

Does Colonic Transit Time Affect Colonic pH?

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INTRODUCTION

Variation in intraluminal colonic pH has potentially important implications for colonic drug delivery^[1-7], alteration of colonic flora^[8-12], colorectal cancer carcinogenesis^[13-15], and regulation of colonic transport processes^[16,17]. The colonic luminal pH progressively rises from the cecum to the rectum^[18-21]. The major determinants of colonic pH are gut bacterial metabolism and colonocyte transport processes. There is a drop in pH by approximately one unit at the ileocecal transition due to generation of short chain fatty acids (SCFA) by colonic bacteria acting on dietary carbohydrates and fiber^[22-26]. The uptake of SCFA by colonocytes along with luminal bicarbonate secretion contributes to the rise in pH in the distal colon^[23,27]. Colonic luminal pH has been studied using a stationary pH electrode introduced by colonoscopy^[18] or by a free falling radiotelemetry capsule^[19,20].

Few studies have looked at the effect of colonic transit time (CTT) on colonic pH^[6,28,29]. In a small study by Lewis *et al* of 13 healthy subjects, senna, bran, and loperamide were used to alter gut transit. A positive correlation between whole gut transit estimated using fecal markers and distal colonic pH was noted^[28]. The bran, however, may have also altered the colon pH by increasing the generation of short chain fatty acids. Thomas *et al* studied 40 patients, 20 healthy controls and 20 with gallstones, and found a positive correlation between CTT, estimated using fecal markers, and distal, but not proximal colonic pH^[29]. Neither of these studies accounted for the known drift of the pH electrodes. The pH sensor drift is a function of time, therefore, studies in subjects with prolonged CTT tend to have a higher magnitude of pH change if drift corrections are not applied. In the present study we have examined the relationship between colonic pH and CTT measured using a radiotelemetry capsule (SmartPill) in healthy controls and constipated subjects.

ABSTRACT

AIM: To assess the effect of colonic transit time (CTT) on pH in the proximal and distal colon.

METHODS: CTT and pH in different regions of the colon were assessed using a wireless capsule manometry system. Healthy controls and patients with chronic constipation based on Rome II criteria were studied. Mean pH was determined in time quartiles of colonic transit, in the first 15 minutes after entry of the capsule into the cecum, and in the last 15 minutes prior to capsule exit from the body and correlated with CTT.

RESULTS: There was a weak, but significant correlation between CTT and pH in the distal colon ($R=0.20$, $p=0.01$ in the 15 minutes prior to body exit, and $R=0.22$, $p=0.01$ in the fourth quartile of CTT). No correlations between CTT and pH were found in the proximal colon. Patients with slow transit constipation tended to have a greater rise in pH from the proximal to the distal colon than those with normal transit constipation or healthy controls.

CONCLUSION: Longer CTT is associated with an increase in pH in the distal, but not proximal colon. The higher pH in the distal colon in slow transit constipation may affect important physiological and pathological processes.

METHODS

Subjects

One hundred sixty eight subjects were enrolled in a study comparing CTT using the SmartPill wireless capsule manometry system versus radio opaque markers^[30]. Eighty seven were healthy controls and 81 had chronic constipation based on Rome II criteria^[31]. The healthy controls had no gastrointestinal symptoms or disorders when screened with the Mayo GI disease questionnaire^[32]. Constipated patients were asked to discontinue all laxatives and drugs that affect motility at least 48 hours prior to the study. After an overnight fast subjects had a standardized meal and then ingested the SmartPill, which is a wireless motility capsule that measures pH, pressure and temperature; data are transmitted to a portable recorder and downloaded to a computer for analysis at the end of study^[30].

Measurement of CTT

CTT was measured as previously described by defining capsule entry into the cecum by a rapid pH drop of >1.0 unit, and capsule exit from the body by a sharp temperature drop and characteristic pressure signature^[30]. Fifteen subjects, including 10 constipated and 5 healthy subjects, were excluded from analysis due to device malfunction or data loss. Five subjects, including 3 constipated and 2 controls, were excluded because of inability to define the ileocecal transition. Thus 148 subjects, 68 constipated and 80 healthy controls, were used for final analysis.

Analysis of pH in different colonic segments

Mean pH was determined in time quartiles of colonic transit and in the fifteen minute intervals after entry into the cecum (proximal colon) and prior to body exit (distal colon) using the manufacturer's

software. An experimentally determined drift correction of the SmartPill pH sensor of 0.01 pH units per hour was applied to the pH data. Constipated subjects were divided into normal and slow transit constipation based on the previously determined 95th percentile cutoff of 59 hours for the healthy controls^[30].

Statistical methods

To describe the observed variability in mean pH and test for differences between groups in this repeated measures design, a multivariate linear model was fit to the data. The endpoint was fit as a function of group, CTT quartile, and group by CTT quartile interaction. To account for the within-subject dependence structure, the model assumed that the distribution of the error terms for each subject to be multivariate normal with zero mean and an unstructured covariance structure. Once the model was fit, specific linear contrasts based on the estimated model parameters were constructed and used to test hypotheses of interest. Differences in univariate measures of pH were assessed using a standard ANOVA model. Spearman's correlation coefficient was used to assess the relationship between pH and CTT. All statistical analyses were carried out using SAS version 9.2 statistical software (Cary, NC).

RESULTS

There was a weak, but significant correlation between CTT and pH in the distal colon. In the 15 minutes prior to body exit the correlation coefficient was $R=0.20$, $p=0.0137$, and in the fourth quartile of colonic transit time the correlation coefficient was $R=0.22$, $p=0.006$ (Figures 1, 2, table 1). No significant correlations between CTT and pH were found in the proximal colon (Table 1). The hydrogen ion concentration in the distal colon increased by 0.10 pH units for every 24 hour increase in colonic transit time.

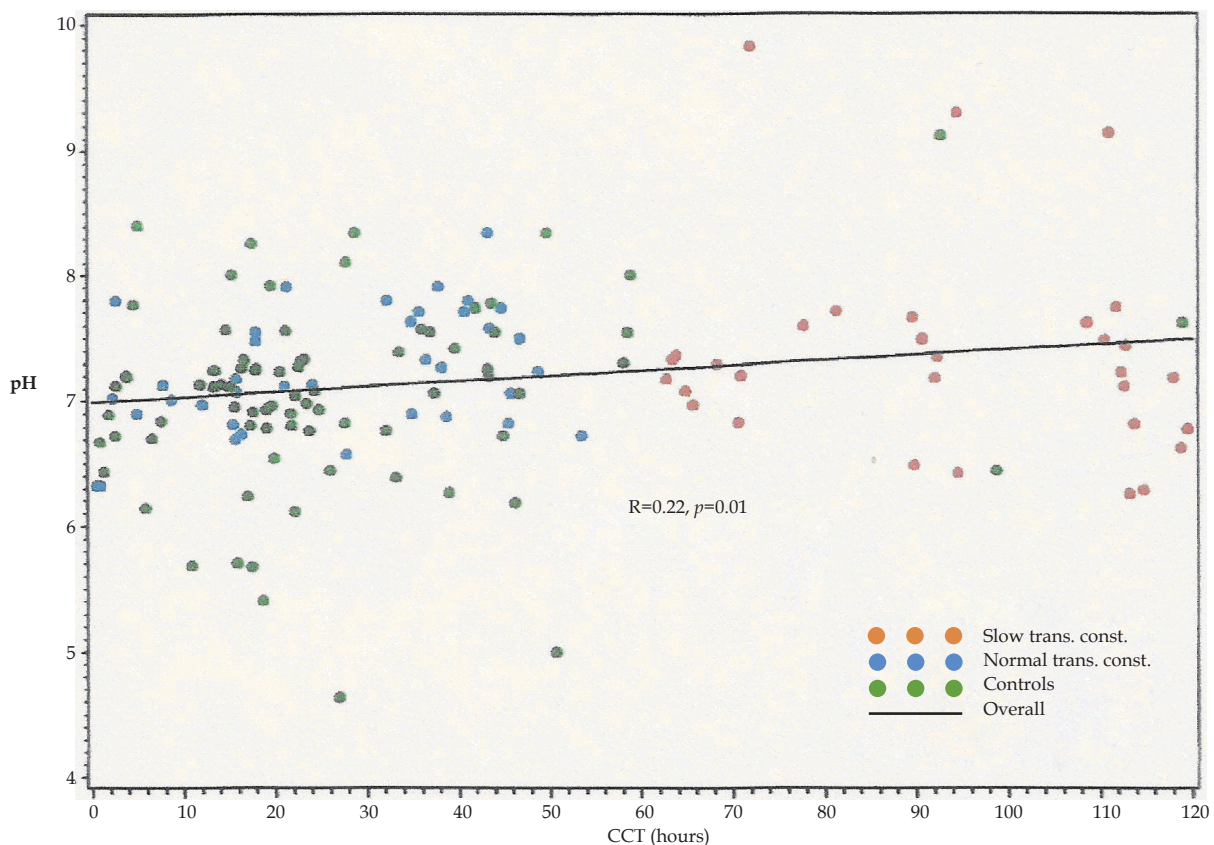


Figure 1 Correlation between CTT and mean colonic pH in the fourth quartile of colonic transit time.

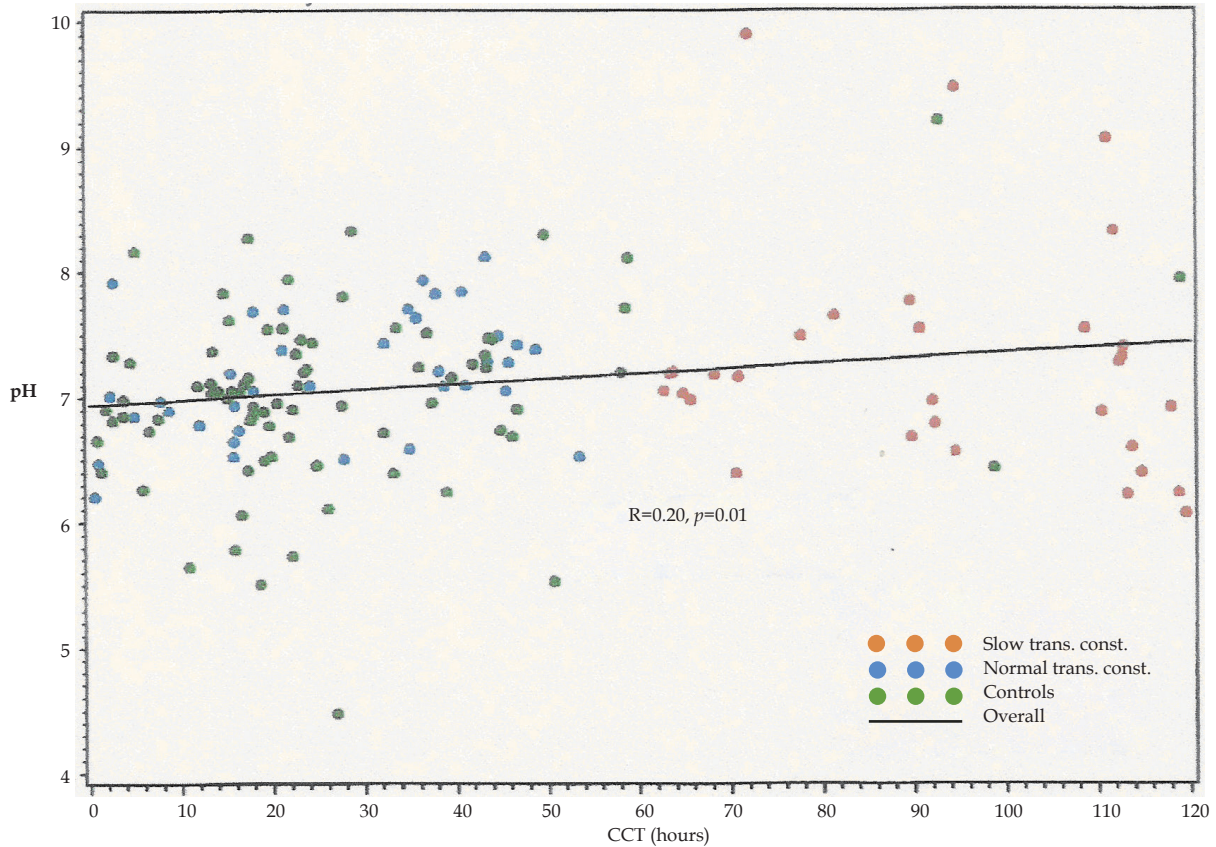


Figure 2 Correlation between CCT and mean colonic pH in the 15 minutes before capsule exit from the body.

	Controls	Normal transit constipation	Slow transit constipation	Correlation (R) between pH and CCT	P value
CTT (h)	27 (22)	27 (26)	90 (25)		
Quartile 1 pH	6.6 (0.5)	6.7 (0.5)	6.6 (0.5)	-0.04	0.54
Quartile 2 pH	6.8 (0.7)	7.0 (0.5)	7.0 (0.8)	0.03	0.67
Quartile 3 pH	7.0 (0.7)	7.3 (0.5)	7.3 (0.8)	0.14	0.08
Quarter 4 pH	7.1 (0.7)	7.2 (0.5)	7.4 (0.5)	0.22	0.01
15 min after cecal entry	6.5 (0.6)	6.7 (0.5)	6.5 (0.5)	0.08	0.36
15 min before body exit	7.0 (0.8)	7.2 (0.5)	7.3 (0.9)	0.20	0.01

There was an increase in the colonic pH during transit from the proximal (15 minutes after cecal entry) to the distal (15 minutes prior to body exit) colon in healthy controls and in subjects with either normal or slow transit constipation (Table 1). The mean rise in pH from the proximal to the distal colon tended to be greater in those with slow transit constipation (0.8 pH units) compared to normal controls (0.5 pH units) or to subjects with normal transit constipation (0.5 pH units) ($p < 0.09$, slow transit constipation versus the other two groups).

DISCUSSION

Few studies have addressed the effect of CCT on colonic pH. Lewis *et al.*^[28] used bran or drugs to alter whole gut transit, and examined the effects on colonic pH. Administration of wheat bran decreased whole gut transit from 69 hours to 39 hours ($p = 0.038$), senna decreased transit from 69 hours to 41 hours ($p = 0.004$), and loperamide increased whole gut transit from 50 hours to 74 hours ($p = 0.004$). Distal colonic pH changed from baseline 7.08 to 6.88 in the wheat bran group ($p = 0.033$), 7.14 to 6.66 in the senna group ($p = 0.039$), and 7.11 to 7.15 in the loperamide group ($p = 0.80$). Distal colonic pH was significantly associated with whole gut transit time ($r = 0.359$, $p = 0.029$)^[28]. A study by Thomas *et al.*^[29] measured

colonic transit time and pH in patients with gallstones and stone-free controls. Patients with gallstones had longer CCT than stone-free controls (36.5 vs 23 hours) and higher distal colonic pH (7.67 vs 7.16). There was a linear relationship between CCT and distal colonic pH ($r = 0.62$, $p \leq 0.001$).

To our knowledge, the present study is the largest to examine the effect of CCT on colonic pH. We measured naturally occurring variations in pH and CCT in healthy controls, slow transit, and normal transit constipation subjects without manipulation by drugs or dietary changes. Alterations in fiber intake in the study by Lewis *et al.*^[28] could have affected colonic pH by affecting colonic bacterial SCFA production in addition to changing CCT. The CCT in the present study was measured simultaneously along with pH by a radiotelemetry device and not estimated from markers. In addition, data were corrected for the well-known time-dependent drift of pH electrodes, an important factor when assessing the impact of transit time on pH. Our results demonstrate a weak, but statistically significant correlation between CCT and pH in the distal, but not proximal colon. A rise in colonic pH from the cecum to the rectum was noted in all patient groups, and tended to be 0.3 pH units greater in those with slow transit constipation versus subjects with normal transit constipation or healthy controls.

Targeted delivery of orally administered drugs to the colon is often attempted by use of a pH sensitive coating, for example mesalamine preparations for treatment of ulcerative colitis. Targeted drug delivery systems utilizing pH coated preparations are also being studied for cancer chemotherapy^[3], treatment of colonic infectious agents^[2], and delivery of nutrients to colon^[33]. Differences in distal colonic pH in patients caused by variations in CTT could significantly influence the dissolution of such preparations and the efficacy of drug delivery to the distal colon.

The colonic bacteria have important roles in human health. Some functions such as folate synthesis, generation of short chain fatty acids, and hydrogen sulfide production are well known. Potential influences of gut microbiota on metabolism and on the pathogenesis of obesity, diabetes, cancer, inflammatory bowel disease, and other disorders are being intensely examined^[8]. A change in colonic pH of one unit or less has been shown to lead to alterations in species composition and metabolic output of the colonic bacteria^[8]. For example, many Firmicutes are more tolerant of an acidic pH, giving them a competitive advantage^[8]. Further studies are required to establish the impact of CTT and the resultant pH changes on colonic drug delivery and colonic physiology and pathophysiology.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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