Heightened colon motor activity measured by a wireless capsule in patients with constipation: relation to colon transit and IBS

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Submitted 9 April 2009; accepted in final form 30 September 2009

PATIENTS WITH CONSTIPATION report a range of complaints including infrequent defecation, passage of hard stools, straining, and a sense of incomplete evacuation (22). Likewise, several pathophysiological defects are described. Some patients exhibit markedly prolonged transit and are considered to have slow transit constipation (STC) (26). Others show impaired anorectal coordination consistent with functional outlet obstruction (also referred to as rectosphincteric dyssynergia) (26). Some patients exhibit normal colonic and anorectal physiological testing; many of these individuals typically report abdominal discomfort or pain and are considered to have constipation-predominant irritable bowel syndrome (C-IBS) (26).

On colon manometry, reductions in motor activity including high-amplitude propagating contractions are observed in patients with the most severe forms of STC, suggesting that impaired contractile activity may cause delays in colon transit (2, 3, 5, 6, 16, 28). Colonic motor patterns in patients with lesser degrees of slow transit are less well characterized. Additionally, most studies have been performed after consumption of lavage solutions to cleanse the colon, which can modify colonic motor patterns (30). IBS patients show inconsistent changes in colonic motor activity both under basal conditions and after stimulation such as with meal ingestion (4, 10). A rigorous comparison of regional contractile patterns in the unprepared colon in patients with varying degrees of STC has not been performed. Furthermore, differences in unprepared colon motor activity in constipated patients with and without IBS are poorly characterized.

In the present investigation, we employed a novel wireless capsule method that continuously measures luminal pH, pressure, and temperature to test three hypotheses. We first hypothesized that contractile activity shows an increasing gradient from proximal to distal colon in healthy humans and patients with constipation. To test this hypothesis, we divided the colon transit time into quartiles with the first quartile reflecting proximal colonic transit and the fourth quartile representing distal colonic transit, and we measured two motor parameters. Second, we hypothesized that colon contractile activity relates to the degree of slow colonic transit. To test the second hypothesis, we compared pressure activity in healthy subjects with three distinct constipation subgroups, namely those with normal transit (colon transit <59 h), those with moderate STC (59–100 h), and those with severe STC (>100 h). Individuals with objective evidence of functional outlet obstruction as a possible cause of constipation were excluded to obtain a more reliable assessment of the contribution of colon contractions to transit. Third, we hypothesized that IBS is associated with increased colon motor activity irrespective of transit time and that the presence of IBS is partly responsible for the observed alterations in colon contractions with constipation. To test this hypothesis, we administered validated Rome II questionnaires to constipated subjects. Results were related to demographic...
variables including age, sex, and body mass index (BMI) to verify that any observed differences were secondary to transit time or subject group. Through these studies, we hoped to gain insight into pathogenic roles for the magnitudes of colon motor activity that controls colon transit and distinguishes C-IBS from functional constipation not secondary to IBS.

MATERIALS AND METHODS

Human Subjects

Thirty-six patients (5 men, 31 women, age 47.4 ± 2.6 yr, BMI 26.7 ± 0.7 kg/m²) with self-reported constipation and who fulfilled Rome II criteria for chronic functional constipation were recruited from eight participating centers for an investigation of whole gut transit (27). Subjects who experienced symptoms for at least 3 mo and reported at least two of the six symptoms of constipation were included. All constipated individuals underwent balloon expulsion testing to determine the presence or absence of functional outlet obstruction. Twenty-one subjects from the parent study with balloon expulsion time >60 s were considered to have functional outlet obstruction and were excluded from the analyses of this investigation (27). All centers employed a common protocol for balloon expulsion testing. After lubrication, a catheter with a deflated balloon was passed 10 cm proximal to the anal verge. The balloon was inflated with 50 ml of water, and the subject was asked to sit on a commode in a private room and to attempt to expel the balloon. Subjects were provided a stop clock that was deactivated upon balloon passage. Subjects with prior gastrointestinal surgery (except appendectomy, cholecystectomy, or cesarean sections) were also excluded.

Fifty-three healthy volunteers (27 men, 26 women, age 37.2 ± 1.6 yr, BMI 25.5 ± 0.6 kg/m²) were recruited using campus-wide advertisements from the eight participating centers. These individuals reported no gastrointestinal symptoms on the Mayo GI Disease Screening Questionnaire. Healthy subjects had no prior gastrointestinal surgery, were not morbidly obese (BMI <35 kg/m²), were on no medications known to affect gut transit, and reported no cardiovascular, endocrine, renal, or hepatic disease.

Before study, any medications that could suppress or neutralize gastric acid and accelerate or delay gut transit were discontinued. Proton pump inhibitors were stopped 7 days, histamine₂ receptor antagonists were stopped 2 days, and antacids were stopped 1 day before capsule ingestion. Prokinetics such as metoclopramide, erythromycin, and domperidone, medications in the anticholinergic and 5-HT₃ receptor antagonist classes, and therapies targeting constipation (including laxatives, enemas, and suppositories) were held for 2 days. Opiate agents and nonsteroidal anti-inflammatory drugs were stopped 7 days before study. Subjects on stable doses (≥6 mo) of antidepresants, oral contraceptives, and antilipid drugs were allowed to remain on these medications. Women of child-bearing potential underwent urine pregnancy testing on the morning of study before capsule ingestion.

Studies at each of the eight participating centers were approved by the local Institutional Review Boards. Before study participation, each subject provided written, informed consent.

Experimental Protocol

After overnight fasting, each subject consumed a standardized 260-kcal nutrient bar (SmartBar; SmartPill, Buffalo, NY) that was comprised of 20% protein, 74% carbohydrates, 3% fat, and 3% fiber with 50 ml of water. The subject then swallowed a pH-, pressure-, and temperature-sensing, wireless capsule (SmartPill) with 50 ml of water. The capsule measures 26.8 mm × 11.7 mm and transmits sensed data at a radio carrier frequency of 434 MHz to a receiver worn by the subject. As part of the parent study, each subject also ingested a capsule containing 24 radioopaque markers (Sitzmarks; Konsyl Pharmaceuticals, Fort Worth, TX) (27). Each subject remained in the study center for at least 6 h after capsule ingestion. Bathroom visits were permitted; however, sleep was not allowed during the initial 6 h after capsule ingestion to prevent any modulatory effects of sleep on upper gut transit. Six hours after capsule ingestion, each subject consumed a 250-ml liquid nutrient meal (Ensure; Abbott Laboratories, Abbott Park, IL) and then left the test facility but continued to wear the receiver unit for ongoing data acquisition. Subjects resumed their normal diets and most medications; however, no alcohol or medications with effects on gut transit were permitted. A formal protocol involving abdominal radiographs (if needed) was followed to confirm capsule passage.

Intraluminal pH assessments were obtained every 5 s for the first 24 h then every 10 s from 24 to 48 h after capsule ingestion. After 48 h, pH was measured every 2.5 min. The capsule was able to detect pH changes in the range from 0.05 to 9.0 with a sensitivity of ± 0.5 pH units. Capsule pressure measurements in the range from 0 to 350 mmHg were acquired every 0.5 s during the first 24 h of recording and every 1 s thereafter and were accurate to within ± 5 mmHg for values <100 mmHg and within ± 10% for pressure >100 mmHg. Temperature determinations in the range from 25 to 49°C were obtained every 20 s in the first 24 h and every 40 s thereafter and were accurate to within 1°C.

Data Analysis

Luminal pH and temperature parameters. pH and temperature data were downloaded from the receiver through a docking station via a USB connection to a Windows PC compatible laptop computer (Dell Latitude; Dell Computer, Round Rock, TX). Digitized data files were then uploaded to a spreadsheet for subsequent analysis (Excel; Microsoft, Redmond, WA). The beginning of the pH recording was defined as the time that the capsule was swallowed. Capsule passage into the duodenum was defined as the point the pH value abruptly rose to at least 2 pH units from the lowest postprandial value to a pH of at least 4 and did not decrease to a value below 4 for more than 10 min at any subsequent time in the recording. Capsule passage from the ileum into the cecum was determined when an abrupt pH decrease of at least 1.0 pH unit was observed at least 30 min after gastric evacuation of the capsule and persisted for at least 10 min. This pH decrease is observed in ~85% of healthy subjects and patients with constipation and has been validated as an indicator of ileocecal transit (14, 27). Any potential subjects from the parent study not exhibiting this decrease were excluded from the analyses performed in this investigation. Temperature was consistent within a range from 96.0 to 99.5°F during capsule transit through the stomach, small intestine, and colon. Anal capsule expulsion was determined by an abrupt 0.045°F/s decrease. Colon transit was calculated from the time of ileocecal passage from the pH recording to anal expulsion as defined by the temperature data (27).

Luminal pressure parameters. Pressure recordings were analyzed from the time of ileocecal capsule passage to the time of anal expulsion. Any subjects from the parent study exhibiting loss of pressure signals for more than 5% of any quartile of colon transit were excluded from the analyses of this investigation. In most instances, such signal dropout occurred as a consequence of the subject placing the receiver too far away during sleep. Two pressure parameters were calculated to quantify colonic motor activity (GIMS Viewer, Release 1.6; SmartPill). Numbers of contractions >25 mmHg in amplitude were measured for a given recording period and standardized to contractions per 15 min to compare recording periods of different length. Likewise, areas under pressure curves (AUC) for pressure activity >25 mmHg were standardized to AUC per 15 min. This calculation was provided by the GIMS Viewer program in the units of mmHg × min. The total colonic transit time for each subject was divided by four, and times for first, second, third, and fourth quartiles of transit were determined. Pressure parameters were quantified for
Colon pH and Motor Profiles in Health and Constipation

Colon transit was determined from the pH recordings obtained from the wireless capsule. In a representative recording from a healthy subject, ileocecal transit was reflected by a 1.3 pH unit decrease 4.5 h after gastric emptying of the capsule (Fig. 1A). Anal expulsion was detected when the temperature abruptly decreased. Subtracting the time the capsule passed the ileocecal junction from the time of anal expulsion resulted in a colonic transit time of 18 h in this healthy individual. Pressure activity during the period of colon transit was variable but showed a significant increase before capsule expulsion (Fig. 1A). In contrast, a patient with constipation exhibited a markedly prolonged colonic transit time of 110 h (Fig. 1B). Despite the presence of severe STC in this individual, prominent pressure activity was present throughout the period of colonic transit. Unlike the healthy subject, pressure activity did not show an increase from the proximal to distal colon.

Colon Motor Activity in Relation to Colon Transit in Health and Constipation

Two pressure parameters for contractions >25 mmHg in amplitude were quantified to provide measures of colon motor activity, namely numbers of contractions per 15 min and AUC per 15 min. Mean numbers of contractions and AUC values were compared in the healthy subjects vs. constipated patients in each of the transit subgroups. Mean numbers of contractions were not different in the three constipation subgroups or compared with the healthy subjects (Fig. 2A). However, mean AUC values were higher in constipated subjects with normal transit (P = 0.01) and moderate STC (P = 0.004) compared with those in healthy subjects (Fig. 2B). Constipated subjects with severe STC exhibited mean AUC values that were not different from values in the healthy subjects or constipated subjects with normal transit or moderate STC (P = NS).

Numbers of contractions and AUC values for each quartile of colonic transit were compared among the different constipation subgroups to determine whether increases in motor activity from the proximal and distal colon were altered in relation to differences in colonic transit. In healthy subjects,
contractions were infrequent during the first quartile but showed progressive increases that were maximal in the fourth quartile ($P < 0.0001$) (Fig. 3A). Significant increases in numbers of contractions were observed from the first to the fourth quartile of colon transit for patients with moderate STC ($P = 0.002$), and marginally nonsignificant differences were found for constipated patients with normal transit ($P = 0.052$) (Fig. 3A). Conversely, numbers of contractions did not significantly increase from the first to the fourth quartile in subjects with severe STC ($P = NS$). Numbers of contractions in constipated subjects with normal transit, moderate STC, and severe STC were not significantly different from those of healthy controls in any quartile ($P = NS$). In healthy subjects, AUC values increased from the first to the fourth quartile of colon transit ($P < 0.0001$) (Fig. 3B). AUC values also significantly increased from the first to the fourth quartile of colon transit in constipated subjects with normal colon transit ($P < 0.0001$), moderate STC ($P < 0.0001$), and severe STC ($P = 0.007$) (Fig. 3B). Compared with healthy subjects, AUC values in constipated subjects with normal transit were increased in the first ($P = 0.006$), second ($P = 0.02$), and third ($P = 0.03$) quartiles, whereas those with moderate STC showed increases in the
second ($P = 0.005$), third ($P = 0.002$), and fourth ($P = 0.01$) quartiles. Conversely, subjects with severe STC exhibited decreases in AUC values compared with those with moderate STC in the second ($P = 0.03$) quartile but were not different from other subject groups in other quartiles ($P = NS$).

When demographic variables were included in the multivariate linear model, reported differences in mean numbers of contractions between subject groups and quartiles of colon transit were consistent and were not explained by differences in age ($P = 0.30$), sex ($P = 0.56$), or BMI ($P = 0.10$). Likewise, differences in AUC between subject groups and quartile were not explained by age ($P = 0.16$), sex ($P = 0.60$), or BMI ($P = 0.85$).

**Colon Motor Activity in Relation to Presence of IBS**

Mean numbers of contractions and AUC values were compared in constipated patients who satisfied the Rome II criteria for C-IBS vs. subjects with functional constipation not secondary to IBS. Mean numbers of contractions were higher in patients with C-IBS compared with healthy subjects ($P = 0.05$) (Fig. 4A). Likewise, mean AUC values were greater in those with C-IBS vs. healthy controls ($P = 0.0006$) and were marginally nonsignificantly greater in patients with C-IBS compared with those with functional constipation ($P = 0.052$) (Fig. 4B). Numbers of contractions increased similarly from the first to the fourth quartile of colon transit in those with C-IBS ($P = 0.02$) and functional constipation ($P = 0.006$) (Fig. 5A). Likewise, AUC increases from the first to the fourth quartile were similar in patients with C-IBS ($P < 0.0001$) and those with functional constipation ($P < 0.0001$) (Fig. 5B). Individuals with C-IBS showed greater numbers of contractions than healthy subjects in the second quartile of transit ($P = 0.04$). Compared with individuals with functional constipation, subjects with C-IBS exhibited significant increases in numbers of contractions in the fourth quartile ($P = 0.02$). Subjects with C-IBS exhibited higher AUC values in the first, second, and fourth quartiles of colon transit compared with healthy subjects (all $P < 0.05$). Compared with healthy controls, subjects with functional constipation showed significant increases in AUC values in the third quartile ($P = 0.008$) and marginally non-significant increases in the second quartile ($P = 0.055$). Subjects with C-IBS exhibited significantly greater AUC values than those with functional constipation only in the fourth quartile ($P = 0.001$).

When demographic variables were included in the multivariate linear model, differences in numbers of contractions between subject groups and quartiles of colonic transit were not explained by differences in age ($P = 0.25$), sex ($P = 0.34$), or BMI ($P = 0.12$). Likewise differences in AUC between subject groups and quartile were not explained by age ($P = 0.24$), sex ($P = 0.88$), or BMI ($P = 0.92$).

Colonic transit values for patients with C-IBS were compared with values from those with functional constipation to determine whether increases in motor activity with C-IBS related to differences in transit time. There were no significant differences in colonic transit time between subjects with C-IBS ($58.6 \pm 10.4$ h) and with functional constipation ($53.8 \pm 7.2$ h) ($P = 0.70$). Within the C-IBS group were five subjects with normal colonic transit (41.7%), five subjects with moderate STC (41.7%), and two subjects with severe STC (16.7%). Within the functional constipation group were 16 subjects with normal transit (66.7%), four subjects with moderate STC (16.7%), and four subjects with severe STC (16.7%) ($P = NS$).

**DISCUSSION**

Constipation is a common complaint of patients referred for advanced testing (22). Some cases are classified as STC on the basis of localized or generalized delays in propulsion of radioopaque or scintigraphic markers (26, 23, 24). Other patients show functional outlet obstruction from dyscoordinated recto-anal activity (26). C-IBS is distinguished by discomfort relieved by defecation or associated with altered stool frequency or form (7, 22).

Fecal transit is regulated by localized mixing contractions that facilitate fluid extraction, high-amplitude propagating contractions (HAPCs) that are the driving forces for stool evacuation, and external influences such as meal ingestion and sleep (17). On manometry, STC is associated with decreased colon contractions, loss of HAPCs, and blunting of gastrocolic

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**Fig. 4.** The mean numbers (A) and AUC values (B) of colon contractions $>25$ mmHg per 15 min are compared in healthy subjects, subjects with constipation-predominant irritable bowel syndrome (C-IBS), and individuals with functional constipation not meeting criteria for C-IBS. Numbers of colon contractions and AUC values were significantly greater in the C-IBS subset compared with healthy subjects.
responses to meals although increased rectosigmoid activity has been observed (2, 3, 5, 6, 16, 28). In contrast, C-IBS is characterized by increased contractile parameters and variable numbers of HAPCs (2, 4, 10, 20). One study related pain in IBS to HAPCs with 95% correlation (9). Motor patterns in constipated patients with normal transit but without IBS are less well defined although reductions in gastrocolonic responses and HAPCs have been noted (1).

Much is known about colon function in severe constipation, but our understanding of contractile profiles in other constipation subgroups is limited. Many colon manometry studies have been performed for childhood constipation or for refractory STC under consideration for colectomy conditions different from those in most constipated adults (2, 5, 12, 15, 16, 24, 25, 28, 29). Motor patterns in constipated individuals with variable transit delays have not been contrasted using a common protocol. Furthermore, contraction parameters in C-IBS have not been related to degrees of transit delay. Second, most manometry studies are performed after cleansing the colon with a lavage solution before catheter placement, raising concern that observed motor patterns may not reflect those under physiological conditions of fecal retention. In studies in constipation, colon transit times were reduced by a mean of 22 h by an oral lavage solution (30).

The present investigation used wireless capsules to quantify transit and contractile activity in unprepared colons from patients in several constipation subgroups. As in prior studies, 58% of constipated patients exhibited normal transit (21, 25). Motor activity increased from the early phase of colon transit to the time before capsule expulsion in healthy individuals and constipated subjects with normal transit and moderate STC with inconsistent increases in severe STC. Constipated patients with normal to moderately delayed transit showed increased motor activity compared with controls. Even with severe STC, motor parameters were not lower than control values. Indeed, only one of six patients with severe STC showed >50% reductions in contractions or AUC compared with healthy subjects. As in prior studies, C-IBS was associated with increased pressure parameters vs. healthy controls. Furthermore, patients with C-IBS showed some increases in motor activity vs. those with functional constipation even though colon transit was similar in the two groups. Some of the increase in contractile activity in the constipation subsets was partly explainable by concurrent C-IBS. However, pressure parameters in subjects with functional constipation without IBS showed slight but significant regional increases compared with values in healthy volunteers, indicating that this patient subset also differs from normal. Analysis of results across values of age, sex, and BMI verified that differences in pressure parameters relating to quartile of transit time or subject group were not attributable to demographic differences. This portion of the multivariate analysis is significant because the parent study observed a significant effect of sex on colon transit (27).

Analysis of transit data from healthy controls from the present study observed prolonged colon transit in women (27.3 ± 2.8 h) vs. men (19.4 ± 2.7 h) (P < 0.05). These findings provide insight into mechanisms of constipation. The greater contractile activity observed distally in healthy and many constipated individuals may serve a beneficial function in propelling firmer stools in this colon region. Anatomic studies observe greater muscle thickness in the distal colon vs. more proximal regions, providing a structural correlate to our findings. Blunting of this increase may contribute to delayed colon transit in patients with severe STC. It is uncertain whether regional luminal diameter variations might contribute to the differences in proximal and distal motor activity measured by the capsule. As with manometry, the capsule measures only contractile activity that occludes the lumen. Presumably, liquid feces in the ascending colon would transmit pressure to the capsule. Thus the device should measure occlusive motor activity with reasonable accuracy comparable to manometry in this region. The finding of increased motor...
activity in constipation likely reflects the inclusion of many subjects with C-IBS. However, subtle increases in pressure activity in functional constipation indicate that augmented contractions are characteristic of constipation in general. It is likely our subjects exhibited less severe constipation than in most studies using colon manometry. The number of subjects being considered for colectomy was not quantified but was likely low. This might explain why so few patients exhibited reduced motor activity in contrast to literature reports. It is possible that our results differ from prior reports because no colon lavage was consummated. Prominently increased contractions in C-IBS are consistent with a possible pathogenic role in producing abdominal discomfort (9). That many patients with delayed transit exhibited increased contractile activity suggests that much of the motor activity in the colon is segmenting rather than propulsive in nature.

This study employed a novel technology to assess ambulatory colon transit and luminal pressure, but the method has limitations. Because the capsule has only one pressure sensor, it cannot characterize contractile propagation. Distinctions could not be made between mixing and propulsive activity, and HAPCs were not detectable. An additional property makes it unlikely that a motility capsule would be optimal for measuring HAPC activity, namely the lack of a stabilizing catheter or other tethering device to maintain a constant position of the pressure port within the colon lumen that would remain stationary as the intense contractile wave passed over. A mobile capsule would be handled in much the same way as stool, especially if the capsule was a component of the fecal bolus. In such an instance, if the capsule was on the leading edge while an HAPC passed, it is possible that a high-amplitude, long-duration contraction would not be recorded or that its contractile characteristics would be diminished. Indeed, in analyses validating the pressure parameters used in this study, some subjects did not exhibit either high-amplitude or long-duration contractions even though they experienced defecation after a normal transit time. Thus, although the capsule can quantify overall colon motor activity, it may be an imperfect detector of HAPCs. A second limitation of the capsule is the inability to distinguish motion artifact from luminal contractions, again because of the single pressure port. With manometry, artifacts are identified as abrupt simultaneous increases in pressure tracings in all recording channels. Pressure increases attributable to abdominal wall straining would give similar appearances as luminal motor activity. However, it is unlikely that subjects would strain in an incrementally increasing fashion as the capsule migrated from the first to the fourth transit quartile or that the very large numbers of contractions observed in some of the constipation subsets would be completely comprised of straining artifact. A third concern is that the capsule is larger than stool and may not be handled physiologically. Studies have observed faster colon transit of capsules and radioopaque markers vs. small particles or liquids (19, 31). Finally, the anatomical location of the wireless capsule cannot be precisely defined. A preliminary study reported that different colon regions exhibit characteristic pH and motor patterns, but there were significant overlaps in these properties (18). Thus the only times the capsule can be definitively localized are immediately after ileocecal transit and before anal expulsion.

The findings of the present investigation may form a foundation for future applications of wireless capsule manometry to manage refractory constipation. Colon transit testing can define patients who may respond poorly to laxatives (e.g., transit time >100 h) and who might be candidates for surgical resection (11). Characteristic motor patterns are observed in neuropathic and myopathic forms of STC (12, 13). Future studies may determine whether capsule methods can distinguish these patterns. Colon manometry can facilitate treatment decisions in managing difficult constipation cases (25, 32). However, applicability of manometry is limited because of the specialized equipment and personnel required and because of demands placed on the patient relating to colon lavage and prolonged recording. The capsule promises to broaden the indications and extend the availability of colon manometric technologies into medical centers other than those specializing in motility disorders.

In conclusion, the present study provides insight into colon motor patterns in health and distinct constipation subgroups. The colon exhibits differential regional motor activity both in healthy individuals and most but not all patients with constipation with greater activity in the distal colon compared with more proximal regions. Constipated patients with normal and moderately (but not severely) delayed colon transit show generalized increases in motor activity. C-IBS is associated with increased motor activity irrespective of colon transit times, which partly explains the increase in colon motor activity in the constipated patients as a whole. However, subtle increases in pressure parameters also are noted with functional constipation that does not satisfy criteria for C-IBS. Observed differences were not secondary to differences in age, sex, or BMI in the distinct subject groups. These findings emphasize the differential effects on transit and motor activity for the different constipation subtypes and provide the foundation for future studies of motor activity in a range of colon motor disorders.

GRANTS

This work was supported by a grant from the SmartPill Corporation.

DISCLOSURES

Drs. Hasler, Rao, Katz, Parkman, Koch, McCallum, Kuo, Sitrin, Lackner, and Chey are consultants for the SmartPill Corporation. Dr. Semler is an employee of the SmartPill Corporation.

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