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Original Article

Regional Differences in Intestinal Contractile Responses to Radial Stretch in the Human Lower Gastrointestinal Tract

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Background/Aims
Radial stretch evokes an increase or decrease in contractions in the lower gastrointestinal tract via mechanosensory enteric neurons that project into the muscle layers. We aim to elucidate the differences in stretch reflexes according to their location in the human colon.

Methods
We used healthy intestinal smooth muscle tissue excised during elective colon cancer surgery. Conventional intracellular recordings from colonic muscle cells and tension recordings of colonic segments were performed. Radial stretch was evoked through balloon catheter inflation. Changes in the membrane potential and frequency, amplitude, and area under the curve of muscle contractions were recorded before and after the radial stretch at proximal and distal segment sites.

Results
In intracellular circular muscle recordings, hyperpolarization was noted at the distal site of sigmoid colonic segments after radial stretch, in contrast to depolarization at all other sites. In tension recordings at proximal ascending or sigmoid colonic segment sites, contractile activation was observed with statistically significant increases in the frequency, amplitude, and area under the curve after radial stretch. Distal sites of ascending and sigmoid colonic segments showed increase and decrease in contraction, respectively.

Conclusion
Radial stretch in the human colon (in vitro) evokes excitatory activity at both proximal and distal sites of the ascending colon and at the proximal site of the sigmoid colon, whereas it elicits inhibitory activity at the distal site of the sigmoid colon.
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Key Words
Colon; Enteric nervous system; Gastrointestinal motility; Lower gastrointestinal tract; Peristalsis

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Introduction

Gastrointestinal (GI) motility disorders are prevalent, have an immensely debilitating effect on the quality of life of affected patients, and are a serious health and economic burden worldwide.[1] Some affected patients do not benefit from current treatment options,[2] and insufficient knowledge on human GI motility limits the development of novel efficient therapies.

The mammalian colon performs multifarious functions essential to the optimal handling of ingested material,[3] such as storing, mixing, and expelling feces, and absorbing fluid; therefore, contractile patterns can vary.[4] The main role of the proximal colon is to mix, absorb excess water and electrolytes, and stack dried feces.[5] In contrast, the distal colon mainly expels fecal material and exhibits intense peristaltic movements.[6] Advanced imaging techniques using high-resolution colonic manometry of the human colon revealed fundamental motility differences between the right and sigmoid colons.[7] Thus, the intrinsic innervation might differ among colonic regions.

Radial stretch is an important stimulus to evoke motility change in the colon. Distension of colonic wall activates intrinsic neurons, resulting in oral contraction and anal relaxation, thereby generating peristalsis and the propulsion of colonic content. In various animal models, studied using isolated colon preparations,[8,9] activation of polarized enteric neural pathways appears to be a basic propulsion mechanism. Through activating a set of reflexes, these pathways form a self-sustaining neuromechanical loop.[10,11] Enteric motor neurons located in the myenteric plexus have nerve endings projecting into the circular muscle (CM), and activity of enteric motor neurons can be modulated by mucosal sensory nerve endings. These polarized enteric circuits create neuromechanical loops to efficiently propel the content with a wide-range of physical properties.[3]

Murine studies using electrophysiological and immunohistochemical approaches have clarified enteric nervous system (ENS) temporal development, including the onset of spontaneous and induced electrical activity and site-specific motility patterns.[12-15] However, evidence is scarce regarding site-specific responses to radial stretch in the human colon. This study aimed to elucidate whether distinct locations in the human colon differ in their stretch reflex using in vitro techniques, including electrophysiological recordings of colonic smooth muscles excised during colon cancer surgery.

Materials and Methods

Tissue Acquisition

We acquired human colon tissue samples from patients undergoing elective radical surgery for non-obstructive colorectal cancer. Freshly isolated ascending colonic segments were obtained from right hemicolectomy specimens, and sigmoid colonic segments were obtained from anterior resection specimens.

After bowel resection, colonic segments were isolated from grossly viable regions, which were without tumor invasion or ischemic insult, and immediately placed in an oxygenated Krebs-Ringer bicarbonate (KRB) solution containing (in mM) 120.4 NaCl, 15.5 $NaHCO_3$, 5.9 KCl, 11.5 glucose, 1.2 NaH_2PO_4, 2.5 $CaCl_2$, and 1.2 $MgCl_2$ (pH 7.3-7.4, 37.5 °C, equilibrated with 97% O_2/3% CO_2).[16]

Cross-sectional Preparation for Intracellular Recordings

As previously reported,[12,16] we dissected 1 × 1-cm intestinal segments in a petri dish coated with Sylgard (Dow Corning Co, Midland, MI, USA). We incised the muscles parallel to the longitudinal muscle fibers with a knife consisting of 2 sharp parallel scalpel blades at 1.5 mm apart. Specimens exposing a cross-section of all muscle layers were equilibrated for at least 2 hours prior to the experiments in an electrophysiological chamber[17] that was constantly perfused with preoxygenated KRB solution at 37.5 ± 0.5℃. Conventional intracellular recordings (ICR) were undertaken using a sharp glass microelectrode filled with 3 mol/L KCl. We connected isolated tissue segments to a pulley system via a string sutured to the lateral bowel side to apply radial stretch using a 1-g weight. We measured transmembrane potentials with a high-input resistance electrometer and recorded them with a computer using Axoscope (Axon Instruments, Union City, CA, USA).[18] We directly recorded the resting membrane potential (RMP; mV), as well as the amplitude (mV) and frequency (cmp) of slow waves. Outputs were measured and analyzed using Graphpad Prism (version 5.0; GraphPad Software Inc, San Diego, CA, USA) and Clampfit (version 10.2; Axon Instruments) software.

Tension Recordings of Bowel Segments

As previously described,[16,17] whole colonic segments were prepared by incising the whole layer of a segment, with the mucosa and submucosa intact, parallel to the longitudinal muscle. Each segment (5 × 2 cm) included a taenia coli. A flat layer of colon seg-

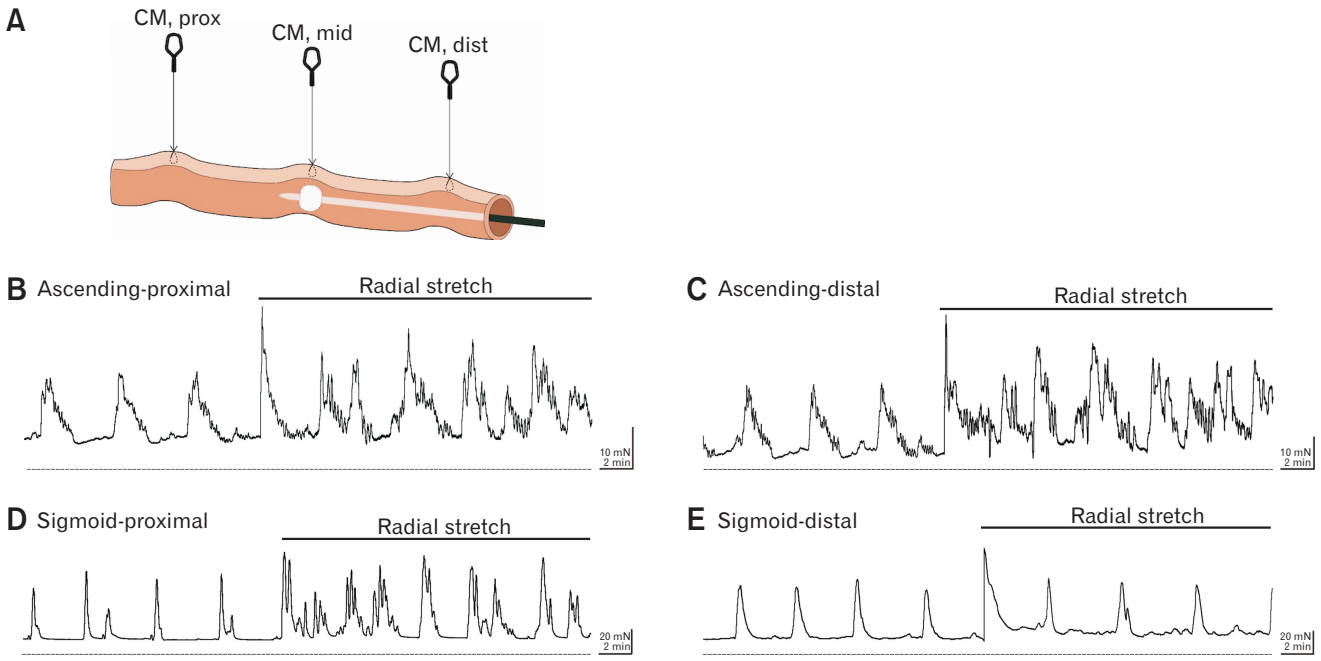

Figure 1. Schematic representation of the mechanical tension recordings and representative changes in segmental motility. (A) Bowel contractions were recorded at 3 sites with stainless steel clips and silk strings connected to a force transducer. Ballooning of a Foley catheter in the middle of an isolated segment induced radial stretch. Tension recordings before and after radial stretch at the proximal site of the ascending (B) and the sigmoid colons (D) and at the distal site of the ascending (C) and the sigmoid colons (E). CM, circular muscle; prox, proximal, mid, middle, dist, distal.

ment was transformed into a tubular shape, mimicking the natural colonic anatomy. Tubular shape segments were made by inserting sutures on one side of whole layer and the opposite side using silk threads. A stainless-steel rod (10 cm in length, 0.2 cm in diameter) was placed inside the segment, parallel to the longitudinal muscle. Stainless-steel spring clips (1.8 cm) were attached to each end of the sutured silk (Fig. 1A). Each clip was attached to an isometric force transducer. CM tension was recorded at 3 sites (proximal, middle, and distal, 2 cm apart) using perpendicular traction via sutures placed at each site. Intraluminal radial stretch was applied using a fine 9-French Foley pediatric urinary catheter (Uro Technology Sdn Bhd, Johor, Malaysia) that was aborally inserted into the colonic segment, and the balloon was positioned in the middle segment without mucosal stimulation. Radial stretch was evoked by 1.0-mL inflation of the balloon for 10 minutes (Fig. 1A).

Colonic segments were equilibrated for at least 2 hours before experiments in a tissue chamber perfused with preoxygenated KRB solution (37.5 ± 0.5℃). Each clip was attached to an isometric force transducer (TST125C; Biopac Systems Inc, Goleta, CA, USA). A resting force of 9.8 mN was applied to each measuring site, and tension was detected using an isometric strain gauge. The frequency (cmp), amplitude (mN), and area under the curve (AUC; mN*min) of migrating motor complexes (MMCs), which have high amplitude and low frequency contraction, were recorded. The AUC was defined as the integrated area under the curve for 10 minutes. Signals were digitized using an MP150 interface and recorded using AcqKnowledge software (Biopac Systems Inc). Data were analyzed offline using Clampfit (version 10.2; Axon Instruments) software.

Drug Administration

After equilibrated regular waves from the tension recording were detected in the experiments, drugs affecting the ENS were perfused into the tissue chamber. After 10 minutes, a stretch stimulus was evoked, and changes in the measured parameters were assessed. The following drugs were used: atropine (1 μM) as an anticholinergic drug, and N^{w}-oxide-L-arginine (NOLA; 100 μM) as a nitric oxide synthase (NOS) inhibitor. All drugs were purchased from Sigma Chemical Co (St. Louis, MO, USA).

Statistical Methods

The results of each experimental group are expressed as mean ± SD or median and range, where appropriate. Wilcoxon signed-rank test was used to compare data between baseline and

stretch responses in the same group. Linear mixed model and generalized linear mixed model analyses were employed to estimate changes in electrophysiological data after radial stretch and to compare results between groups as the mean and slope difference. The model included coefficients for the random intercept in each group. All statistical analyses were performed by an independent, experienced biostatistician using SAS 9.4 (SAS Institute Inc, Cary, NC, USA) and R 3.6.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) software. Data were plotted using GraphPad Prism 5.0 (GraphPad Software Inc). All statistical tests were 2-sided, and a P-value of < 0.05 indicated a statistically significant difference.

Ethics Statement

The procurement and use of human intestinal specimens were approved by the Institutional Review Board of Seoul National University Hospital (Approval No. H-0603-071-170). No personal information was collected; all samples used in the experiments were de-identified and discarded in accordance with the institutional review board guidelines, and there was no secondary use of the samples.

Results

Membrane Potential Recordings

ICR were successfully performed in 11 colonic tissue samples. The transmembrane potentials in colonic specimens before and after radial stretch are presented in Table 1.

Radial Stretch-induced Responses of the Membrane Potential at the Proximal Site

At the proximal sites, stretch-induced changes of slow wave patterns were detected in all bowel segments (Fig. 2). RMP was significantly depolarized, and the frequency and amplitudes of slow waves were enhanced in the ascending and sigmoid colons (Table 1). These results indicated that the changing patterns of slow wave at the proximal site did not differ between the bowel regions.

Radial Stretch-induced Membrane Potential Responses at the Distal Site

Changes in slow wave patterns after radial stretch were observed in all distal sites of the bowel segments (Fig. 2). Depolarized RMP and increased slow wave amplitude were observed in the ascending colon; however, they were not observed in the sigmoid colon. The slow wave frequency increased in the ascending colon; on the contrary, there was a decreased frequency in the sigmoid colon (Table 1). Accordingly, the changes in slow wave patterns at the distal site differed significantly among the regions.

Tension Recordings of the Bowel Segments

We evaluated 103 intestinal samples in total. After equilibration, 68 samples (yield, 66.0%) showed measurable MMCs. The intestinal samples used for further analyses comprised the ascend-

Table 1. Changes in the Slow Wave Before and After Radial Stretch

Direction	Bowel	Parameter	Control	Stretch	P-value
Proximal					
	Ascending colon	RMP	−55.0 ± 13.8	−51.2 ± 15.4	0.038
		Amp	25.4 ± 3.2	30.7 ± 5.7	0.043
		Freq	8.6 ± 3.8	12.0 ± 4.9	0.041
	Sigmoid colon	RMP	−56.3 ± 10.8	−52.9 ± 12.2	0.042
		Amp	39.8 ± 11.8	44.7 ± 10.9	0.046
		Freq	12.2 ± 6.8	20.8 ± 9.3	0.028
Distal					
	Ascending colon	RMP	−49.8 ± 9.3	−47.2 ± 10.9	0.043
		Amp	40.2 ± 9.3	47.3 ± 6.6	0.028
		Freq	12.8 ± 9.9	20.5 ± 8.6	0.028
	Sigmoid colon	RMP	−54.4 ± 2.8	−55.3 ± 3.8	0.197
		Amp	49.8 ± 6.2	43.3 ± 5.5	0.068
		Freq	15.6 ± 10.0	6.8 ± 1.1	0.043

Amp, amplitude (mV); Freq, frequency (cpm); RMP, resting membrane potential (mV).
Ascending colon (n = 5), sigmoid colon (n = 6).
Data are presented as mean ± SD.

ing colon (n = 23) and sigmoid colon (n = 45). Table 2 presents detailed analyses of the tension recordings before and after radial stretch. Figure 1 shows representative changes of MMCs after radial stretch in the ascending and sigmoid colons.

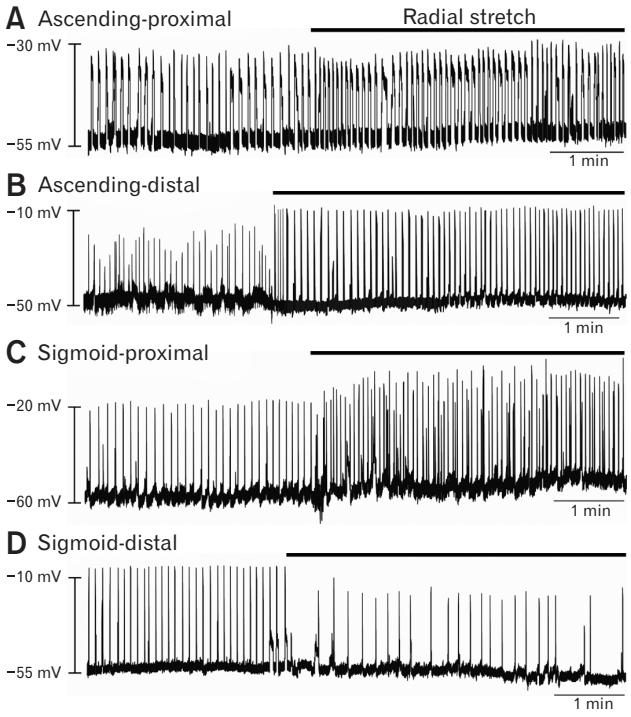

Figure 2. Representative changes in membrane potentials. Electrophysiological recordings before and after radial stretch at the proximal site of (A) the ascending and (C) the sigmoid colons and at the distal site of (B) the ascending and (D) the sigmoid colons.

Radial Stretch-induced Contractile Responses at the Proximal Site

In the ascending colon, the frequency, amplitude, and AUC of MMCs were significantly increased at the proximal site after stretch (Table 2 and Fig. 1B). Similarly, at the proximal site of the sigmoid colon, radial stretch significantly increased the frequency, amplitude, and AUC of MMCs (Table 2 and Fig. 1D). These results show that radial stretch increased MMCs at the proximal site of both colons.

Radial Stretch-induced Contractile Responses at the Distal Site

At the distal site of the ascending colon, contractile activation after radial stretch was observed with significant increases in the frequency, amplitude, and AUC of MMCs (Table 2 and Fig. 1C). However, radial stretch significantly decreased the frequency, amplitude, and AUC of MMCs at the distal site of the sigmoid colon (Table 2 and Fig. 1E). These findings show that radial stretch-induced contractile responses at the distal site differed significantly between the bowel regions, with an increase in the ascending colon and a decrease in the sigmoid colon.

Tension Recordings in Response to Radial Stretch Following Drug Administration

A total of 47 intestinal samples were used to evaluate drug

Table 2. Changes in Segmental Tension Recordings Before and After Radial Stretch

Direction	Bowel	Parameter	Control	Stretch	*P*-value
Proximal					
	Ascending colon	Freq	0.4 (0.2-0.8)	0.6 (0.3-0.9)	0.003
		Amp	16.6 (4.5-50.5)	24.4 (8.2-91.8)	< 0.001
		AUC	349.4 (66.2-913.0)	646.7 (225.1-2045.9)	< 0.001
	Sigmoid colon	Freq	0.1 (0.1-0.7)	0.4 (0.1-1.1)	< 0.001
		Amp	12.0 (4.1-51.0)	16.9 (5.0-55.0)	< 0.001
		AUC	262.0 (27.6-1327.2)	411.1 (36.2-1554.9)	< 0.001
Distal					
	Ascending colon	Freq	0.4 (0.2-0.8)	0.5 (0.3-0.9)	< 0.001
		Amp	18.1 (2.1-92.4)	32.4 (0.9-106.8)	0.002
		AUC	364.9 (107.5-1241.7)	765.4 (47.5-2011.2)	< 0.001
	Sigmoid colon	Freq	0.4 (0.2-0.9)	0.3 (0.1-0.9)	0.022
		Amp	23.1 (6.0-71.6)	16.7 (4.0-58.0)	< 0.001
		AUC	355.8 (66.5-1099.1)	306.6 (24.7-965.7)	0.001

Amp, amplitude (mN); AUC, area under the curve of migrating motor complexes for 10 minutes (mN*min); Freq, frequency (/min).
Ascending colon (n = 23), sigmoid colon (n = 45).
Data are presented as median (range).

Table 3. Changes in Segmental Tension Recordings in Response to Radial Stretch After the Administration of Atropine (1 μM)

Direction	Bowel	Parameter	Control	Stretch	*P*-value
Proximal					
	Ascending colon	Freq	7.0 (2.0-10.0)	7.0 (2.0-8.0)	1.000
		Amp	12.5 (5.5-28.8)	9.0 (3.7-23.1)	0.018
		AUC	326.2 (19.7-850.8)	296.3 (19.8-764.6)	0.236
	Sigmoid colon	Freq	6.0 (2.0-13.0)	5.0 (2.0-12.0)	0.069
		Amp	20.0 (14.2-38.2)	10.5 (7.0-28.4)	0.004
		AUC	80.0 (38.3-817.9)	51.8 (17.9-586.7)	0.004
Distal					
	Ascending colon	Freq	7.0 (4.0-16.0)	7.0 (2.0-15.0)	0.373
		Amp	10.8 (5.4-72.4)	8.0 (2.8-63.4)	0.028
		AUC	711.1 (20.0-1485.6)	493.4 (11.3-1286.7)	0.018
	Sigmoid colon	Freq	5.0 (2.0-12.0)	4.0 (2.0-12.0)	0.141
		Amp	22.9 (12.8-47.4)	14.9 (5.6-42.9)	0.004
		AUC	85.6 (34.9-990.7)	71.3 (31.3-555.4)	0.004

Amp, amplitude (mN); AUC, area under the curve of migrating motor complexes for 10 minutes (mN*min); Freq, frequency (/min).
Ascending colon (n = 7), sigmoid colon (n = 11).
Data are presented as median (range).

Table 4. Changes in Segmental Tension Recordings in Response to Radial Stretch After the Administration of N^{w}-oxide-L-arginine (100 μM)

Direction	Bowel	Parameter	Control	Stretch	*P*-value
Proximal					
	Ascending colon	Freq	5.5 (3.0-6.0)	5.5 (4.0-8.0)	0.201
		Amp	6.9 (4.5-39.1)	12.1 (5.8-26.4)	0.463
		AUC	343.6 (38.6-923.9)	371.6 (43.8-996.0)	0.137
	Sigmoid colon	Freq	5.5 (2.0-18.0)	11.0 (2.0-25.0)	0.039
		Amp	9.9 (3.0-35.0)	24.6 (5.2-76.4)	0.005
		AUC	272.7 (34.1-704.2)	470.5 (127.5-1047.0)	0.013
Distal					
	Ascending colon	Freq	4.5 (3.0-12.0)	6.0 (3.0-16.0)	0.034
		Amp	14.3 (5.5-36.3)	16.9 (10.1-26.7)	0.463
		AUC	463.8 (36.7-1376.0)	554.5 (52.3-2014.2)	0.028
	Sigmoid colon	Freq	5.5 (1.0-11.0)	8.0 (2.0-27.0)	0.052
		Amp	10.2 (3.6-24.3)	22.1 (9.9-74.8)	0.007
		AUC	313.0 (24.0-583.0)	601.9 (62.3-954.9)	0.007

Amp, amplitude (mN); AUC, area under the curve of contractile waves for 10 minutes (mN*min); Freq, frequency (/min).
Ascending colon (n = 6), sigmoid colon (n = 10).
Data are presented as median (range).

effects on the stretch response. The intestinal samples used for analysis comprised the ascending colon (n = 18) and sigmoid colon (n = 29). Among them, 34 samples (yield, 72.3%) showed measurable MMCs after equilibration. Table 3 shows the changes in MMCs following radial stretch after administration of atropine (1 μM), an anticholinergic agent. Regardless of the bowel region, MMCs were decreased due to radial stretch at both the proximal and distal sites. After perfusion with NOLA (100 μM) to inhibit NOS, the distal responses to colonic stretch were all characterized with contractions (Table 4). The changing patterns of MMCs due to radial stretch did not differ, regardless of the presence or absence of NOLA. These changing patterns in MMCs differed significantly depending on the presence or absence of NOLA. These results indicated that nitric oxide (NO) might be involved in the decrease of MMCs due to radial stretch at the distal site in the sigmoid colon.

Discussion

To the best of our knowledge, this study is the first to evaluate regional differences in the stretch reflex in the human colon using in vitro techniques, including electrophysiological recordings of intestinal smooth muscles. In ICR experiments, depolarized RMP and increased amplitude and frequency of slow wave in response to radial stretch were observed at the proximal and distal sites of the ascending colon, as well as at the proximal site of the sigmoid colon, whereas there was a decrease in frequency of slow wave at the distal site of the sigmoid colon. In tension-recording experiments, enhanced MMCs after radial stretch were observed at both sites of the ascending colon and the proximal site of the sigmoid colon; however, reduced MMCs were noted at the distal site of the sigmoid colon after radial stretch.

Colonic motility is considered to result from the physiological harmonization of multiple overlapping and coordinated mechanisms. The electrical activities of interstitial cells of Cajal (ICC) following the activation of various ion channels change the membrane potential of smooth muscle cells (SMCs).[15] The myogenic myenteric ICC provoke slow waves in SMCs and function as a pacemaker for the generation of spontaneous phasic contractions. Normal colonic motility reflects the interplay of these overlapping control mechanisms including the ENS, ICCs, and autonomic innervation.[13,19] These mechanisms propagate over short or long distances through patterning a range of contractions that may be static or move in retro- or anterograde directions, and present with a variety of amplitudes.[14] Considered together, the layered interactions between the neurotransmitters, spontaneous phasic contractions, and MMCs, are not independent but rather influence each other. Therefore, these contractions contribute to the regulation of critical colonic functions, including transit time, absorption, stool consistency and frequency, meal responses, and continence.

Each colonic region has a different function. Recently, advanced imaging techniques of the human colon using high-resolution colonic manometry have revealed fundamental motility differences between the proximal and distal colons.[7] Since gut functions vary along regions of the colon, intrinsic innervation may also differ.

Colonic motility is regulated by a combination of excitatory and inhibitory neural activity. Neurotransmission of acetylcholine, tachykinins, NO, and ATP are involved in formation of MMCs.[20] Acetylcholine is the most prevalent neurotransmitter released from excitatory motor neurons that have choline acetyltransferase, and it mediates GI contraction. NO is the most predominant neurotransmitter released from inhibitory motor neurons that have neuronal NOS and it restricts GI contraction.[21] There are regional differences in the effects of these neurotransmitters on the MMCs of the murine colon. The underlying cause of these differences remain unclear, but differences in the distribution of neurons, the relative density ratio of excitatory and inhibitory motor neurons, and receptor distribution may be important factors.[20]

ICC plays a key role in cholinergic and nitrergic neurotransmission.[22] Expression of ICC and nitrergic neurons not only exhibit regional differences, but also decreases with age. These age-related reductions influence the descending colon more severely than the ascending colon.[23,24] While NO is not required for the generation of MMCs, it is essential for the modulation of MMCs and is also involved in the maintenance of smooth muscle relaxation during the intervals between MMCs.[25] Reduced nitrergic neurotransmission may inhibit the decrease of MMCs at the distal site of the sigmoid colon during the radial stretch. These phenomena may explain the mechanisms underlying constipation in the elderly population.

Platelet-derived growth factor receptor α-positive (PDGFRα$^+$) cells are also located close to the ENS and are electrically coupled to SMCs by gap junctions. The distribution of PDGFRα$^+$ cells is higher in the distal colon than in the proximal colon.[26] Unlike ICC, these cells have the potential to transmit nitrergic signals to SMC, although PDGFRα$^+$ cells are mainly responsible for purinergic inhibitory neurotransmission.[27,28] Inhibitory neurotransmission through PDGFRα$^+$ cells may contribute to the reduction of MMCs at the distal site of the sigmoid colon during radial stretch, although we were unable to provide evidence for this in the present study.

Segmental movement is dominant in the proximal part of the colon, whereas propulsive movement is dominant in the distal part of the colon. Our present study findings support this regionally different functions of the colon. In the ascending colon, both the proximal and distal sites of the colon contracted in response to radial stretch with a short time lag to retain luminal contents longer. In contrast, proximal contraction and distal relaxation of the sigmoid colon during radial stretch are triggered simultaneously to expel luminal contents. The responses were altered by atropine and NOLA in both the ascending and the sigmoid colons. These results suggest the possibility that radial stretch-induced colonic responses are mainly mediated by cholinergic and nitrergic neurons. However, the involvement of purinergic neurons cannot be excluded. Considered together, it is possible that colonic motility possesses regional differences due to the amount and classes of innervation in each colonic region varying amongst each other.

This study has several limitations. First, because of limited laboratory facilities, we could not perform simultaneous microelectrode recordings from CM cells at both the oral and aboral ends, which would have shown the polarized reflex more effectively. Second, the inherently small sample size of human specimens may have limited the statistical power to detect significant differences, especially in the electrophysiological study. Third, this is an in vitro study that used bowel segments to mimic the intact colon. Thus, it is difficult to ascertain the extent to which normal human physiology is reflected in isolated specimens. Furthermore, histological alterations including inflammatory infiltrates associated with the original pathophysiological alterations might alter the motor responses observed. Finally, we could not determine the mechanisms underlying regional differences. In the future, studies which use a combination of recordings at both the cellular and organ levels to identify stretch response mechanisms in the human gut are warranted.

In conclusion, the results of this in vitro study indicate that radial stretch evokes excitatory responses at both sites of the ascending colon and at the proximal site of the sigmoid colon. In contrast, it elicits an inhibitory response at the distal site of the sigmoid colon. Atropine decreased these reactions during the radial stretch in both the ascending and sigmoid colons, while NOLA exacerbated them. These findings suggest that cholinergic and nitrergic neurons may underlie radial stretch-induced colonic responses. Therefore, colonic motility may vary between colonic regions due to difference in the amount and classes of innervation. This study draws attention to the stretch reflex as a potential factor in determining functional differences in the human colon.

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Author contributions: Heung-Kwon Oh, Tae Sik Sung, Seung-Bum Ryoo, and Kyu Joo Park contributed to conception and design; drafting the article and revising it critically for important intellectual content; and final approval of the version to be published.

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