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High-resolution anatomical correlation of cyclic motor patterns in the human colon: evidence of a rectosigmoid brake

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\textbf{Contributions to Manuscript}

P.G.D., G.O. conception and design of research; J.W.A technical expertise and hardware design; A.Y.L., P.D., P.G.D., J.P.K., L.K.C analyzed data; A.Y.L., P.G.D., I.P.B., G.O. interpreted results; A.Y.L., P.D. prepared figures; A.Y.L., P.G.D., G.O. drafted manuscript; All authors review and approval of manuscript.

\textbf{Running Head}

High-resolution study on cyclic motor patterns

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Keywords

Colonic motility; High-resolution manometry; Rectosigmoid brake
Abstract

Colonic cyclic motor patterns (CMPs) have been hypothesized to act as a brake to limit rectal filling. However, the spatiotemporal profile of CMPs, including anatomical origins and distributions, remains unclear. This study characterized colonic CMPs using high-resolution (HR) manometry (72 sensors, 1 cm resolution) and their relationship with proximal antegrade propagating events. Nine healthy volunteers were recruited. Recordings were performed over 4 h, with a 700 kcal meal given after 2 h. Propagating events were visually identified and analyzed by pattern, origin, amplitude, extent of propagation, velocity, and duration. Manometric data were normalized using anatomical landmarks identified on abdominal radiographs. These were mapped over a three-dimensional anatomical model. CMPs comprised a majority of detected propagating events. Most occurred postprandially and were retrograde propagating events (84.9 ± 26.0 retrograde vs. 14.3 ± 11.8 antegrade events per 2 h, p = 0.004). The dominant sites of initiation for retrograde CMPs were in the rectosigmoid region, with patterns proximally propagating by a mean distance of 12.4 ± 0.3 cm. There were significant differences in the characteristics of CMPs depending on the direction of travel and site of initiation. Association analysis showed that proximal antegrade propagating events occurred independently of CMPs. This study accurately characterized CMPs with anatomical correlation. CMPs were unlikely to be triggered by proximal antegrade propagating events in our study context. However, the distal origin and prominence of
Retrograde cyclic motor patterns (CMPs) are the dominant motor patterns in a healthy prepared human colon. The major sites of initiation are in the rectosigmoid region, with retrograde propagation, supporting the idea of a ‘rectosigmoid brake.’ A significant increase in the number of CMPs is seen after a meal. In our study context, the majority of CMPs occurred independent of proximal propagating events, suggesting that CMPs are primarily controlled by external innervation.
Introduction

Colonic motility disorders are prevalent and have a significant impact on the quality of life (26, 36). Although millions of medical visits take place each year for the diagnosis and treatment of colonic motility disorders in the US alone (35), many patients are dissatisfied with their treatment (11, 17, 20). A major contributing factor is the lack of detailed knowledge concerning colonic motor patterns to guide the development of effective therapies.

Most existing studies on colonic motility have focused predominantly on high-amplitude propagating sequences (HAPs) (3, 5), which may be diminished in patients with colonic motility disorders (6, 31). The recent introduction of high-resolution (HR) manometry permits the assessment of colonic motor patterns in substantially finer spatiotemporal detail (2, 13, 14, 18). The improved resolution has made it possible to better characterize motor patterns with shorter extents of propagation, and cyclic motor patterns (CMPs) have emerged as a dominant feature in HR recordings (13, 14). Dinning et al have demonstrated that these CMPs are repetitive pressure events occurring at a frequency of 2–6 cycles per minute (cpm), most commonly observed in the rectosigmoid region, and predominantly retrograde propagating (13). Activity at a similar frequency range has also been described in the past using terms including rectal motor complex or periodic rectal motor activity (25, 27, 29, 33). An apparent increase in CMPs in response to motor events in the proximal colon prompted Rao and Welcher (33) to hypothesize that they
serve as a brake to prevent the untimely flow of contents into the rectum and to maintain continence.

The potential clinical significance of CMPs is shown in a number of HR manometry studies. The number and amplitude of CMPs increases after a meal in healthy subjects (13) but the meal response is not seen in patients with slow transit constipation (14). Normal bowel function following distal bowel resection may be partly related to the restoration of CMPs (38). Distal colonic CMPs may also increase in response to sacral neuromodulation, further suggesting that they may play a role in maintaining fecal continence (28).

Despite the importance of CMPs in understanding normal colon function, they remain poorly understood. This study aimed to use HR data to expand on the existing knowledge on CMPs by better characterizing their spatiotemporal dynamics and anatomical location. The study also addressed whether CMPs are associated with propagating events that occur in the proximal regions of the colon. We hypothesize that colonic HR manometry better defines CMPs and refines our understanding of their ability to serve as a braking mechanism to limit rectal filling. Employing a technique previously developed by our group (10), manometric data were mapped onto a three-dimensional (3D) anatomical model of the colon for improved visualization.
**Material and Methods**

**Study population**

The study population comprised nine subjects (three men and six women, median age, 51 years; range, 30–69 years). All subjects had no known gastrointestinal disorders and had normal bowel function, which was defined as having between three bowel movements a day and one bowel movement every 3 days. This population overlapped with that of a previous study that compared pre- and postprandial colonic motor patterns (13); however, all analyses in the current study were original and focused on different parameters and outcomes.

This study was approved by the Southern Adelaide Health Service/Flinders University Human Research Ethics Committee. All subjects provided written informed consent.

**Study protocol**

Fig. 1 shows the study workflow. A fiber optic colonic HR manometry catheter employing 72 sensors placed at 1 cm intervals was used (Fig. 1a). The study protocol, catheter placement, and data acquisition have been described in a previous publication (13). Recordings commenced within 60 min of a subject waking from sedation. Baseline recording was performed for 2 h; then, each subject received a 700 kcal meal consisting of a sandwich and 300 mL of a protein- and
calorie-dense nutritional drink (TwoCal HN Vanilla, Abbott Nutrition, Columbus, OH). Recordings then continued for an additional 2 h.

Upon the completion of manometry measurements, the catheter position was confirmed on an abdominal radiograph taken approximately 5 h after placement. The catheter’s position was registered against defined radiological anatomical landmarks (hepatic flexure, splenic flexure, mid-sigmoid colon, and rectosigmoid junction) (Fig. 1b). In all subjects, the most proximal sensor reached beyond the splenic flexure, and in seven subjects, the most proximal sensor reached beyond the hepatic flexure. The distal sensor ended at the rectosigmoid junction in three subjects, while the remaining subjects’ recordings extended into the rectum.

Manometric data analysis

Manometric data analysis was performed using a custom-designed software package (PlotHRM, Flinders University, Australia). A total of 2,160 min of data were analyzed across all nine subjects and consisted of 120 min each of pre- and postprandial data from each subject. Event detection and pattern recognition were based on previously described methods and definitions (13). In the present study, the analysis focused on the anatomical correlation of CMPs and on the association between CMPs and antegrade propagating events arising in the proximal recording regions. CMPs were defined as repetitive propagating events with a frequency range of between 2 and 6 cpm. The amplitude, extent of propagation, velocity, and
duration of CMPs were calculated according to their point of origin for each propagating event. They were labeled as antegrade or retrograde (Fig. 1c–e).

**Anatomical correlation of CMPs**

CMPs in the postprandial period were analyzed in MATLAB (r2010a, MathWorks, MA) for anatomical correlations. To create an overall representation of datasets, data from each subject were normalized between 1 and 70 virtual sensors and then averaged across all subjects. Normalization was done by registering the actual sensor position from the radiographic image to the locations of the hepatic flexure, splenic flexure, mid-sigmoid colon, and rectosigmoid junction. Data were interpolated within each group of virtual sensors as follows: sensors 10–30 represented data between the hepatic and splenic flexures, sensors 31–50 represented data between the splenic flexure and mid-sigmoid colon, sensors 51–60 represented data between the mid-sigmoid colon and rectosigmoid junction, and sensors 61–70 represented data distal to the rectosigmoid junction. The number of virtual sensors allocated to each region was based on the average length of each region measured on the subjects’ radiographs. Data were classified as retrograde and antegrade propagating events. The summary metrics of the number, amplitude, velocity, extent of propagation, and duration of CMPs were generated based on the interpolated value from the pooled data of all subjects at every virtual sensor.

Results are shown in histograms, with smoothed lines drawn using the Savitzky–Golay method to aid trend detection (34). The accuracy of the normalization process was validated by conducting a two-sample $t$ test comparing raw data from each
region to normalized data from the same region for every metric. No significant

differences were found between subject-specific raw data and normalized data for

any metric (p values ranged from 0.2 to 1.0).

A 3D virtual anatomical model of the summary metrics was developed based on a

previously described method (10). A data point cloud representing the anatomy of a
generic human colon was extracted from an existing database of CT colonography

images (9, 24). A total of 127,303 data points were selected, from which a surface

mesh consisting of 254,394 triangular geometric elements (surfaces) was fitted and

imported into CMGUI (CMISS, University of Auckland, New Zealand) (10). Using the

3D colon model, a one-dimensional centerline was created to represent and register

the locations of virtual sensors to anatomical locations on the colon model. The

summary metrics were projected onto the surface mesh by matching data on the

colon surface point to data on the virtual sensor using the minimum Euclidean

distance to the surface point.

Correlation between CMPs and proximal propagating events

An association probability analysis method originally reported by Weusten et al

(40) was used to determine whether a temporal association existed between CMPs

and antegrade propagating events originating in a proximal colonic region. Pre- and

postprandial data from each subject were divided into 1 or 5 min epochs for

analysis. Each epoch was scored for the presence or absence of antegrade

propagating events and CMPs. A 2 × 2 contingency table was constructed based on
four possible outcomes: CMPs and proximal antegrade propagating events present (C+P+), CMPs present and proximal antegrade propagating events absent (C+P−), CMPs absent and proximal antegrade propagating events present (C−P+), and both motor patterns absent (C−P−). A two-tailed Fisher’s exact test was used to calculate the probability that the observed association between CMPs and proximal antegrade propagating events occurred by chance alone. The association probability was calculated as \((1 - p) \times 100\%\). Following the methods of Weusten et al (40), the association probability value was only considered when the proportion of CMPs that occurred in the presence of proximal antegrade propagating events was higher than that of antegrade propagating events in the total recorded period.

Statistical analysis

Results are reported as mean ± SEM. Statistical analysis was performed using Prism 6 (GraphPad Software, Inc., La Jolla, CA) unless stated otherwise. Wilcoxon signed-rank tests were used to compare the means. The significance threshold was set at \(p < 0.05\).

A mixed-effects model analysis (SAS 9.4, SAS Institute Inc., Cary, NC) was used to test whether the characteristics of CMPs in the postprandial period differed depending on the location and direction of travel. Manometric data were divided into four regions delineated by the splenic flexure, mid-sigmoid colon, and rectosigmoid junction. Data were log- or cubic-root transformed to achieve normal distribution. Sensor location and direction were set as fixed effects.
Results

Occurrence and classification of colonic motor patterns

Table 1 shows the number and type of propagating events recorded during the pre- and postprandial periods. CMPs contributed most of the propagating events. Examples of CMPs are shown in Fig. 1c–e. The number of CMPs that occurred in the postprandial period was significantly higher than the number that occurred in the preprandial period (99.2 ± 36.6 vs 3.9 ± 3.8 per 2 h, p = 0.008). This difference was primarily due to postprandial CMPs traveling in the retrograde direction. Across all subjects, the amount of time for which CMPs occurred increased from 1.5% in the preprandial period to 26.9% in the postprandial period. They occurred in clusters lasting 11.1 ± 1.6 min. HAPSs were observed in five subjects, and all occurred in the postprandial period.

The manometric characteristics of CMPs are summarized in Table 2. No antegrade CMPs were detected in the preprandial period. For retrograde CMPs, significant increases in the amplitude, extent of propagation, and duration of each propagating event occurred in response to the meal. In the postprandial period, the velocity and extent of propagation were significantly greater in the retrograde direction than in the antegrade direction.

Fig. 2a–d shows representative examples of the spatiotemporal relationships of CMPs and HAPSs in the postprandial period in four subjects. There was significant
interindividual variability in CMPs occurring in the postprandial period, but all subjects exhibited periods of sustained CMPs and relative quiescence.

Anatomical correlation of CMPs in the postprandial period

As there was a limited number of propagating CMPs in the preprandial period, the analysis of anatomical correlations focused only on CMPs in the postprandial period. Antegrade CMPs were observed in two subjects and retrograde ones in all subjects. When raw data were grouped into regions separated by the specified anatomical landmarks, 63% of antegrade CMPs initiated in the sigmoid colon, while 59% of retrograde CMPs initiated in the sigmoid colon and rectum. Summary data produced after normalization again showed that a majority of antegrade CMPs were in the sigmoid colon (Fig. 3a, c), while retrograde CMPs most commonly occurred in the sigmoid colon and rectum, with more intense foci at the rectosigmoid junction (Fig. 3b, d).

The characteristics of CMPs in the postprandial period originating at each anatomical point are shown in Fig. 4. The peak amplitude for antegrade CMPs was located in the sigmoid colon, whereas that for retrograde CMPs was at the rectosigmoid junction (Fig. 4a). The extent of propagation for antegrade CMPs showed a downward trend, with higher values starting more proximally. For retrograde CMPs, however, the extent of propagation was lower in motor patterns starting proximally and then stayed mostly constant from the descending colon to the rectum (Fig. 4b). The velocity was lower in the sigmoid colon for antegrade and
retrograde CMPs (Fig. 4c). The duration of antegrade CMPs was shorter in the sigmoid colon, whereas that of retrograde CMPs increased as they approached the rectum (Fig. 4d).

Correlation between CMPs and proximal antegrade propagating events

In the preprandial period, no CMP was temporally associated with antegrade propagating events when analyzed using either 1 or 5 min epochs. In the postprandial period, 94.1 ± 3.1% of CMPs occurred in the absence of proximal antegrade propagating events when data were analyzed using 1 min epochs. When data were analyzed using 5 min epochs, 68.9 ± 11.1% of CMPs occurred in the absence of proximal antegrade propagating events. None of the subjects had a significant association probability value of >95% using the association definition adopted from Weusten et al (40).
Discussion

In this study, we expanded on the existing knowledge on CMPs from HR manometry (13) by accurately describing their anatomical point of origin and relationship with proximal antegrade propagating events. Our analysis showed that retrograde CMPs primarily originated in the sigmoid colon and rectum, although they also occurred in the descending and transverse colon to a lesser extent. Antegrade CMPs occurred less frequently, and when they did, their sites of origin were primarily within the sigmoid colon. Our data also demonstrated that within the limitations of our current experimental context, approximately 95% of distal colonic CMPs occurred in the absence of proximal propagating events.

Colonic motility studies using traditional methods have primarily focused on HAPs (5, 31), whereas other motor patterns have been more difficult to study (12). Cyclic activities have been recognized for many years, but their characteristics and relevance have been debated (8, 16, 25, 29, 30, 37). Kumar et al (25) performed prolonged manometry in 12 healthy human volunteers using two pressure gauges placed 10 cm apart in the anal canal and rectum. They noted clusters of powerful contractions in the rectum (>50 mmHg, 2-3 cpm), with each cluster lasting 3–10 min and occurring more frequently at night. Another cluster of 5-6 cpm contractions was predominantly noted in the postprandial period.
Prior et al (29) performed manometry using water-perfused catheters with recordings taken at 4, 8, and 14 cm from the anal verge. They also noted clusters of cyclical contractions, mostly isolated to a single sensor, with amplitudes ranging from 10 to 55 mmHg and lasting 3–30 min. While these studies usefully outlined activities resembling CMPs, the limited number of sensors and their spacing at sparse distances is known to give imprecise data (12). CMPs have received limited attention and have been the subject of only a few studies, limiting their utility in serving as potential biomarkers of disease or in the development of therapies to treat motility disorders (14, 28, 39).

The most prominent paper supporting the clinical significance of CMPs was published by Rao and Welcher (33). They proposed a distal braking mechanism that limits rectal filling. In contrast to our data, their group demonstrated that 81% of nocturnal cycles and 94% of daytime cycles temporally correlated with motor events in the proximal colon. This temporal association led to the proposal that CMPs were triggered by the arrival of stool or gas in the rectum. In the current study, we examined the association between CMPs and proximal propagating events using 1 and 5 min epochs. Our use of 1 min epochs was based on the assumption that proximal propagating events are propulsive, so the bolus would travel ahead of the events detected by manometry (7, 15). If CMPs were initiated by proximal events, they would therefore have to occur in a close temporal sequence with a proximal propagating event. However, we were unable to show a significant association between proximal propagating events and CMPs within the 1 min epoch.
When using the 5 min epochs, just under a third of CMPs were temporally associated with proximal propagating events; however, none of the subjects had a significant association probability value. Despite our limited sample size, the use of a validated methodology of correlation means we can be confident that these outcomes are statistically robust (40).

Possible explanations for the difference in findings between our study and those of Rao and Welcher include differences in the study protocol used. Subjects in their study underwent prolonged (>24 h) ambulatory recordings (33). Prolonged recording would allow the colon to fill, potentially increasing the number of antegrade propagating events including HAPSs (13). In our study, only a few HAPSs were recorded, which restricted our ability to fully evaluate distal colonic events that occur after HAPSs. Cyclic activity occurring in response to proximal propagating events in the colon certainly has merit. In a full colon, HAPSs have been shown to increase after a meal (3, 31), and HAPSs are associated with spontaneous defecation (4, 21). Despite that, most people do not defecate after every meal. It is therefore probable that HAPSs may trigger a breaking system such as that suggested by Rao (33). Interestingly, in children with slow transit constipation, bisacodyl-induced HAPSs were shown to be associated with both retrograde propagating contractions and bursts of contractions (18). This increase in activity may act as a brake, potentially preventing defecation from occurring in these children. However, while HAPSs may trigger cyclic activity, it is also true that in our study most CMPs occurred without preceding HAPSs or any proximal antegrade propagating events.
Therefore, these proximal events are not an essential requirement for the initiation of CMPs. Furthermore, an increase in postprandial CMPs has been shown to commence within a minute of a meal, usually long before the occurrence of any proximal propagating event (13).

Intestinal motility is coordinated by multiple overlapping mechanisms (23). Based on our findings, we propose that CMPs are primarily initiated by extrinsic innervation, as seen in the gastrocolic reflex (22). This mechanism prepares the distal colon for the arrival of contents from the proximal regions well in advance of the actual arrival of colonic contents. The distal dominance and retrograde nature of propagation still support the theory that CMPs serve as a braking mechanism to limit rectal filling, as previously hypothesized (13, 33).

We also present here additional improvements in the 3D visualization technique previously reported by our group (10). Using closely spaced sensors and abdominal radiography, we were able to accurately register propagating pressure waves to their anatomical location. The 3D models, which can be shown as static or rotating images, allow users to see the precise location and distribution of specific colonic motor patterns. These methods will be useful in future studies to permit the identification of normal and abnormal colonic activities.

The current study has some limitations. It was performed in the prepared colons of healthy volunteers. We have previously shown a lack of appropriate increase in
CMPs in patients with slow transit constipation (14); however, we have not applied
the current method of analysis to patients. We acknowledge that the sample size
was limited, but it was similar to other colonic manometry studies in the healthy
population (19, 32). We feel that our results are still valid given that CMPs were
universally seen in all studied subjects and that there were adequate numbers of
CMPs seen in each subject for the association analysis. Support for the theory of
retrograde CMPs serving as a brake is based on indirect manometric evidence.
Whether pressure changes translate into actual luminal flow remains to be
determined, although modeling studies suggest that registered pressure events are
likely to be propulsive (1). Further functional studies are needed to determine the
clinical significance of CMPs and whether alterations in these patterns play a role in
colonic motility disorders.

In conclusion, this study characterized human CMPs with anatomic correlation. We
propose an alternative control mechanism for CMPs. The distal origin and
prominence of retrograde CMPs support the theory of a “rectosigmoid brake” as a
mechanism for limiting rectal filling. This study serves as a baseline for future
studies on the functional impact of altered CMPs on colonic motility.

Acknowledgements

Dr. Arier Chi Lun Lee (School of Population Health, University of Auckland, New
Zealand) for her statistical support.
Grants

This project and/or research team members were funded by research grants from the New Zealand Health Research Council, the US NIH (R01 DK64775), the Riddet Institute CoRE, and the Medical Technologies CoRE. Peng Du was supported by a Rutherford Discovery Fellowship. Colonic high-resolution manometric data were recorded in Australia with funding from the National Health and Medical Research Council of Australia (ID: 1064835).

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

References


**Figure Captions**

Fig. 1. Colonic HR manometry workflow. (a) Fiber optic HR catheter containing 72 sensors at 1 cm intervals; (b) Radiograph of a fiber optic HR catheter in a human colon. (c), (d), and (e) Examples of CMPs. Antegrade CMPs are shown using blue arrows, and retrograde CMPs are shown using red arrows.

Fig. 2. The spatiotemporal relationship of CMPs of four subjects. Black lines represent HAPSs. Red lines represent retrograde propagating events. Blue lines represent antegrade propagating events. HF-hepatic flexure, SF-splenic flexure, SG-mid-sigmoid colon, RSJ-rectosigmoid junction.
Fig. 3. The anatomical point of origin of CMPs. (a) Antegrade CMPs. (b) Retrograde CMPs. (c) and (d) 3D colon representation of Fig. 3a,b. HF-hepatic flexure, SF-splenic flexure, SG-mid-sigmoid colon, RSJ-rectosigmoid junction.

Fig. 4. Characteristics of CMPs according to the anatomical point of origin. (a) Amplitude; (b) Extent of propagation; (c) Velocity; (d) Duration. HF-hepatic flexure, SF-splenic flexure, SG-mid-sigmoid colon, RSJ-rectosigmoid junction. The p values listed indicate probabilities of an association between the direction and location of CMPs.

Tables

Table 1. Number of propagating events before and after a meal

<table>
<thead>
<tr>
<th></th>
<th>Preprandial</th>
<th>Postprandial</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAPS</td>
<td>0</td>
<td>1.2±0.6</td>
</tr>
<tr>
<td>Long single</td>
<td>0.4±0.2</td>
<td>2.1±0.8*</td>
</tr>
<tr>
<td>Short single</td>
<td>- antegrade</td>
<td>1.7±1.1</td>
</tr>
<tr>
<td>Cyclic</td>
<td>- antegrade</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>- retrograde</td>
<td>3.9±3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84.9±26.0*</td>
</tr>
</tbody>
</table>

* p<0.05 (significant increase after a meal)
Table 2. Characteristics of CMPs from all sensors in the pre- and postprandial periods

<table>
<thead>
<tr>
<th></th>
<th>Preprandial</th>
<th>Postprandial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antegrade</td>
<td>Retrograde</td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>-</td>
<td>13.8±1.8</td>
</tr>
<tr>
<td>Extent of propagation (cm)</td>
<td>-</td>
<td>5.7±0.3</td>
</tr>
<tr>
<td>Velocity (cm/s)</td>
<td>-</td>
<td>1.4±0.2</td>
</tr>
<tr>
<td>Duration of each propagating event (s)</td>
<td>-</td>
<td>9.5±0.9</td>
</tr>
</tbody>
</table>

* p<0.05 (significant difference between antegrade and retrograde CMPs)