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**RELATING GASTRIC SCINTIGRAPHY AND SYMPTOMS TO MOTILITY CAPSULE
TRANSIT AND PRESSURE FINDINGS IN SUSPECTED GASTROPARESIS**

SHORT RUNNING TITLE: MOTILITY CAPSULE FINDINGS IN GASTROPARESIS

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For the NIDDK Gastroparesis Clinical Research Consortium (GpCRC)

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ABSTRACT

Background: Wireless motility capsule (WMC) findings are incompletely defined in suspected gastroparesis. We aimed to characterize regional WMC transit and contractility in relation to scintigraphy, etiology, and symptoms in patients undergoing gastric emptying testing.

Methods: 209 patients with gastroparesis symptoms at NIDDK Gastroparesis Consortium centers underwent gastric scintigraphy and WMCs on separate days to measure regional transit and contractility. Validated questionnaires quantified symptoms.

Key Results: Solid and liquid scintigraphy were delayed in 68.8% and 34.8% of patients; WMC gastric emptying times (GET) were delayed in 40.3% and showed 52.8% agreement with scintigraphy; 15.5% and 33.5% had delayed small bowel (SBTT) and colon transit (CTT) times. Transit was delayed in ≥ 2 regions in 23.3%. Rapid transit was rarely observed. Diabetics had slower GET but more rapid SBTT versus idiopathics ($P \leq 0.02$). GET delays related to greater scintigraphic retention, slower SBTT, and fewer gastric contractions ($P \leq 0.04$). Overall gastroparesis symptoms and nausea/vomiting, early satiety/fullness, bloating/distention, and upper abdominal pain subscores showed no relation to WMC transit. Upper and lower abdominal pain scores ($P \leq 0.03$) were greater with increased colon contractions. Constipation correlated with slower CTT and higher colon contractions ($P = 0.03$). Diarrhea scores were higher with delayed SBTT and CTT ($P \leq 0.04$).

Conclusions & Inferences: WMCs define gastric emptying delays similar but not identical to scintigraphy that are more severe in diabetics and relate to reduced gastric contractility. Extragastric transit delays occur in $>40\%$ with suspected gastroparesis. Gastroparesis symptoms show little association with WMC profiles, although lower symptoms relate to small bowel or colon abnormalities.

Key Words: Gastric emptying, scintigraphy, small bowel and colon transit, contractility

KEY POINTS

- Wireless motility capsule (WMC) findings in suspected gastroparesis and relations to symptoms have been poorly defined.

- Evaluation of patients with gastroparesis symptoms revealed gastric emptying delays with WMCs that were similar to scintigraphy, were related to reduced contractility, and were often associated with extragastric or generalized transit delays; symptoms correlated poorly with WMC profiles.
- These findings provide insight into motor abnormalities in gastroparesis pathogenesis and form a basis for future investigations studying the impact of WMC testing on clinical care.

INTRODUCTION

Gastroparesis presents with nausea, vomiting, early satiety, fullness, bloating, and pain with objective evidence of delayed gastric emptying (1). The diagnosis of gastroparesis may be made by scintigraphy or by gastric emptying breath testing (2, 3, 4). A third method, wireless motility capsule (WMC) testing, is approved to quantify gastric emptying in suspected gastroparesis by detecting pH increases as the capsule passes from the stomach to duodenum (5). WMC gastric emptying times correlated well with scintigraphic emptying in a smaller prior report (5).

Although presumed to originate in the stomach, gastroparesis symptoms are non-specific and may be reported with other lower functional gastrointestinal disorders (6, 7). Gastroparesis patients also describe bowel disturbances suggesting involvement of multiple gut regions (8, 9). WMC methods offer expanded capabilities over scintigraphy, providing small bowel and colon transit measurements in generalized motility disorders (10, 11, 12). Retrospective WMC series have defined extragastric transit delays in some patients with presumed gastroparesis (13, 14). The WMC pressure sensor estimates contractility in different gut regions (15). Reduced gastric and colon contractions have been defined in small gastroparesis cohorts (16, 17). However, abnormalities of transit and contractility in different gut regions have not been contrasted in patients with diabetic versus idiopathic gastroparesis.

The importance of gastric and extragastric transit and contractility abnormalities in causing gastroparesis symptoms is unproved. Symptom severities measured using standardized questionnaires from a large registry of patients with such symptoms were not different in those

with delayed versus normal gastric emptying measured by scintigraphy (18). In that report, a novel patient subgroup with similar symptoms as gastroparesis but with normal emptying, termed chronic unexplained nausea and vomiting (CUNV), was defined. In one retrospective WMC assessment of patients with generalized dysmotility symptoms, upper and lower gut symptoms did not predict transit abnormalities (12). However, duodenal contractility on WMC tests negatively correlated with overall symptom severity in another small gastroparesis cohort (19). Drawbacks of older WMC studies in gastroparesis include their retrospective nature, small sample sizes, non-standardized gastric scintigraphy methods, and lack of symptom characterizations using validated surveys.

This investigation related prospective WMC data from a large, multicenter cohort from the NIDDK Gastroparesis Consortium to standardized gastric scintigraphy findings and gastrointestinal symptoms quantified by validated questionnaires. Specific aims were to: (i) characterize WMC gastric and extragastric transit and contractility in suspected gastroparesis, including comparisons in diabetic versus idiopathic patients, (ii) associate gastric emptying delays measured by WMC and scintigraphy with other transit and contractility measures in suspected gastroparesis and provide insight into CUNV pathogenesis, and (iii) relate symptom severity to WMC transit and contractility to ascribe potential pathogenic roles for motor dysfunction to symptom genesis. These analyses defined the breadth and pathophysiologic importance of motor abnormalities in suspected gastroparesis to form a foundation for future studies investigating the impact of WMC testing on decision making and outcomes. Some data within this study were presented at Digestive Disease Week in 2015 and 2016 (20, 21).

MATERIALS AND METHODS

Patient Populations

Two hundred nine patients with suspected gastroparesis underwent WMC testing after enrollment in the Gastroparesis Registry 2 (GpR2) at the 8 centers of the Gastroparesis Clinical Research Consortium (GpCRC) from March 2013 to March 2016 (ClinicalTrials.gov NCT01696747). Patients reported gastroparesis symptoms ≥ 12 weeks duration and showed no

organic disease on endoscopy within 12 months before enrollment. WMC testing was not performed in patients with known bezoars (poorly organized food residue was permitted), dysphagia, prior gut surgery, GI strictures, prior inflammatory bowel disease or diverticulitis, frequent nonsteroidal anti-inflammatory drug use, and cardiac medical devices (gastric stimulators, insulin pumps, glucose monitors were permitted). Attribution of gastroparesis to diabetic versus idiopathic versus other etiologies was made by site investigators based on patient self-report and medical record review. Within 6 months before GpR2 enrollment, patients underwent scintigraphy to quantify solid and liquid gastric emptying. The solid phase meal was comprised of ^{99m}Tc -sulfur colloid labeled egg substitute meals which included 120 grams EggBeaters®, 2 slices of bread, 30 grams strawberry jam, and 120 mL water (255 kcal, 72% carbohydrate, 24% protein, 2% fat, 2% fiber)(3). One-hundred forty-nine of the 209 patients underwent concurrent liquid gastric emptying scintigraphy with consumption of 120 mL ^{111}In -DTPA (diethylenetriaminepentaacetic acid) labeled-water along with the solid meal (22).

Studies were approved by Institutional Review Boards at all Clinical Centers and the Data Coordinating Center. Patients provided written informed consent. All authors had access to study data and reviewed and approved the final manuscript.

WMC Testing

Patients underwent WMC (SmartPill®, Medtronic, Minneapolis, MN) testing using accepted protocols (14, 15, 23). The WMC measures 26.8 mm x 11.7 mm and transmits data to a receiver. WMC sensors measure intraluminal pH (every 5 seconds for the first 24 hours, every 10 seconds from 24-48 hours, and every 2.5 minutes after 48 hours; accurate to ± 0.5 pH units), pressure from 0-350 mmHg (every 0.5 seconds for the first 24 hours, every second afterwards; accurate to ± 5 mmHg < 100 mmHg and $\pm 10\%$ > 100 mmHg), and temperature from 25-49°C (every 20 seconds for the first 24 hours, every 40 seconds afterwards; accurate to $\pm 1^\circ\text{C}$)(14, 15, 23). Before WMC testing, patients stopped proton pump inhibitors for 7 days, and histamine₂ receptor antagonists, prokinetics (metoclopramide, domperidone, erythromycin), opiates, anticholinergics, cannabinoids, over the counter laxatives, isotonic polyethylene glycol electrolyte preparations, and prescription laxatives (lubiprostone, linaclotide, misoprostol) for 3 days. On the evening before testing, insulin-requiring diabetics injected half of their usual long-

acting insulin dose. Patients fasted overnight before testing. Urine pregnancy tests were performed for female patients of child-bearing potential on the day of WMC ingestion. Fingertick glucose measurements were made in diabetic patients; studies were rescheduled if fasting glucose levels exceeded 270 mg/dL. Each patient then ingested one SmartBar[®] (Medtronic, Minneapolis, MN) with similar caloric content as the radiolabelled egg substitute meal (255 kcal, 66% carbohydrate, 17% protein, 2% fat, 3% fiber) over 10 minutes with ≤ 50 mL water. After consuming the SmartBar[®], the WMC was swallowed with another 50 mL of water. Patients fasted for 6 hours after WMC ingestion and then resumed normal diets. They were instructed to keep the data receiver within 3 feet of their bodies at all times for the next 4-7 days until they returned the data receiver. Patients continued to abstain from proton pump inhibitors and medications that influence gut transit over this 4-7 day period.

Gastric emptying times (GET) were calculated from the time of WMC ingestion to when the capsule passed into the duodenum, as defined by abrupt ≥ 2 pH unit increases from the lowest postprandial value to levels ≥ 4 that persisted for at least 10 minutes. WMC ileocecal junction transit was detected when pH decreased ≥ 1.0 pH unit for at least 10 minutes ≥ 30 minutes after pyloric passage. WMC small bowel transit times (SBTT) were calculated from the end of the GET period to ileocecal junction passage. Anal WMC evacuation was detected by abrupt 0.025°C per second decreases in temperature. WMC colon transit times (CTT) were calculated from the end of the SBTT period to the time of anal capsule expulsion. WMC contractions >10 mmHg in amplitude were quantified in the hour before GET to measure gastric contractility while contractions in the hour after GET determined small bowel contractility as described previously (13). Motility indices (MI) in the hour before (gastric) and after GET (small bowel) were calculated from the logarithmic transformation of the areas under the contraction curves. Numbers of contractions >25 mmHg in amplitude per hour and MI were calculated for the entire period of colon transit using accepted methods (24). Normal gastric emptying times (GET) (≤ 5 and $>1:45$ hours), small bowel transit times (SBTT) (≤ 6 and $>2:15$ hours), and colon transit times (CTT) ($\leq 58:45$ and $>4:30$ hours) were defined in a recent report (23). Severely delayed GET (>12 hours) was defined as previously (16). Numbers of contractions and motility indices (MI) for each region were calculated as measures of contractility (16, 23). Numbers of gastric and small bowel contractions $<29/\text{hour}$ and $<36/\text{hour}$ and gastric and small bowel MI <9.82 and

<10.57, respectively, have been defined as below the 5th percentile for normal volunteers (16). Normal cutoffs for numbers of contractions and MI for the colon have not been defined. Patients also were stratified into those with high versus low contraction numbers and MI in each region such that roughly half were in each group to relate symptoms to contractility.

Symptom Assessment

Symptoms were quantified by modified Patient Assessment of Upper Gastrointestinal Disorders Symptoms (PAGI-SYM) questionnaires enumerating 22 symptoms from 0 (no symptoms) to 5 (most severe)(25). Overall gastroparesis severity was determined by the Gastroparesis Cardinal Symptom Index (GCSI) score, which includes 9 questions from the PAGI-SYM (26). PAGI-SYM subscale scores for upper GI symptoms were calculated for nausea/vomiting, postprandial fullness/early satiety, bloating/visible distention, and upper abdominal pain/discomfort. The nausea/vomiting subscale score was the mean of scores for 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], and vomiting. The postprandial fullness/early satiety subscale score was the mean of scores for stomach fullness, not able to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite. The bloating/visible distention subscale score was the mean of scores for bloating [feeling like you need to loosen your clothes] and stomach or belly visibly larger. The upper abdominal pain/discomfort subscale score referred to symptoms above the navel, while the lower abdominal pain/discomfort subscale score described symptoms below the navel. PAGI-SYM subscale scores for lower abdominal pain/discomfort and individual symptom scores for constipation and diarrhea quantified lower GI symptoms.

Data Comparisons

Delayed scintigraphic solid gastric emptying (>10% 4 hour retention and/or >60% 2 hour retention) was compared in patients with normal versus delayed WMC GET to determine agreement between methods. Delayed SBTT and CTT were related to normal versus delayed GET to correlate gastric emptying with extragastric transit (23). WMC gastric, small bowel, and

colon contraction numbers and MI were compared between normal versus delayed GET to relate contractility to gastric emptying. Scintigraphy and WMC measures were compared in diabetic versus idiopathic patients to contrast motor abnormalities between etiologies. Although their data were incorporated into analyses of the entire cohort, post-fundoplication gastroparesis patients were not included in subgroup analyses related to etiology due to the small sample size (N=8). Data from patients with rapid scintigraphic gastric emptying (<38% 1 hour retention), GET (N=10), SBTT (N=8), and CTT (N=6) were not analyzed separately due to small samples and were pooled in with normal transit groups. To gain insight into CUNV pathogenesis, GET, SBTT, CTT results were compared in patients with normal versus delayed solid scintigraphy. Gastric, small bowel, and colon contraction numbers and MI were contrasted with normal and delayed solid scintigraphy to ascertain if CUNV presents with specific contractility profiles.

Overall GCSI scores, PAGI-SYM subscores, and individual PAGI-SYM lower GI symptoms were compared in those with delayed versus normal GET, SBTT, and CTT and with high versus low numbers of contractions and MI in the hour before and after GET and during the period of colon transit.

Statistical Analyses

Exploratory data analyses using means, medians, standard deviation and interquartile ranges (IQR) were applied to WMC and scintigraphic measures and by comparing patients with diabetic versus idiopathic gastroparesis, normal versus delayed GET, and normal versus delayed scintigraphy. Differences between groups were compared using Wilcoxon rank-sum testing for continuous measures or Fisher's exact test for categorical measures. T-tests compared symptoms by high versus low categories of gastric, small bowel, and colon contractions. Patients with normal versus delayed WMC GET were compared graphically using medians (IQRs) to 4 hour solid and 1 hour liquid retention percentages, SBTT, and CTT. Symptom profiles were plotted as means and 95% confidence intervals by normal versus delayed GET, SBTT, and CTT. Nominal, two-sided P-values with no adjustments for multiple comparisons are presented; comparisons were hypothesis-driven. Analyses were performed using SAS (version 9.3, SAS Institute, Cary, NC) and Stata (Release 13, Stata Corporation, College Station, TX) software.

RESULTS

Transit and Contractility Abnormalities

Figure 1 shows recordings from patients with (A) normal transit, (B) mildly delayed GET (5 hours, 32 minutes), (C) severely delayed GET (90 hours, 32 minutes), (D) delayed CTT (>136 hours, 21 minutes), and (E) diffusely delayed GET (10 hours, 32 minutes), SBTT (13 hours, 21 minutes), and CTT (94 hours, 16 minutes).

Transit determinations for the whole group included patients with diabetic, idiopathic, and post-fundoplication etiologies. Delayed solid (4 hour retention) and liquid (1 hour retention) scintigraphic gastric emptying were observed in 68.8% and 34.8% of patients, respectively (Table 1). WMC transit abnormalities including delayed and rapid transit were found in 73.3%. Delays were noted in 66.3% including delayed GET in 40.3%, SBTT in 15.5%, and CTT in 33.5%. Generalized delays involving ≥ 2 of the 3 regions were observed in 23.3%. Severe GET delays were found in 28.8% of patients. Fifty-eight of 132 patients with delayed scintigraphy had delayed WMC GET (43.9% positive agreement) while 42/60 with normal scintigraphy had normal GET (70.0% negative agreement). Overall agreement between 4 hour scintigraphic retention and GET was 52.8% with a kappa of 0.12, (95% CI 0.002, 0.23); agreement between 2 hour scintigraphic retention and GET was 58.7% with a kappa of 0.16 (95% CI 0.02, 0.29). Rapid gastric scintigraphy was found in 6/188 (3.2%). Rapid GET was noted in 10/200 (5.0%), SBTT in 8/168 (4.8%), and colon in 6/169 (3.6%) patients.

Numbers of WMC contractions and MI in each region are shown in Table 1. Reduced numbers of gastric contractions and gastric MI were found in 25.6% and 21.4% and decreased numbers of small bowel contractions and small bowel MI were noted in 13.7% and 16.4%, respectively.

Data acquisition was incomplete in small numbers of patients. No reliable WMC transit data were acquired in 5/201 (2.5%). The WMC remained in the stomach during the entire recording in 9/196 (4.6%), reflecting profound GET delays. Anal expulsion did not occur during the recording in 34/196 (17.3%) preventing definitive CTT determination. However, it was

possible to determine that CTT was delayed in 24/34 (70.6%) of those cases in which anal expulsion was not observed. Transient data loss was noted in 27/196 (13.8%) preventing accurate transit determination in at least one region.

Relation of Scintigraphy and WMC Measures to Etiology

Subgroup analyses relating to etiology focused on comparisons between diabetic versus idiopathic patients and excluded the small number of post-fundoplication patients. Solid scintigraphic gastric retention was greater in diabetic versus idiopathic patients ($P=0.04$); liquid emptying was not different between etiologies (Figures 2A and 2B). Diabetics had longer WMC GETs (Figure 2C) ($P=0.02$) and more diabetics exhibited delayed GETs ($P=0.01$) versus idiopathic patients ($P=0.01$) (Table 1). Overall agreement between 4 hour scintigraphic retention and GET in diabetics was 57.6% with a kappa of 0.14 (95% CI 0.0, 0.36), while agreement in idiopathic patients was 49.2% with a kappa of 0.09 (95% CI 0.0, 0.22). Agreements were not significantly different between etiologies ($P=0.64$). Conversely, SBTTs were longer in idiopathic patients ($P=0.01$). No other WMC transit or contractility measure related to etiology (Table 1).

Relation of Gastric Emptying to Other Measures

Scintigraphic solid gastric retention was greater in patients with delayed ($N=118$) versus normal ($N=76$) GET ($P=0.001$) (Figure 3A). Liquid scintigraphic retention also was higher with delayed GET ($P=0.02$) (Figure 3B). Percentages of patients with solid scintigraphic delays trended higher with delayed versus normal GET ($P=0.08$); percentages with severely delayed solid emptying were greater with delayed GET ($P=0.007$) (Table 2). Percentages of patients with delayed liquid scintigraphy were similar with delayed and normal GET.

SBTT and CTT values were similar in patients with delayed ($N=53$) versus normal ($N=110$) GET (Figures 3C and 3D). SBTT delays ($P=0.04$) but not CTT delays were more prevalent among those with GET delays (Table 2).

Numbers of gastric contractions in the hour before capsule emptying were lower with delayed GET ($P=0.02$) and percentages of patients with low contraction numbers were higher

with delayed versus normal GET ($P=0.0003$)(Table 2). Gastric MIs in the hour before capsule emptying were lower with delayed GET ($P=0.0004$) and percentages with low MI were greater with delayed versus normal GET ($P=0.01$). Numbers of colon contractions/hour were lower with delayed GET ($P=0.02$). Numbers of small bowel contractions and MI and percentages with reductions in small bowel contractions and MI were not different with delayed versus normal GET.

GET, SBT, and CTT values and percentages of patients with regional WMC delays were similar with delayed versus normal scintigraphic emptying (Table 3). Numbers of gastric, small bowel, and colon contractions and MI and percentages with reductions in contractions and MI in the three regions were not different with delayed versus normal scintigraphy (Table 3).

Relation of Regional Transit and Contractility to Symptoms

Overall GCSI and PAGA-SYM subscale scores for nausea/vomiting, early satiety/postprandial fullness, bloating/visible distention, and upper and lower abdominal pain/discomfort were not different with delayed versus normal GET, SBTT, and CTT (Figures 4A, 4B, 4C). Constipation scores were higher in patients with delayed CTT ($P=0.03$); diarrhea scores were lower in patients with delayed SBTT ($P=0.04$) and with delayed CTT ($P=0.01$)(Figures 4D, 4E, 4F).

PAGA-SYM upper abdominal pain/discomfort subscale scores were greater in patients with higher versus lower numbers of colon contractions ($P=0.03$)(Table 4). Overall GCSI scores and nausea/vomiting, early satiety/postprandial fullness, and bloating/distention subscale scores were not different in relation to any contractility measure. Lower abdominal pain/discomfort subscale ($P=0.02$) and constipation scores ($P=0.03$) were greater in those with higher versus lower colon contraction numbers.

DISCUSSION

This investigation is the largest, most comprehensive prospective analysis of gastric plus extragastric transit abnormalities in suspected gastroparesis using WMC methods. Although WMCs are employed much less often than scintigraphy to measure gastric emptying, our sample

size compared favorably to many large published studies using gastric scintigraphy (27, 28, 29). Additional strengths of this study included its multicenter structure with recruitment of well characterized patients, its separate analyses of diabetic versus idiopathic etiologies, its standardized analyses of diverse transit and contractility measures, and its association of motor findings to symptom profiles using validated surveys.

As in the initial study comparing scintigraphic and WMC findings in patients with prior diagnoses of gastroparesis, solid phase gastric emptying measured by scintigraphy correlated with WMC GETs in our investigation (5). We expanded on this by showing additional associations of liquid emptying with GETs. Unexpected findings of the present investigation included a device agreement of only 52.8% between WMC and scintigraphic gastric emptying measures and a lower prevalence of emptying delays with WMC versus nuclear medicine tests. In the original report, correlations were stronger ($R=0.73$) and WMCs detected 21% more delays than scintigraphy (5). There are several potential explanations for these differences between the two studies. Most importantly, WMC and scintigraphic tests were performed on separate days in the current investigation while they were concurrent in the initial investigation. Coefficients of variability of up to 31% are seen on serial gastric emptying measurements regardless of the method of testing, suggesting that emptying rates are inconsistent from day to day in health and in gastroparesis (4, 5, 30). Thus, much of the disparity between our investigation and the Kuo study may relate to different day testing. Secondly, it is established that gastric emptying of digestible solids like the egg substitute meals ingested during scintigraphy is mediated by different mechanisms (i.e. fed motor pattern) than for indigestible solids like the WMC (fasting migrating motor complexes)(31, 32). This raises the possibility that emptying rates measured by the two techniques may be inherently different. Thirdly although the caloric composition of the nutrient bars ingested during WMC testing in this study is similar to the egg substitute meals consumed with scintigraphy, subtle differences in emptying profiles have been reported for the two meals (23). However, the magnitude of the difference in gastric emptying rates between the two meals is likely too small to explain the disparate observations of the current study and the original report. This discrepancy will be addressed by ongoing multicenter studies comparing the two techniques when performed simultaneously in patients believed to have gastroparesis.

These large, prospective investigations will definitively determine if stratification of patients into those with and without delayed gastric emptying is substantially different with the two methods.

We also confirmed extragastric WMC transit delays previously documented in studies employing less rigorous patient characterizations (13, 14). Small bowel and colon delays were found in >40% of patients with suspected gastroparesis and nearly 20% exhibited generalized impairments. SBTT delays were associated with GET delays suggesting possible common motor impairments across gut regions, but did not correlate with gastric scintigraphy delays. This finding is consistent with the different physiology of indigestible versus digestible solid emptying (31, 32). A novel finding of our study was its characterization of rapid transit in different regions in small numbers of patients with suspected gastroparesis (23). Others have observed rapid gastric emptying in up to 41% patients with dyspepsia using scintigraphy, but none have examined rapid WMC transit (33, 34). In this investigation, rapid transit was found in too few patients (5%) for subgroup analyses.

Novel regional contractility findings were acquired from our WMC pressure data. The association of delayed GET with reduced gastric but not small bowel contractions contrasts with an earlier study in which small bowel and gastric contractility were decreased only with GET >12 hours (16). However, that investigation only included 8 patients with mildly delayed GET (<12 hours) and was too small to be definitive. Decreases in colon contractions related to delayed GET but not scintigraphic gastric emptying. Similarly reduced numbers of colon contractions were noted in diabetics with delayed GET in post-hoc analyses of the original WMC investigation, supportive of diffuse dysfunction in some patients with gastroparesis symptoms (5, 17). The present study extended these findings to idiopathic patients. The preservation of normal small bowel contractions and MI in those with delayed GET suggests this gut region is less susceptible to disruption in patients with generalized dysmotility.

Our large sample allowed us to contrast transit and contractility in idiopathic disease versus diabetes. Prior studies showed no gastric scintigraphy differences between etiologies, but we found more severe emptying delays in diabetics versus idiopathic patients using both WMCs and scintigraphy (9). However, device agreements between scintigraphy and WMCs were similar in diabetic and idiopathic patients. Furthermore, SBTTs were shorter in diabetics than in idiopathic patients. Physiologic studies have noted differences in gastric pH and pancreatic

polypeptide release in diabetic versus idiopathic gastroparesis suggesting more severe vagal impairments with diabetes (35, 36). Our findings support differential pathogenesis of transit impairments in relation to etiology, perhaps secondary to different degrees of vagal dysfunction.

The comprehensive associations of symptoms with transit and contractility included in this study complement detailed published observations by the Gastroparesis Consortium relating symptoms to scintigraphic gastric emptying (18). Gastroparesis symptoms showed little correlation with GETs or other WMC transit or contractility measures; only numbers of colon contractions positively associated with upper abdominal pain severity. These findings suggest symptoms of gastroparesis are not solely determined by gastric, small intestinal, or colon transit. Furthermore, these observations are at odds with a prior smaller study reporting higher global gastroparesis symptoms with reduced small bowel contractions (19). Individual symptoms were not examined in that previous investigation. Similarly, another study employing dichotomous symptom assessments found no symptom correlation with WMC measures (12).

This investigation raises new questions about CUNV pathogenesis. We hypothesized that WMC testing would uncover distinct extragastric transit or contractile profiles in patients with normal gastric scintigraphy given the symptom overlaps of gastroparesis and the lower functional bowel disorders (8, 9). However, no WMC small bowel or colon transit or contractility abnormalities were specific for those with normal scintigraphy suggesting that no regional transit or phasic motor pattern is definitive for symptom genesis in CUNV. These findings warrant consideration of other pathophysiologic contributors including impaired gastric accommodation, altered luminal sensation, myoelectric dysfunction, or central nervous system abnormalities not detectable by gastric emptying testing as causes of CUNV pathogenesis (37, 38, 39).

Our analyses associated lower GI symptoms in patients with suspected gastroparesis to WMC transit and contractility. In contrast to gastroparesis symptoms, diarrhea related to rapid SBTT and CTT while constipation scores were higher in those with delayed CTT and increased colon contractions and lower abdominal pain correlated with higher colon contractility. These findings parallel a prior WMC study, in which patients with constipation-predominant irritable bowel syndrome showed greater contractility than those with functional constipation (24).

This investigation had limitations. Although most agents affecting transit were discontinued for study conduct, some maintenance medications (e.g. antihypertensives, antidepressants) might have influenced WMC measures. Because patients returned data recorders 4-7 days after WMC ingestion, definitive CTT determination was not possible in some individuals. However, in more than two thirds of these patients we were still able to diagnose delayed CTT. It would have been impractical to lengthen the data collection period to define CTT in the remainder. Glycemic control was not monitored in diabetics, thus acute hyperglycemic effects on transit or contractility cannot be excluded (40). Despite drawbacks, these important findings provide a foundation for additional investigations defining impacts of WMC performance on patient management. As with other methods of emptying testing including scintigraphy, there are few published studies which objectively demonstrate that quantifying the rate of gastric emptying influences any symptom or resource utilization outcome in suspected gastroparesis. However in one investigation, scintigraphic gastric retention >20% was associated with superior outcomes versus milder impairments supporting the utility of emptying testing (41). Future studies will define if WMC testing leads to different treatment decisions versus scintigraphy. Further, it is uncertain if treating small bowel or colon transit or contractility abnormalities detected by WMC testing has additional impact on patient outcomes. In an uncontrolled pediatric study, osmotic laxatives reduced gastric emptying delays and improved dyspeptic symptoms in children with functional dyspepsia (42). Larger controlled trials could validate the concept that gastroparesis improves with treatments targeting distal gut dysfunction.

In conclusion, WMCs define similar but not identical gastric emptying delays as scintigraphy which are more severe in diabetics and correlate with reduced gastric and colon contractility. Extragastric or generalized transit delays occur in >40% of patients with gastroparesis symptoms. Upper GI symptoms correlate poorly with WMC defects and do not distinguish gastroparesis from CUNV, although lower GI symptoms associate with transit and contractility abnormalities. These findings provide insight into gastroparesis pathogenesis and form a basis for future investigations studying the impact of WMC testing on clinical care.

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ABBREVIATIONS

CTT (colon transit time)

CUNV (chronic unexplained nausea and vomiting)

DTPA (diethylenetriaminepentaacetic acid)

GCSI (Gastroparesis Cardinal Symptom Index)

GET (gastric emptying time)

GI (gastrointestinal)

GpCRC (Gastroparesis Clinical Research Consortium)

NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases)

PAGI-SYM (Patient Assessment of Upper Gastrointestinal Disorders Symptoms)

SBTT (small bowel transit time)

WMC (wireless motility capsule)

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TABLES

Table 1: PREVALENCE OF TRANSIT DELAYS AND CONTRACTILITY ABNORMALITIES IN PATIENTS WITH SUSPECTED DIABETIC OR IDIOPATHIC GASTROPARESIS

	Measure	All Patients N (%) or Median (IQR)	Diabetic Patients N (%) or Median (IQR)	Idiopathic Patients N (%) or Median (IQR)	P Value Diabetic vs. Idiopathic Patients
Transit measures	Delayed scintigraphic 4 hour solid retention >10%	132/194 (68.8%)	48/66 (72.7%)	84/126 (66.7%)	0.42
	Rapid scintigraphic 1 hour solid retention <38%	6/188 (3.2%)	4/66 (6.1%)	2/124 (1.6%)	0.18
	Delayed scintigraphic 1 hour liquid retention >50%	48/137 (34.8%)	14/44 (31.8%)	34/94 (36.2%)	0.70
	Delayed WMC GET >5 hours	81/201 (40.3%)	34/66 (51.5%)	42/128 (32.8%)	0.01
	Rapid WMC GET <1:45 hours	10/201 (5.0%)	2/66 (3.0%)	8/128 (6.2%)	0.50
	WMC SBTT (hours)	4.05 (3.19, 5.39)	3.55 (2.85, 4.69)	4.12 (3.30, 5.68)	0.01
	Delayed WMC SBTT >6 hours	26/168 (15.5%)	4/49 (8.2%)	21/114 (18.4%)	0.15
	Rapid WMC SBTT <2:15 hours	8/168 (4.8%)	4/49 (8.2%)	4/114 (3.5%)	0.24
	WMC CTT (hours)	41.6 (20.6, 67.7)	45.9 (21.9, 64.0)	38.7 (20.3, 69.2)	0.73
Delayed WMC CTT >59 hours	55/164 (33.5%)	17/49 (34.7%)	36/111 (32.4%)	0.86	

	WMC delays in ≥ 2 regions	38/163 (23.3%)	10/47 (21.3%)	26/113 (23.0%)	1.00
Contractility measures	Gastric contractions/hour	56 (27, 119)	49 (35, 120)	56 (24, 119)	0.70
	Reduced gastric contractions (<29 /hour)	41/160 (25.6%)	9/45 (20.0%)	31/107 (29.0%)	0.31
	Gastric motility index (MI)	11.5 (10.3, 12.6)	11.6 (10.4, 12.6)	11.5 (9.9, 12.6)	0.67
	Reduced gastric MI (<9.82)	33/154 (21.4%)	6/45 (13.3%)	26/107 (24.3%)	0.19
	Small bowel contractions/hour	137.5 (67, 230)	148 (86, 303)	136 (65, 206)	0.17
	Reduced small bowel contractions (<36 /hour)	20/146 (13.7%)	3/41 (7.3%)	17/105 (16.2%)	0.19
	Small bowel motility index (MI)	12.7 (11.4, 13.8)	12.9 (11.8, 14.4)	12.6 (11.1, 13.5)	0.11
	Reduced small bowel MI (<10.57)	24/146 (16.4%)	5/41 (12.2%)	19/105 (18.1%)	0.46
	Colon contractions/hour	125 (87, 163)	108 (80, 155)	129 (91, 165)	0.30

N=sample size

IQR=interquartile range

Table 2: RELATION OF WMC GET TO ABNORMALITIES OF OTHER MEASURES

	Measure	Normal GET (≤ 5 hours) N (%)	Delayed GET (> 5 hours) N (%)	P Value
Transit measures	Delayed scintigraphic solid gastric emptying ($>10\%$ 4 hour retention)	74/116 (63.8%)	58/76 (76.3%)	0.08
	Severely delayed scintigraphic solid gastric emptying ($>35\%$ 4 hour retention)	18/116 (15.5%)	25/76 (32.9%)	0.007
	Delayed scintigraphic liquid gastric emptying ($>50\%$ 1 hour retention)	26/84 (31.0%)	22/54 (40.7%)	0.27
	Delayed WMC SBTT (>6 hours)	12/110 (10.9%)	13/53 (24.5%)	0.04
	Delayed WMC CTT (>59 hours)	36/106 (34.0%)	17/54 (31.5%)	0.53
Contractility measures	Gastric contractions/hour	64 (38, 130)	35 (11, 61)	0.02
	Reduced gastric contractions (<29 /hour)	18/105 (17.1%)	23/50 (46.0%)	0.0003
	Gastric motility index (MI)	11.7 (10.7, 12.7)	10.6 (8.7, 11.9)	0.0004
	Reduced gastric MI (<9.82)	16/105 (15.2%)	17/50 (34.0%)	0.01
	Small bowel contractions/hour	138 (77, 223)	124 (63, 255)	0.92
	Reduced small bowel contractions (<36 /hour)	13/104 (12.5%)	7/45 (15.6%)	0.81
	Small bowel motility index (MI)	12.7 (11.6, 13.8)	12.6 (11.3, 14.0)	0.74
	Reduced small bowel MI (<10.57)	16/104 (15.4%)	8/45 (17.8%)	0.92
	Colon contractions/hour	130 (91, 192)	115 (86, 139)	0.02

N=sample size

Table 3: RELATION OF REGIONAL TRANSIT AND CONTRACTILITY TO DELAYED VERSUS NORMAL SCINTIGRAPHIC GASTRIC EMPTYING

	Measure	Normal 4 Hour Scintigraphy Median (IQR) or N (%)	Delayed 4 Hour Scintigraphy Median (IQR) or N (%)	P Value
Transit measures	WMC GET (hours)	4.0 (3.0, 14.8)	4.6 (3.2, 14.9)	0.36
	Delayed WMC GET (> 5 hours)	18/60 (30.0%)	58/132 (44.0%)	0.09
	WMC SBTT (hours)	4.12 (3.23, 5.43)	3.97 (3.15, 5.37)	0.49
	Delayed WMC SBTT (>6 hours)	9/49 (18.4%)	16/114 (14.0%)	0.48
	WMC CTT (hours)	38.7 (19.6, 74.0)	41.9 (21.9, 65.0)	0.65
	Delayed WMC CTT (>59 hours)	18/50 (36.0%)	35/110 (31.8%)	0.53
Contractility measures	Gastric contractions/hour	56.0 (29.0, 104.0)	54.0 (24.0, 120.0)	0.80
	Reduced gastric contractions (<29/hour)	9/43 (20.9%)	31/109 (28.4%)	0.42
	Gastric motility index (MI)	11.5 (10.7, 12.5)	11.4 (9.9, 12.6)	0.40
	Reduced gastric MI (<9.82)	5/43 (11.6%)	27/109 (24.8%)	0.08
	Small bowel contractions/hour	155.0 (112.0, 231.0)	129.0 (61.0, 222.0)	0.24
	Reduced small bowel contractions (<36/hour)	2/39 (5.1%)	18/107 (16.8%)	0.10

	Small bowel motility index (MI)	12.9 (12.3, 14.0)	12.6 (11.1, 13.9)	0.16
	Reduced small bowel MI (<10.57)	3/39 (7.7%)	21/107 (19.6%)	0.13
	Colon contractions/hour	138 (90, 162)	126 (84, 162)	0.55

N=sample size

IQR=interquartile range

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Table 4: RELATION OF SYMPTOMS TO CONTRACTILITY MEASURES

PAGI-SYM Symptom Characteristic		Number of Gastric Contractions in Hour Before Gastric Emptying (Mean±SD)			Number of Small Bowel Contractions in Hour After Gastric Emptying (Mean±SD)			Number of Colon Contractions per Hour (Mean±SD)		
		High	Low	P Value	High	Low	P Value	High	Low	P Value
Upper GI symptoms	Overall GCSI score	2.6±1.0	2.7±1.1	0.92	2.6±1.1	2.7±1.0	0.66	2.7±1.1	2.4±1.0	0.15
	Nausea/vomiting subscore	1.8±1.4	1.7±1.2	0.53	1.7±1.3	1.9±1.3	0.30	1.9±1.4	1.6±1.2	0.32
	Postprandial fullness/early satiety subscore	3.2±1.3	3.3±1.1	0.76	3.2±1.2	3.3±1.1	0.65	3.2±1.2	3.1±1.1	0.58
	Bloating/visible distention subscore	3.0±1.7	3.0±1.6	0.93	3.0±1.7	2.9±1.7	0.77	3.0±1.7	2.5±1.6	0.12
	Upper abdominal pain/ discomfort subscore	2.6±1.7	2.8±1.4	0.52	2.6±1.7	2.8±1.4	0.46	3.0±1.4	2.4±1.5	0.03
Lower GI symptoms	Lower abdominal pain/ discomfort subscore	2.1±1.5	1.9±1.5	0.31	2.1±1.6	1.8±1.4	0.34	2.2±1.5	1.6±1.3	0.02
	Constipation score	2.3±1.7	2.8±1.8	0.10	2.4±1.7	2.7±1.8	0.41	3.1±1.6	2.4±1.7	0.03
	Diarrhea score	1.6±1.7	1.5±1.6	0.61	1.7±1.7	1.4±1.6	0.18	1.2±1.7	1.8±1.6	0.07

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FIGURE LEGENDS

Figure 1: Representative WMC recordings from patients with (A) normal transit throughout, (B) mildly delayed GET, (C) severely delayed GET, (D) delayed CTT, and (E) generalized GET, SBTT, and CTT delays are shown (normal GET ≤ 5 hours, normal SBTT ≤ 6 hours, normal CTT $\leq 58:45$ hours). Transit times are calculated from pH transitions (red tracings) and temperature changes (green tracings). Pressure recordings are shown in blue.

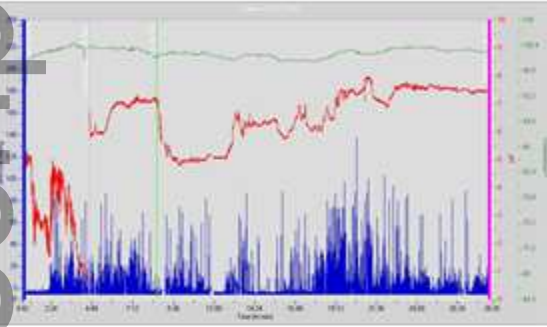
Figure 2: Disease etiologies were related to solid (A) and liquid (B) scintigraphic gastric emptying and WMC GET (C). Solid scintigraphic gastric retention ($P=0.02$) and WMC GET ($P=0.04$) values were greater among diabetic (open bars) versus idiopathic (gray bars) patients, while liquid scintigraphic emptying was not different between etiologies.

Figure 3: Solid (A) and liquid (B) gastric emptying were compared with normal (open bars) versus delayed (gray bars) WMC GETs. Solid ($P=0.001$) and liquid ($P=0.02$) retention were greater with delayed GETs. SBTT (C) and CTT (D) were compared with normal (open bars) versus delayed (gray bars) GETs. Extragastric transit was not different in relation to GET.

Figure 4: Overall GCSI and subscale scores for nausea/vomiting (N/V), early satiety/fullness (Fullness), bloating/distention (Bloating), and upper abdominal pain/discomfort (Upper Pain) were not different with delayed versus normal GET, SBTT, or CTT (A, B, C). Lower abdominal pain/discomfort subscale scores (Lower Pain) were similar with delayed and normal GET, SBTT, and CTT. Constipation scores were higher with delayed CTT ($P=0.03$); diarrhea scores were lower with delayed SBTT ($P=0.04$) and CTT ($P=0.01$)(D, E, F).

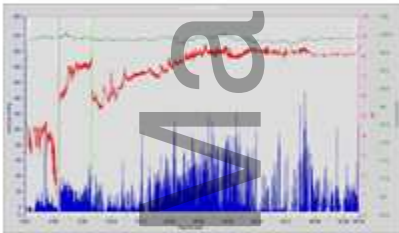
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A) Normal Transit



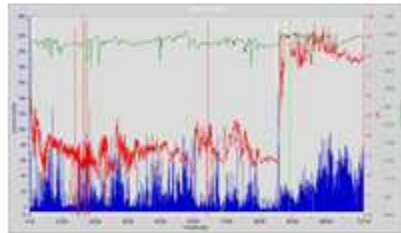
Region	Time (hr:min)
GET	3:48
SBTT	4:00
CTT	19:39

B) Mild GET Delay



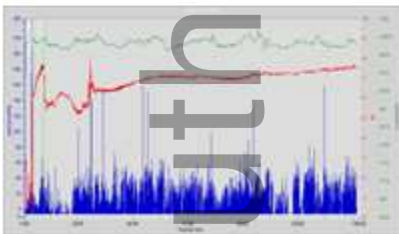
Region	Time (hr:min)
GET	5:32
SBTT	5:24
CTT	44:03

C) Severe GET Delay



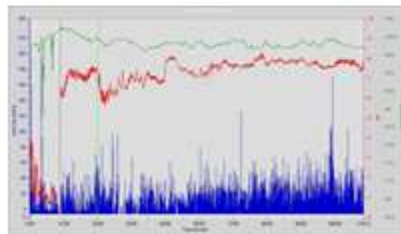
Region	Time (hr:min)
GET	90:32
SBTT	3:44
CTT	26:57

D) CTT Delay



Region	Time (hr:min)
GET	3:13
SBTT	4:57
CTT	>136:21

E) Generalized Delay



Region	Time (hr:min)
GET	10:32
SBTT	13:21
CTT	94:16

Figure 1

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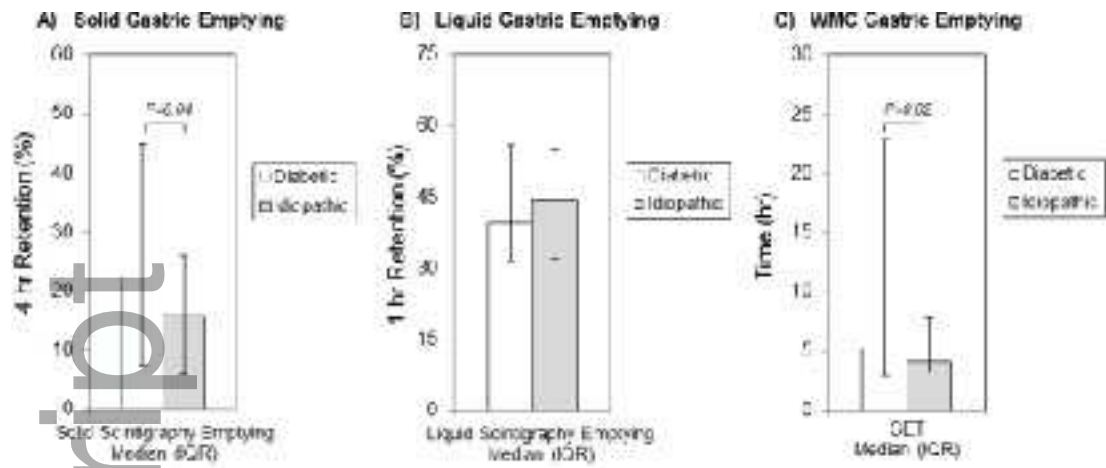


Figure 2

nmo_13196_f2.tif

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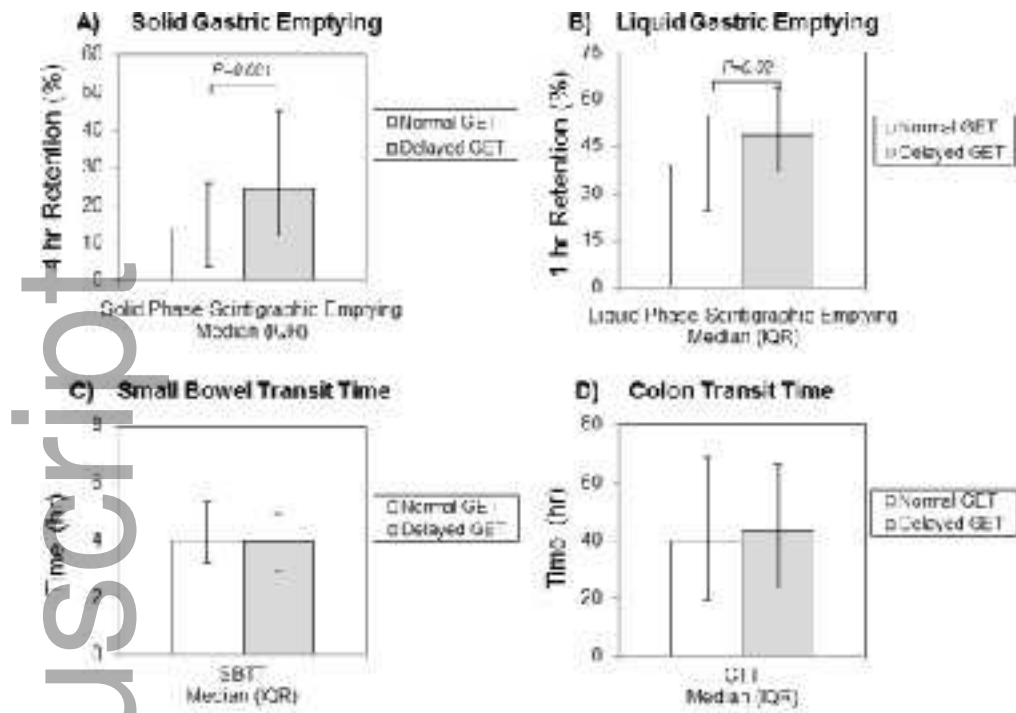


Figure 3

nmo_13196_f3.tif

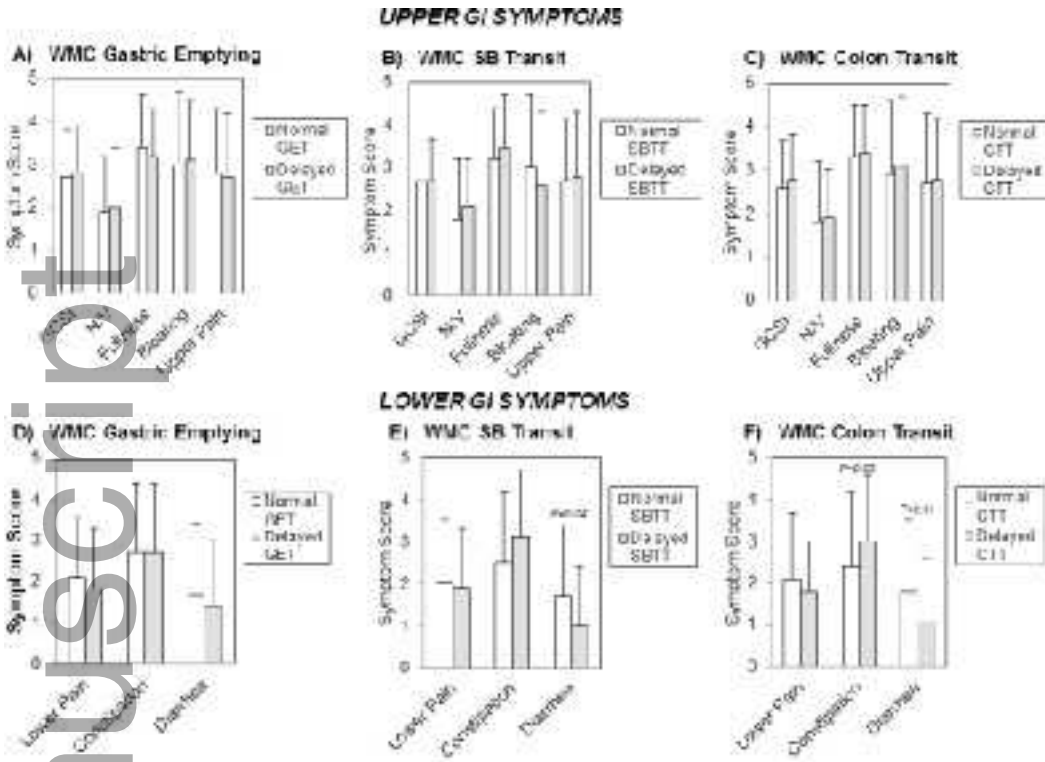


Figure 4

nmo_13196_f4.tif