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Colonic motor response to wakening is blunted in slow transit constipation as detected by wireless motility capsule

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Abstract

Background: Chronic constipation may be categorized as normal transit (NTC), slow transit (STC), or outlet obstruction. Colonic wake response is a relative increase in colonic motility upon awakening. Colonic manometry studies have demonstrated attenuated wake response in STC. We sought to evaluate wake response among healthy (H), NTC, and STC patients using wireless motility capsule (WMC).

Methods: A retrospective study of WMC data from a multicenter clinical trial and a tertiary gastroenterology clinic was performed. WMC motility parameters of contraction frequency (Ct) and area under the contraction curve (AUC) were analyzed in 20-min windows 1-h before and after awakening. *T*-tests compared parameters between H, NTC, and STC. Linear regression analysis was performed to determine if outlet obstruction confounded data. A receiver operating characteristic curve demonstrated optimal Ct cut-offs to define blunted wake response.

Results: A total of 62 H, 53 NTC and 75 STC subjects were analyzed. At 20, 40, and 60 min after awakening, STC subjects had significantly lower mean Ct when compared to H ($p < 0.001$) and NTC ($p < 0.01$). Linear regression demonstrated that outlet obstruction was not associated with a decreased wake response ($\beta = 3.94$, (CI -3.12 – 1.00), $P = 0.27$). Defined at the Ct threshold of 64 at 20-min post-wake, blunted wake response sensitivity was 84% and specificity was 32% for chronic constipation.

Conclusion: Findings of an impaired wake response in subjects with STC and not NTC adds further evidence to neuronal dysfunction as an etiology of STC, and identifies a possible temporal target for pharmacologic intervention.

Introduction

The prevalence of chronic constipation worldwide is 16%, and it is more common in women, elderly people, and those of lower socioeconomic status¹. Chronic constipation may arise from direct bowel dysfunction or as a result of secondary causes, however when no demonstrable

physiologic abnormality is present it may be described as a functional gastrointestinal disorder as defined by Rome IV Criteria². Patients with chronic constipation report impaired quality of life comparable to other chronic conditions, and consequently tend to contribute considerably to physician visits and other healthcare costs^{3,4}.

Chronic constipation may be classified into three categories based on colonic transit and pelvic floor function: normal transit constipation (NTC), slow transit constipation (STC), and defecatory disorders. Diagnostic testing in patients refractory to therapy often includes anorectal

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manometry and rectal balloon expulsion testing (BET) to exclude pelvic floor dysfunction, and if necessary, colonic transit tests may follow¹. The wireless motility capsule (WMC) is a non-invasive diagnostic tool capable of measuring intraluminal pressure and pH throughout the whole GI tract, assessing both transit and contractility. While only the transit parameters are commonly used in clinical practice, contractile parameters measured by WMC include contraction count (Ct) to define the number of luminal contractions during a period of time and area under the pressure curve (AUC), an integral of contraction frequency to calculate the amplitude of gut contractility over time⁵.

Normal colonic motility involves coordination by the underlying neuroenteric circuitry of colonic contraction in response to meals and diurnal cycle that are detectable by manometry^{6,7}. There is relative contractile colonic quiescence during sleep with an increase in motility after awakening, often resulting in a bowel movement. Previous studies have characterized this “wake response” using colonic manometry over 24 h of monitoring^{6,8–10}. The invasive nature of this procedure has limited the extent to which the colonic wake response has been studied in adults with chronic constipation, particularly among different subtypes.

In contrast to earlier studies that suggested that the wake response was normal in STC^{10,11}, Rao et al. reported that the colonic wake response is blunted in STC compared to healthy controls using 24-h colonic manometry¹². No known prior study has observed the wake response with WMC, which measures some of the parameters of traditional manometry but is less invasive and thus better tolerated for observing physiologic phenomena among patients in the community. An impaired wake response may be an indicator of underlying neuropathy driving chronic constipation. We hypothesized that patients with STC will have an impaired colonic wake response that is detectable by WMC. This study aims to assess the ability of WMC to measure the wake response among patients with chronic constipation.

Methods

Subject enrollment

This was a retrospective study of patients from two independent clinical databases. The first database was a multicenter clinical trial conducted from 2009–2011 that compared the GI motility of patients with chronic constipation defined by Rome II criteria to healthy controls¹³. The second cohort was taken from the clinical practice database of a tertiary GI motility clinic at Massachusetts General Hospital (MGH) that had undergone WMC testing from 2009–2014, and did not include healthy controls. All available patients between the ages of 18–65 that underwent BET, had no history of gastric bezoars, or previous gastrointestinal surgery with the exception of

uncomplicated appendectomy, cholecystectomy, or cesarean sections, were considered for analysis. Healthy subjects were recruited in the multicenter clinical trial using the Mayo GI disease questionnaire¹⁴. Study protocols for the multicenter clinical trial was approved by the IRB at each center (Protocol# 2004P002157, 2006P000532, 2008P002398). Review of clinical data for the study was approved by the Institutional Review Board at MGH (Protocol# 2014P001465).

Study protocol

Pressure and pH data were obtained with the WMC system (Medtronic, Minneapolis, MN) consisting of an ingestible capsule, a receiver, and display software as described previously¹⁵. Data was analyzed using the GIMS version 3.0 display software (Medtronic, Minneapolis, MN).

In both the multicenter clinical trial patients and in patients from the motility clinic, patients were asked to discontinue medications that could affect gastric pH and gastrointestinal motility such as laxatives, prokinetics, anticholinergics, antidiarrheals, opioids, H₂ antagonists and proton pump inhibitors prior to and during the WMC testing, per protocol¹⁶. Patients who had been taking stable doses (at least 6 months) of antidepressants, oral contraceptives, and lipid-lowering agents were allowed to continue use of these agents. Subjects in the multicenter trial and patients from the motility clinic underwent the same protocol of ingesting an egg sandwich meal with a total caloric value of 255 kcal (2% fat, 1 g fiber, 180 cc volume) or SmartBar meal with a total caloric value of 260 kcal (2% fat, 2 g fiber, 105 cc volume) with 120 cc water following an overnight fast. Subjects then swallowed the WMC with an additional 50 cc of water. 6 h after capsule ingestion, all subjects consumed a second meal consisting of Ensure[®] (Abbott Laboratories, IL, USA) (250 ml, 250 kcal, protein 9 g, carbohydrates 40 g, fat 6 g, fiber 0 g) per protocol due to safety concerns for diabetic subjects. Water was taken ad-libitum thereafter.

Subjects left the study center with the data receiver for continuous data acquisition from the capsule and a diary for recording bowel movements, food intake, sleep, wake, and gastrointestinal symptoms (pain, nausea, cramping). Restrictions included no strenuous activities or prolonged aerobic activity, no alcohol, and no gastrointestinal medications that could affect motility. Ad libitum feeding was allowed. At 48 to 120 h post ingestion, the subjects came back to the study center and returned the data receiver and the diary.

Colonic wake response analysis

To record awakening, subjects push the “event” button on the WMC monitor before going to bed and after waking up and annotate both in a diary. The recorded WMC events were then correlated with diary entries and

Table 1 Two-tailed *t* test comparison of mean colonic transit time (CTT) and contractility parameters (Ct, AUC) in multicenter trial and MGH clinic cohorts

	CTT (h: min)	Baseline			Wake to +20 min			+20–40 min			+40–60 min		
		Ct	AUC	Wake events	Ct	AUC	Wake events	Ct	AUC	Wake events	Ct	AUC	Wake events
Multicenter trial	69:14	11.81	1358.82	92	45.57	3383.36	75	43.86	3352.22	85	46.55	3740.67	87
MGH clinic	61:55	13.43	1771.23	114	45.00	4372.09	93	38.31	4572.58	102	41.01	4322.54	96
<i>P</i> -value	0.20	0.38	0.14		0.90	0.08		0.17	0.054		0.26	0.31	

pH tracings to quantify transit times of gastric emptying, small bowel transit, and colonic transit^{5,13}. Only events that occurred while the capsule resided in the colon were considered for analysis. Normal colonic transit time (CTT) was defined as less than 59 h in accordance with prior studies¹⁷.

Contractility parameters of interest included Ct and area under the contraction curve (AUC). Data 1 h prior to and after awakening were obtained and divided into 20-min windows to be used for analysis. Pre-wake windows were averaged and used as baseline, with the 20 min prior to awakening excluded from baseline analysis to avoid errors from imprecise diary entry. Windows that overlapped with other events (i.e., meal consumption, bowel movement) were excluded to avoid confounding the analysis. Windows recorded outside of the colon were also excluded from analysis. To ensure data integrity, only windows with greater than 80% retained data were included in accordance with prior studies utilizing WMC¹⁸.

Statistical analysis

To determine if WMC was capable of detecting the wake response, paired *t*-tests were performed comparing contractility parameters of the three post-wake windows against baseline. Comparisons amongst healthy volunteers, NTC, and STC using unpaired *t*-tests were performed between respective baseline and post-wake windows. Subjects were stratified with respect to evidence of outlet obstruction on BET, with outlet obstruction defined as balloon expulsion failure after 2 min of attempt. An age-adjusted and sex-adjusted linear regression analysis was performed to determine if outlet obstruction was associated with a decreased wake response. To estimate capsule location, CTT was divided into quartiles to represent location with the first quartile representing proximal colon and fourth quartile representing distal colon, similar to previous work with WMC¹⁹ with subsequent comparison of respective wake events between cohorts.

All statistical analyses were performed with Bonferroni corrections with statistical significance determined when

$p < 0.05$. A receiver operating characteristic (ROC) curve was created from the multicenter clinical trial data as a training dataset. Optimal cut-offs were calculated by means of the Youden J-Index from the multicenter clinical trial cohort with sensitivity and specificity determined through application of the cutoff to the clinical practice database.

Results

Subject characteristics

Patients were selected from two cohorts that had undergone WMC testing: the multicenter trial ($n = 242$) and MGH clinic ($n = 217$). Among these subjects, healthy volunteers ($n = 62$) from the multicenter trial and those with clinical symptoms of chronic constipation from both the multicenter trial ($n = 51$) and MGH clinic ($n = 77$) were selected. In those with constipation, there was no statistically significant difference between the two cohorts with respect to CTT or contractile parameters (Table 1). Cohorts were combined and stratified by CTT into healthy controls, NTC, and STC. Subject diaries were correlated to WMC event markers to determine the number of wake events with sufficient data capture (Table 2, Supplemental Fig. 1).

WMC assessment of wake response

All subject groups—healthy, NTC, STC—had statistically significant increases in contractility parameters following awakening when compared to baseline after Bonferroni correction ($p < 0.001$). At baseline prior to awakening, there was no significant difference in the mean contraction frequency (Ct) between the three groups ($p > 0.15$). In the 20 min, 20–40 min, and 40–60 min after awakening, STC subjects had significantly lower mean Ct when compared to healthy controls ($p < 0.001$) and NTC ($p < 0.01$) (Fig. 1, Table 3). The AUC was significantly higher at baseline for NTC and STC compared to healthy controls, and there were no significant differences in mean AUC between the three subject groups in the post-wake analysis period with the exception of NTC and STC in the 40–60-min window.

Table 2 Total number of subjects and wake events in each 20-min analysis window, stratified by transit time

Subjects	Wake events			
	Baseline	Wake to +20 min	+20–40 min	+40–60 min
Healthy <i>N</i> = 62	57	50	47	57
Normal transit constipation <i>N</i> = 53	64	48	52	58
Slow transit constipation <i>N</i> = 75	142	120	135	125

Table 3 Contractility parameters (Ct and AUC) before and after wake events (N) among healthy controls, normal transit constipation (NTC), and slow transit constipation (STC) subjects

	Baseline			Wake to +20			+20 to +40			+40 to +60		
	Ct	AUC	<i>N</i>	Ct	AUC	<i>N</i>	Ct	AUC	<i>N</i>	Ct	AUC	<i>N</i>
Healthy	8.96	761.25	57	67.78	4924.35	50	58.09	3723.02	47	57.91	4071.99	57
NTC ^a	12.03	1562.43	64	55.52	4524.64	48	53.83	4811.21	52	53.78	5066.08	58
STC	13.01	1598.14	142	41.15	3693.11	120	35.83	3712.29	135	38.94	3572.56	125
<i>p</i> -value STC vs. Healthy	0.09	0.002		<0.001	0.05		<0.001	1.97		0.001	0.73	
<i>p</i> -value STC vs. NTC	1.24	1.81		0.006	0.38		<0.001	0.24		0.009	0.03	

^aContractility parameter differences were not statistically significant between Healthy and NTC subjects except for AUC at baseline ($p = 0.04$).

Balloon expulsion testing

Subjects with normal and STC were stratified by presence of outlet obstruction on BET (Table 4). No statistically significant differences in Ct were observed between patients with delayed and normal BET in the respective NTC and STC cohorts. In both NTC subgroups (normal and delayed BET), there were no significant differences in Ct post-awakening when compared to healthy individuals. Both STC subgroups showed significantly decreased Ct compared to healthy controls in all post-wake windows ($p < 0.01$) (Fig. 2). STC subjects with a prolonged BET showed decreased Ct in all post-wake windows compared to all subjects with NTC ($p < 0.05$) (Fig. 2). STC subjects with a normal BET had decreased Ct 20 to 60 min after awakening compared to all NTC subjects ($p < 0.05$) (Fig. 2). The 20-min window immediately after awakening showed the greatest change in Ct from baseline, and was used for further exploratory analyses. To further assess the impact of outlet obstruction as measured by BET on wake response, age- and sex-adjusted linear regression analyses demonstrated that prolonged BET was not associated with a decreased wake response in this 20-min post-wake window ($\beta = 3.94$ (CI -3.12 – 1.00), $p = 0.27$).

Estimating capsule location

In the first quartile, there were no significant differences in Ct count between subject groups. Whereas in the

second quartile, STC had significantly decreased Ct compared to Healthy and NTC ($p < 0.05$) in the last 40 min after wake. In the third quartile, STC showed significantly decreased Ct only compared to Healthy individuals within the first 40 min after waking ($p < 0.01$). Finally, in the fourth quartile, STC had significantly decreased Ct compared to Healthy and NTC ($p < 0.001$) in the entire 60 min after waking up. In all cases, there were no significant differences between Healthy and NTC subjects. (Supplemental Table 1).

Diagnostic accuracy

An observable, although blunted, wake response in STC suggests dysfunction is primarily from neuropathy, rather than myopathy. Using the multicenter clinical trial cohort, an ROC curve (AUC = 0.6764) was constructed to determine the diagnostic accuracy of using Ct in the first 20-min post-wake window (a presumed marker of blunted wake response) to predict colonic neuropathy as evidenced by STC (Fig. 3). The maximum value of Youden's index for the ROC curve corresponded to a Ct threshold of 54.01. Applying this Ct threshold to the second, clinical cohort yielded a sensitivity of 74.6% and a specificity of 54.2%. To maximize sensitivity for the detection of STC, a Ct threshold of 64 was used to define blunted wake response (sensitivity 84%, specificity 32%).

Table 4 Total number of subjects and wake events in each 20-min analysis window, stratified by balloon expulsion testing (BET)

	Wake events			
	Baseline	Wake to +20 min	+20–40 min	+40–60 min
Normal transit constipation (N = 53)				
Negative BET N = 45	53	40	43	47
Positive BET N = 8	11	8	9	11
Slow transit constipation (N = 75)				
Negative BET N = 45	88	67	81	73
Positive BET N = 30	55	54	55	53

Discussion

Using two cohorts of patients that had undergone WMC testing, we compared the colonic motor response to awakening in subjects with chronic constipation and healthy controls. WMC testing allowed for simultaneous detection of diurnal variation in colonic contractility as well as transit time, and significant differences were observed between healthy controls, NTC, and STC subjects. Both NTC and STC cohorts demonstrated an observable increase in colonic contractility upon awakening from sleep; however, STC was associated with a significantly decreased contraction frequency (Ct) 1-h after awakening when compared to both healthy volunteers and NTC. There were no significant differences in wake response between healthy volunteers and NTC subjects. Stratifying these cohorts by BET results also demonstrated observable decreases in Ct in both subgroups of STC compared to both healthy controls and NTC, with no significant differences between those with a prolonged BET vs. those with a normal BET within the NTC and STC cohorts, which persisted after multivariable adjustment.

This study builds on prior work from Rao et al. demonstrating a blunted colonic wake response in STC compared to healthy controls, further supporting impaired wake response as a possible indicator of neuropathy in the evaluation of chronic constipation¹². Through use of WMC to study colonic wake response rather than 24-h colonic manometry used in prior studies, we observed that in patients with STC wake-response is not only blunted with respect to healthy controls, but to subjects with NTC as well. There were no significant wake response differences between healthy controls and NTC subjects. These findings therefore suggest that STC and NTC may have fundamentally different mechanisms of pathogenesis, with the former perhaps representing a neuropathic motility defect as evidenced by a blunted wake response and the latter a sensory phenomenon akin to the abnormalities seen in

patient with irritable bowel syndrome. Although data from our group and others suggests that a sizeable proportion of patients with prolonged BET have concomitant slow transit by radiopaque marker studies with reflexive slowing of colonic motility as a proposed explanatory model, this data suggests that the blunted wake response observed in STC is independent of outlet obstruction as measured by BET with similar findings among NTC patients as well^{20,21}.

Colonic motor activity is a coordinated effort by the underlying neuronal and hormonal mechanisms²². Decreased interstitial cells of Cajal, lower ganglionic density and size in the myenteric plexus, and reduced glial cells have been previously demonstrated in STC^{23–25}. Additionally, Coleski et al. recently reported that diabetic subjects with gastroparesis had reduced colonic contractions compared to control and diabetics with normal gastric emptying²⁶. Thus it is postulated that neuronal changes contribute to the altered colonic contractility seen in our data. Given the therapeutic goal of restoring healthy colonic transit and contractile patterns in patients with STC, our findings may highlight a potential therapeutic target. Perhaps patients with a blunted wake response would benefit from a short-acting stimulant laxative dosed on awakening to jumpstart colonic motility and restore an important physiologic characteristic of normal colonic transit, while those with an intact wake response might preferentially benefit more from an osmotic agent without the discomfort frequently attributed to stimulant laxatives²⁷. Because stimulant laxative interventions to treat a blunted wake response have low risks compared to treatments for other diseases, we sought to identify a Ct cutoff that would maximize sensitivity to identify the most patients that could benefit from treatment. That said, the training data set derived from the clinical trial may not be reflective of the population at large and further studies may be needed to define optimal cutoff points for the identification of the wake response.

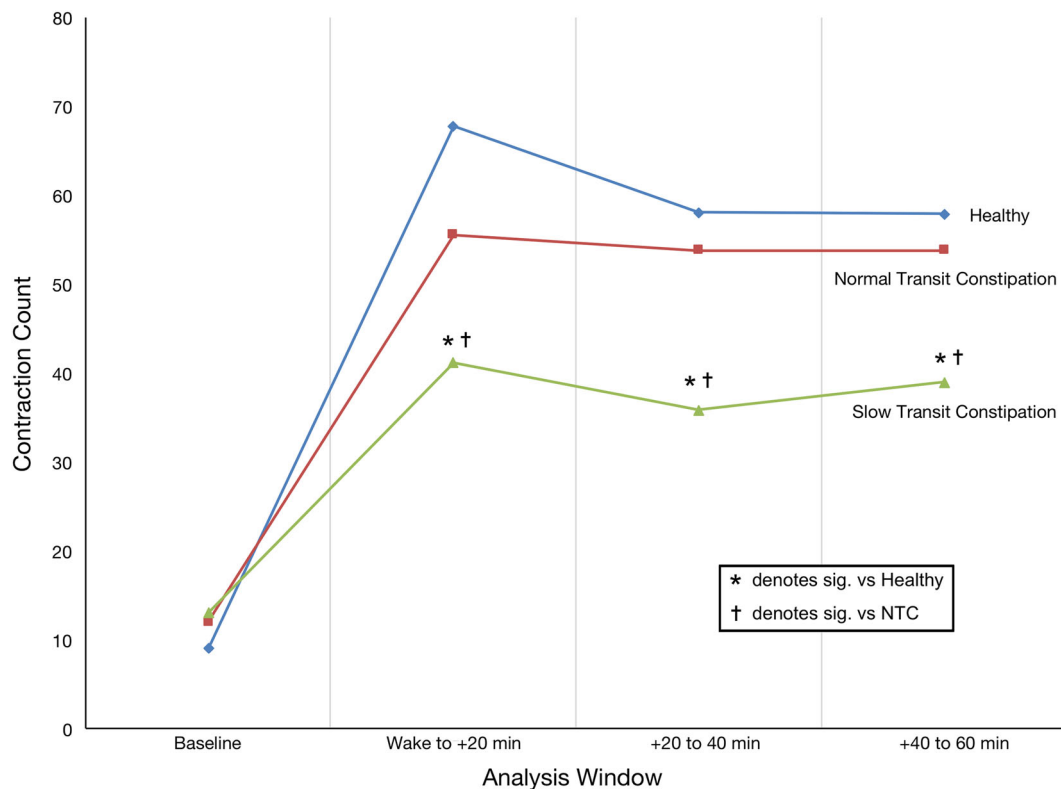


Fig. 1 Contraction frequency (Ct) prior to (Baseline) and in 20-min segments following wake events for healthy controls, normal transit constipation (NTC), and slow transit constipation (STC) subjects

Prior studies have used 24-h colonic manometry to assess wake response, however, they have differed in their method of analysis. Ranging from assessing colonic contraction frequency in 30-min windows^{9,11}, to 1-h windows¹², previous studies have examined how wake response differs regionally within the colon. Here, we investigated the post-wake contractility response in 20-min windows over the course of an hour post-wake. This allowed us to observe the dynamic change that occurs within that timeframe. In healthy individuals, the peak colonic contractility is observed in the first 20 min after awakening, after which there is a slight decrease and plateau in the subsequent 40 min of observation (Fig. 1, Fig. 2). The physiologic peak in contractility that occurs in healthy patients immediately upon awakening is a potentially useful temporal target in which to time pharmacotherapy as it may build upon a blunted response and induce a bowel movement. Future clinical study is needed to determine if timing laxative use shortly after awakening ultimately influences bowel movement frequency in patients identified with STC or a blunted colonic wake response.

The prior 24-h colonic motility studies utilized low-resolution catheters where pressure transducers were spaced up to 15 cm apart^{9,12}, limiting assessment.

Recently, high-resolution manometry catheters have become available to overcome this limitation, however has yet to assess the colonic wake response²⁸. To our knowledge, this is the largest study of the colonic wake response in healthy volunteers and chronic constipation subjects, likely facilitated by the less invasive and more tolerable nature of WMC compared to traditional manometric techniques, which require colonoscopy and fluoroscopy. WMC does not require bowel preparation prior to the study which may alter colonic motility²⁹ and can be performed in a more ambulatory nature that is not confined within a clinic or laboratory^{9,12}. Simultaneous transit time recording identifies cases of STC and other regional gut-transit delay. The WMC study duration of 5 days allowed for the analysis of multiple wake events per subject measured in an ambulatory setting that may serve as a more accurate reflection of routine colonic function.

The study was not without limitations. As this was a retrospective analysis, we were unable to correlate sleep stage with contractile parameters, which have been shown to be suppressed during slow-wave sleep and increased during REM³⁰. We were unable to adjust for temporal effects of undetectable stimuli (i.e., cephalic phase from thoughts of meal consumption)

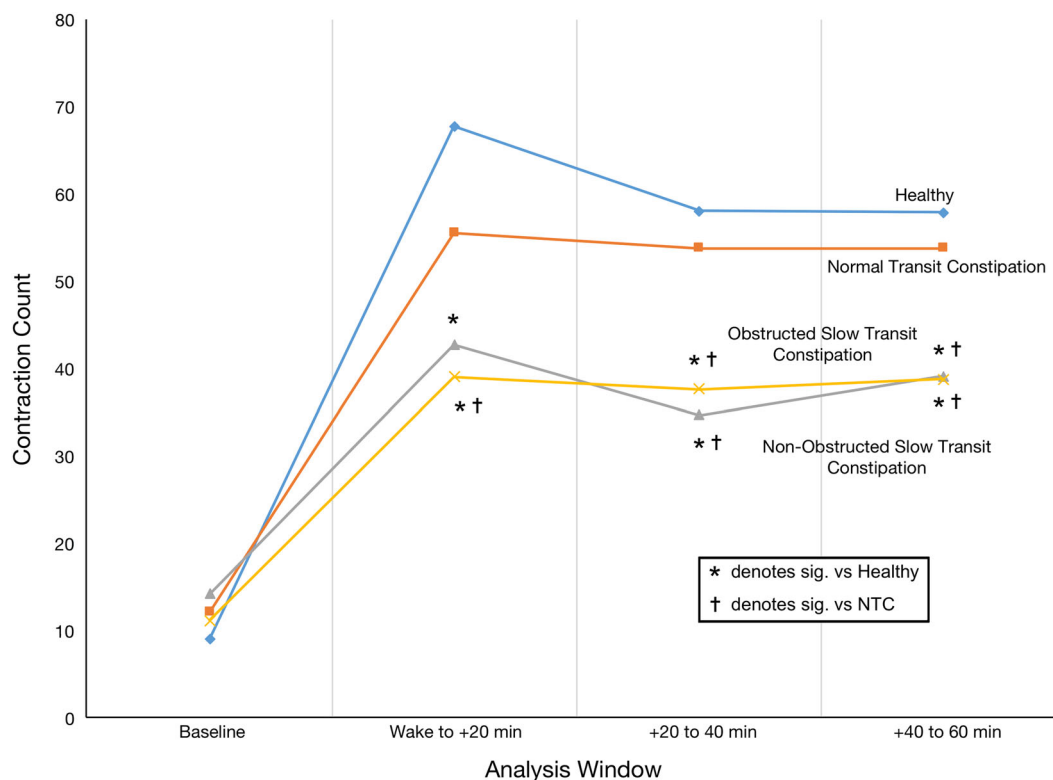


Fig. 2 Contraction frequency prior to and in 20-min segments following wake for healthy controls, normal transit constipation and slow transit constipation subjects with and without outlet obstruction by balloon expulsion testing

that may influence contractility, and were subject to patient compliance with recording events on their WMC monitor and corresponding diaries. A limitation of WMC is that at any point in time, motility is only measured at a fixed location unlike manometry, which can simultaneously assess multiple colonic locations for the presence of high amplitude propagated contractions contributing to peristalsis. Limiting recorded wake events to those in which WMC monitors captured >80% of data decreased the sample size of study, however ensured fidelity of the data (Supplemental Fig. 1).

Furthermore, we were unable to assess colonic tone or capsule location within the colon which has previously been shown to be a factor in contractility. A previous study has demonstrated increased contractile frequency in the proximal colon⁹, with another study showing no significant regional variations amongst STC patients¹², both via manometric evaluation.

Hasler et al. previously characterized colonic contractility with WMC by dividing CTT into quartiles as a surrogate for location, with the first quartile representing proximal colon, and the fourth quartile representing more distal colon¹⁹. In similar fashion, a sub-analysis was performed and categorized each wake event into

corresponding quartile. In the last three quartiles, there was decreased Ct in STC subjects compared to healthy individuals, although in varying time windows. NTC subjects still behaved similar to Healthy individuals. (Suppl Table 1) Our results contrast the findings by Hasler et al. where Ct count did not differ between constipation and Healthy subjects in all quartiles. This is likely because their study observed contractility for the entire quartile and included periods of sleep and thus motor quiescence, potentially decreasing the overall Ct average, whereas the present study focused on discrete motor activity during known wake periods. The attenuation of the colonic wake response in STC captured by capsule technology seems most evident in the distal region as decreased Ct was seen for the entire 60 min after waking.

The above quartile method is an imperfect solution to localize the WMC. Recent advances have been made to more accurately locate telemetry capsules using electromagnetic tracking in an ambulatory setting³¹. Data from healthy volunteers using this technology have suggested that luminal flow does not progress linearly with respect to time³², spending most of transit time between the cecum and splenic flexure. While promising, this technology in current form only measures contraction

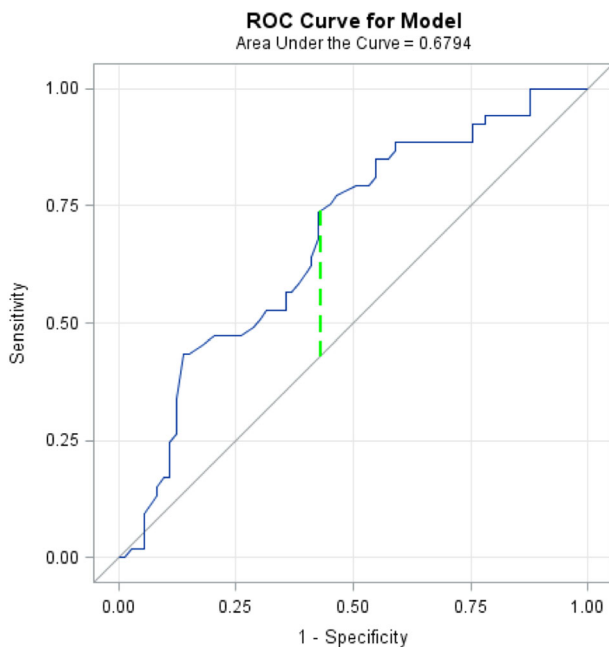


Fig. 3 Receiver operating characteristic curve of Ct in the first 20-min post-wake window as a predictor of slow transit constipation. Solid blue: ROC curve; Solid gray: Chance level; Dashed green: maximum value of Youden's index for the ROC curve

frequency and lacks manometric capability, therefore has limited assessment of contractile strength. Another disadvantage includes a 60-h battery life that would limit assessment of STC subjects.

With WMC, despite an imperfect solution for colonic localization, assessing the wake response still provides a global sense of colonic dysfunction in STC and it remains a clinically available tool to measure transit and contractility simultaneously in a non-invasive manner. Our data still support prior manometry findings that contractility is overall decreased in STC¹⁰.

In conclusion, diurnal variation in colonic motor activity is a well-described phenomenon that requires coordination by intact neuroenteric circuitry and presents as a potential clinical biomarker for neuropathy. Our observation of an impaired wake response in subjects with STC, and not NTC, adds further evidence to neuronal dysfunction as an etiology in this subset of chronic constipation. The contractile response in the first hour after awakening suggests that this may be the optimal timeframe for pharmacologic intervention. By using WMC technology to identify defects in the wake response among patients with STC, we have added to the available means for classifying the pathophysiologic abnormalities in chronic constipation with the recognition a possible therapeutic target for pharmacologic intervention.

Study Highlights

1. What is current knowledge

- Colonic wake response is a relative increase in colonic contractility upon awakening.
- Colonic manometry studies have detected attenuated wake response in patients with STC.

2. What is new here

- Ambulatory WMC demonstrates an impaired wake response in subjects with STC.
- NTC subjects have an intact colonic wake response.

3. Translational impact

- An impaired wake response adds further evidence to neuronal dysfunction as an etiology of STC.
- WMC non-invasively measures the colonic wake response in an ambulatory environment.
- This provides a possible temporal target for pharmacologic intervention on wakening in STC.

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Conflict of interest

Guarantor of the article: Braden Kuo

Specific author contributions: B.S., K.B., and K.S. performed the research, analyzed the data, and wrote the paper. J.S. edited the paper. L.G. designed the research study. B.K. designed the research study, analyzed the data, and wrote the paper. Compliance with ethical standards

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