
18	No abnormalities	No abnormalities	Normal motility	77	5:52
19	Missing data	No abnormalities	Rumination	47	7:21
20	Missing data	Missing data	Normal motility	43	3:48

SB, small bowel.

ranging from 7 to 16.75 hours. The wireless motility capsule test had a sensitivity of 100% and specificity of 50% for detecting gastroparesis compared with the scintigraphic gastric emptying study at 2 hours. There was a positive association between the 2 studies, with $P < .02$ and Spearman rank correlation of 0.5 indicating a moderate correlation. There was also statistically significant associations between delayed wireless motility capsule test SBTT and delayed scintigraphic gastric emptying study and wireless motility capsule test GET (both $P < .05$) (Table II).

Comparison of Wireless Motility Capsule Test and ADM Results

In 20 patients who underwent both the wireless motility capsule test and ADM, 14 (70%) had an abnormal GET on the wireless motility capsule test, and the other 6 had a normal capsule emptying time. Of those with abnormal GET, 4 patients were classified with mild gastroparesis and 10 were classified with severe gastroparesis.

Patients with Normal GET. Of the 6 patients with normal GET, 5 had a normal ADM result (Table II), and 1 was diagnosed with rumination and no other ADM abnormality. Despite the normal GET and ADM findings, 2 of these 6 patients had abnormal gastric and small bowel contractility parameters, and 1 had isolated abnormal small bowel contractility; thus, 3 of 6 (50%) had a contractility abnormality (Table II).

Patients with Mild Delay in GET. All 4 patients with mild gastroparesis had normal gastric and small bowel contractility data, but 3 of the 4 had abnormalities (hyperactivity/rumination, rumination, and neuropathic pattern) detected by ADM (Table II).

Patients with Severe Delay in GET. Ten patients had severe gastroparesis detected by the wireless motility capsule test, of whom 7 could be evaluated for gastric contractility (3 could not be evaluated owing to missing data) and 7 could be evaluated for small bowel contractility (3 could not be evaluated owing to missing data). Overall, 8 patients were evaluable by the wireless motility capsule test in at least 1 contractile window (Table II). Five of these 8 patients (62.5%) had abnormal contractility parameters, all 5 with gastric contractility abnormalities and 1 also with small bowel contractility abnormalities (Tables II and III). Only 2 of the 8 patients with severe gastroparesis had normal gastric and small bowel contractility. One of these 2 patients had a normal ADM vresult, and the other was diagnosed with rumination with no other ADM abnormality. Of the 10

Table III. Contractile abnormalities in the antrum and duodenum detected by the wireless motility capsule test and ADM in groups with delayed GET of varying severity

	Wireless motility capsule test		
GET	Abnormal gastric	Abnormal small bowel	ADM*
Normal (n = 6), n (%)	2 (33.3)	3 (50)	0 (0)
Mild gastroparesis (n = 4), n (%)	0 (0)	0 (0)	2 (50)
Severe gastroparesis (n = 8), n (%)	5 (62.5)	1 (12.5)	1 (12.5)

*Excluding rumination.

patients with severe gastroparesis detected by the wireless motility capsule test, the ADM was normal in 4 and abnormal in 6, 1 with an ADM diagnosis of antral hypomotility and 5 with rumination.

Diagnostic Yield. Overall, 50% of the ADM studies were abnormal in our 20-patient cohort. Of the 10 abnormal ADM studies, 7 were cases of rumination only. In the 20 patients, 17 (85%) had abnormal contractility parameters in either the gastric window or small bowel window on the wireless motility capsule test and/or an abnormal GET. A dichotomous comparison yields a significant diagnostic difference between ADM and the wireless motility capsule test ($P < .01$) if rumination detected by ADM is considered abnormal. However, if rumination (a disorder believed to be functional) is excluded, then only 3 of 20 cases (15%) had an abnormal ADM result. This change also yields a diagnostic difference between the 2 tests ($P < .01$).

Presence of MMCs by ADM and the Wireless Motility Capsule Test. On ADM, MMCs were detected in all patients studied. On the wireless motility capsule test, contractility patterns previously correlated with MMCs[8] were also seen in all patients.

Tolerability and Safety of the Wireless Motility Capsule Test. The wireless motility capsule test was well tolerated in all subjects, and there were no side effects in any of the patients.

Discussion

Although several methods for assessing pediatric GI motility are currently available, most require a lengthy procedure, are invasive, or include exposure to radiation. Manometry studies typically take several hours, can be uncomfortable, and are not widely available. Scintigraphic gastric emptying studies are available at most pediatric GI centers, but there is no consensus as to the study protocol or the definition for diagnosing gastroparesis in children, which differs from that in adults.[9] Our study explores an alternative technique for diagnosing pediatric GI motility disorders using a test that is more convenient for the patient and the medical provider, is less invasive, and involves no radiation.

We found a moderate correlation between scintigraphic gastric emptying study results and the time that the wireless motility capsule was present in the stomach. There was excellent sensitivity, with the wireless motility capsule test not missing any cases of gastroparesis diagnosed by scintigraphic gastric emptying studies. This sensitivity is higher than that reported in a recent adult study.[1] The wireless motility capsule test did diagnose more cases of gastroparesis compared with scintigraphic gastric emptying studies, however, yielding a moderate specificity for detecting gastroparesis if scintigraphic gastric emptying studies are considered the gold standard. There are several possible reasons for this discrepancy. In these children, the scintigraphic gastric emptying studies were performed for only 2 hours, not for 4 hours, because there are no standards for 4-hour gastric emptying studies in children. Allowing the additional 2 hours might have identified more cases of gastroparesis,[10] as suggested by the adult literature. Correlation is much higher for 4-hour gastric emptying study results than for 2-hour results, because emptying of the capsule is more closely related to nearly complete emptying of the meal (<10%). At 2 hours, there is much greater fluctuation of the potential projected time needed to empty a meal.[1] However, a recent study evaluating 1499 patients with scintigraphic gastric emptying study data found good correlation of gastric retention in patients at 2 hours compared with 4 hours.[11] The fact that the wireless motility capsule test did not miss any cases of gastroparesis compared with the gold standard suggests that the wireless motility capsule test may be a good screening tool for gastroparesis in pediatric populations. The wireless motility capsule test is already validated for evaluation of suspected gastroparesis in adults.[12]

Another interesting finding in this study is the association between gastroparesis and delayed SBTT. Of our 6 patients with delayed SBTT, 5 had gastroparesis on scintigraphic gastric emptying studies, and all 6 had gastroparesis on the wireless motility capsule test. In previous studies in adults who completed both scintigraphic gastric emptying and the wireless motility capsule studies, no association was found between gastroparesis and delayed SBTT.[1] This was true both in patients with diabetic gastroparesis and in patients with nondiabetic gastroparesis. The reasons for referral to a motility center differed greatly between the adults in that study and the patients in our study, however. Several wireless motility capsule studies have shown that many patients with symptoms of dysmotility in one GI region often have abnormalities in other regions as wells.[2] Kuo et al[12] examined wireless motility capsule test data in patients with clinically suspected gastroparesis and found that 20% had delayed SBTT as well. This finding suggests that patients with upper GI symptoms can have coexisting gastric and small bowel transit abnormalities, both of which may be contributing to symptoms.

Currently, ADM and colonic manometry are the most widely accepted methods for measuring pressures through the upper and lower GI tract. Although the wireless motility capsule test does not measure contractility in the same manner as ADM owing to its free-floating nature, it is possible that the wireless motility capsule test could be a reliable screening tool for contractile abnormalities as well. In addition to detecting contractile abnormalities, the wireless motility capsule test's ability to determine transit times provides a second variable for diagnosing symptomatic patients that ADM lacks.

In symptomatic patients, even in those with normal gastric emptying and normal ADM, a subset might have contractility abnormalities. In the present study, 50% of the patients with normal GET and ADM findings had gastric and/or small bowel contractility abnormalities identified by the wireless motility capsule test. This abnormal contractile response was apparently not severe enough to cause a delay on scintigraphic gastric emptying studies. The abnormalities were not

detected by the ADM either. Thus, ultimately there was a group of symptomatic patients in whom traditional testing (scintigraphic gastric emptying studies and ADM) yielded normal results but the wireless motility capsule test was able to detect a physiological abnormality, which might account for the symptoms. This increased diagnostic yield could be clinically helpful in directing treatment and merits further investigation.

Gastric and/or small bowel contractility abnormalities were common in our patients with severe gastroparesis (62.5%). This is consistent with the literature in adult patients with severe gastroparesis, which reports an increased frequency of contractility abnormalities.[5] Rumination is a diagnosis confirmed by ADM, but wireless motility capsule test results suggest that contractility abnormalities may be common in these patients, particularly if gastric emptying is severely delayed. Thus, rumination, gastroparesis, and contractility abnormalities often coexisted in our patients. Future studies are need to investigate whether the contractility disorders contribute to function and/or symptoms.

When comparing ADM and the wireless motility capsule test, wireless motility capsule test contractility was abnormal in 1 of 3 patients with an abnormal ADM excluding rumination and in 5 of 10 patients with an abnormal ADM including rumination. ADM excluding rumination was abnormal in 1 of 8 patients (12.5%) with abnormal contractility identified by the wireless motility capsule test. When rumination is included, ADM was abnormal in 4 of 8 patients (50%). Thus, it may be speculated that the wireless motility capsule test is more sensitive than ADM for diagnosing motor abnormalities in the upper GI tract. However, these results also suggest that the 2 tests may examine different aspects of GI function and may yield complementary information, particularly in patients with a prolonged GET. The literature includes early encouraging results regarding the utility of contractility measurements, including the detection of decreased contraction frequency in the stomach in gastroparesis,[3] blunting of the small bowel fed response in gastroparesis,[13] and abnormal small bowel pressure parameters when both gastric emptying study and GET are normal.[14] The present study provides another example of the abnormal contractility measurements frequently seen in symptomatic patients.

MMCs were present in all patients studied by ADM, and a contractility pattern considered equivalent to MMCs also was detected in all patients. In this study, the percentage of false-positive results could not be determined, given that no cases of absent MMC were detected by ADM. An interesting scenario would have been a patient with severe myopathy and no MMCs by ADM, to examine whether the wireless motility capsule test would also show poor contractility with no MMCs by amplitude criteria; however, we did not have a case like this in our series.

This study has several limitations. The first is its small sample size. A larger number of patients would help strengthen the study's power and possibly increase the correlation between results of the scintigraphic gastric emptying studies and of the wireless motility capsule test. The correlation likely also would have been stronger had a 4-hour scintigraphic gastric emptying study been used. Another limitation is the lack of healthy pediatric controls; however, the aim of this study was to compare the findings from the current gold standard studies (ADM and scintigraphic gastric emptying) with those from a new device. Thus, having a control group was not as important, because this study was comparing 2 diagnostic tests against each other to evaluate their similarity. The patients in our series had a variety of symptoms of sufficient severity to warrant referral to a motility center. A third limitation is the difference in the timing of the scintigraphic gastric emptying studies compared with the wireless motility capsule test, and the fact that none of the patients underwent concomitant wireless motility capsule and ADM testing. This limits the concordance of data when comparing the results of scintigraphic gastric emptying studies and ADM with those of the wireless motility capsule test.

In summary, we studied symptomatic adolescents using scintigraphic gastric emptying studies, ADM, and the wireless motility capsule test, with the goal of identifying the diagnostic yield of each test and exploring how they compare in detecting motor abnormalities in the GI tract. Studies of larger numbers of patients with symptoms suggestive of upper GI dysmotility, with comparison with healthy adolescents, are needed to further investigate the correlation between ADM and wireless motility capsule test, better understand the significance of the test findings regarding pathophysiology of the disease, and identify the optimal pediatric patient population for this emerging technology. ■

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50 Years Ago in *The Journal of Pediatrics*

A Note on Studies of Salt Excretion in Sweat: Relationships between Rate, Conductivity, and Electrolyte Composition of Sweat from Patients with Cystic Fibrosis and from Control Subjects

Gibson, LE, di Sant'Agnese, PA. J Pediatr 1963;62:855-67

The sweat test is inseparably linked to cystic fibrosis (CF). In fact, early observations of high salt losses in the sweat of patients with CF not only led to the development of the sweat chloride test in 1959, but also attracted researchers to work on sweat glands to search for the primary disease defect. Using a highly innovative approach, Gibson and Sant'Agnese built a device to demonstrate in vivo a linear relation between sweat secretion and salt excretion. Knowing that sweat glands consist of a coil secreting a precursor fluid and a tubule system to reabsorb salt, the authors concluded that the precursor fluid (and not tubular fluid re-absorption) is different and, thus, defective in CF. Today, we know that defective re-absorption of salt in the sweat tubule system is responsible for elevated sweat sodium and chloride concentrations in patients with CF. The precursor fluid, the primary fluid secreted in the coil of sweat glands, is isotonic and unaltered in CF.

Over the past 5 decades, knowledge of sweat gland physiology has advanced greatly. Epithelial impermeability to chloride ions in the sweat tubule was identified as the primary defect in CF in 1983, well before the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene was first cloned in 1989. Although the sweat test remains the gold standard used to diagnose CF, we recognize its limitations in identifying patients with milder or atypical disease.

We have developed a method assaying *CFTR* as a secretory channel following inhibition of the cholinergic pathway and sweat stimulation with β-adrenergic drugs.[1] This β-adrenergic secretory sweat test distinguishes between healthy controls, heterozygote carriers, and subjects with milder CF variants, thus extending the spectrum for identifying CFTR dysfunction. As was the case 50 years ago, detailed understanding of sweat gland physiology continues to further our understanding of CF pathobiology, which is again of particular interest today in light of emerging novel therapies modulating expression and function of the CFTR protein.

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