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Sensations of Gas and Pain and their Relationship to Compliance during Distension in Human Colon

Johanna Iturrino^{1,2}, Michael Camilleri^{1,2,4}, Irene Busciglio¹, Duane Burton¹, and Alan R. Zinsmeister³

¹Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), College of Medicine, Mayo Clinic, Rochester, MN

²Division of Gastroenterology and Hepatology, College of Medicine, Mayo Clinic, Rochester, MN

³Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, College of Medicine, Mayo Clinic, Rochester, MN

⁴Department of Physiology and Biomedical Engineering, College of Medicine, Mayo Clinic, Rochester, MN

Abstract

Background—Colonic mechanosensory afferents “in parallel” to circular muscle activate prevertebral ganglion reflexes; “in series” afferents convey visceral sensation to the central nervous system; and pain receptors are activated with muscle distension. Our aim was to analyze the relationships of gas and pain sensations during graded distensions and the association of sensations with colonic compliance in conscious humans.

Methods—The data were acquired in a prior study performed in 60 healthy volunteers (aged 18–75 y) under baseline conditions... Colonic compliance was measured in response to 4mmHg stepwise balloon distensions to estimate pressure at half-maximum volume ($Pr_{50\%}$). Sensation ratings for gas and pain were averaged over distensions at 16, 24, 30 and 36mmHg above baseline operating pressure. Associations between mean gas and pain ratings, and colonic compliance were assessed with Pearson correlations.

Key Results—Gas and pain sensations were significantly correlated at all levels of distension (all $p < 0.001$). Significant inverse correlations between $Pr_{50\%}$ and sensations of gas and pain were observed, suggesting that lower compliance was associated with lower sensations. Up to 25% of the variance in sensation may be attributed to colonic compliance.

Conclusions and Inferences—These data are consistent with the hypothesis that, if circumferential colonic receptors are stimulated by distension to mediate gas and pain in humans, they are, at least partly, arranged “in parallel” to the muscle layer.

Keywords

visceral afferents; splanchnic; in series; in parallel receptors

Corresponding Author: Michael Camilleri, M.D., Mayo Clinic, Charlton 8-110, 200 First St. S.W., Rochester, MN 55905, camilleri.michael@mayo.edu Tel: 507-266-2305.

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INTRODUCTION

Visceral hypersensitivity plays a role in the pathophysiology of functional gastrointestinal disorders including irritable bowel syndrome [IBS (1,2)]. Patients with IBS have a lower threshold for pain on colonic or rectal balloon distention without a difference in viscus compliance (3–6). Sensation involves activation of gut mechanoreceptors in response to the distending stimulus (1,7).

The afferent innervation of viscera consists mainly of unmyelinated fibers without specialized receptor endings (8). The encoding properties of visceral sensory receptors include discrete ranges in the innocuous and noxious domains as well as intensity encoders that are activated by a full range of stimulus intensities (8). Intensity-encoding mechanoreceptors in the bladder and gastrointestinal tract have a low threshold to mechanical stimulation, but they encode both innocuous (e.g. sensation of distension or “gas”), and noxious intensities (pain or urge to void) as the stimulus intensity or duration increase (9,10). Although patients report sensations such as pain, colic, discomfort, bloating, gas or distension, it has been proposed previously that the same mechanoreceptors mediate non-noxious sensations of rectal or bladder fullness, which evolves to discomfort and pain, if the sensation is maintained (10), possibly due to the occurrence of reflex contraction in response to the distension (11). Patient experience is clearly not solely the result of the peripheral mechanisms; increased colonic sensitivity in IBS is strongly influenced by a psychological tendency to report pain and urge (12).

It is unlikely that specialized sensory organs such as the Pacinian corpuscles located in the serosa are activated by intraluminal colonic distension, unless this results in torsion of the mesentery supporting that section of colon as occurs with cecal or sigmoid volvulus. Mechanoreceptors in the gut wall are located in the smooth muscle and the serosal layer. The classical literature, based on animal models, suggests that mechanoreceptors arranged *in parallel* to the muscle fibers respond to stimuli that elongate the viscus (such as distension and relaxation) and are inactivated when the muscle contracts (Figure 1). In contrast, mechanoreceptors that are arranged *in series* respond to stimuli that increase the tension within the wall of the hollow viscus (contraction superimposed to distension), and are inactivated upon muscle relaxation [Figure 1 (1,13)].

Our first aim was to assess, in conscious humans, whether gas and pain sensations from colonic distension are mediated by the same receptors; we surmised that a high degree of correlation between sensation ratings of gas and pain in response to a range of colonic distensions would suggest involvement of the same sensory receptors. Our second aim was to assess the relationship between colonic compliance and sensations. To address these two aims, we analyzed data from previous experiments on colonic compliance and sensation obtained in the pre-treatment phase of a study evaluating the effect of pregabalin on colonic sensory and motor function in healthy adults (14).

MATERIALS AND METHODS

Study Design, Randomization, Allocation to Treatment and Participants

We have previously described in detail our methods (14). Briefly, we analyzed data from 60 healthy volunteers, aged 18 and 75 years, who underwent colonic barostat studies before administration of any treatment.

Participants

Participants were recruited at a single center, by a single coordinator, between April 2010 and January 19, 2011. The study was approved by the Mayo Clinic Institutional Review

Board and was registered on the ClinicalTrials.gov website (NCT01094808). All data were collected in the Clinical Research Unit at Mayo Clinic in Rochester, Minnesota.

Healthy volunteers were recruited from a preexisting database of 200 healthy volunteers residing within 150 miles of Rochester, Minnesota, or through local advertisement. All participants gave signed, informed consent. Candidates who were eligible for the study underwent: (i) a complete history and physical examination, (ii) Abridged Bowel Disease Questionnaire (15) to ensure they had no current or chronic gastrointestinal symptoms, (iii) and the Hospital Anxiety and Depression Questionnaire (16) to screen all volunteers for psychiatric comorbidities.

Volunteers were excluded if they had prior abdominal surgery (other than appendectomy, laparoscopic cholecystectomy, cesarean section, vaginal or laparoscopic hysterectomy or tubal ligation); chronic gastrointestinal or systemic illnesses and use of medications that could affect gastrointestinal motility; history of uncontrolled hypertension, chronic renal insufficiency (serum creatinine >1.5mg/dL) and psychiatric or psychologic dysfunction. In all women of childbearing potential, a urine pregnancy test was performed within 48 hours of the administration of study drug and conduct of the colonic intubation study.

Colonic Tube Placement

Colonic tube placement, motility and sensation were assessed as in previous studies conducted in our laboratory (17,18) and as described previously (14).

Experimental Protocol to Assess Colonic Motor and Sensory Function

The experimental protocol is described in detail elsewhere (14). In summary, colonic compliance was assessed by the ascending methods of limit [ramp-like increases of 4mmHg at 30 seconds per step up to a maximum of 60mmHg unless the participant reported pain (17,18)]; this was the limit set by the Mayo Clinic Institutional Review Board. The maximum volume was estimated as the highest volume in the plotted pressure-volume curve. In all cases the compliance had reached a plateau at the highest pressures imposed in the barostat balloon. The operating pressure was then established for each individual participant as the pressure at which respiratory artifact could be identified in the barostat balloon volume tracing. Randomized-order phasic distensions were applied at 16, 24, 30 and 36mmHg above the operating pressure to measure the sensations of gas and pain. Each distension lasted 1 minute and was followed by an equilibration period at the operating pressure for 2 minutes. During the distensions, participants also used the 100mm VAS to rate the intensity of gas and pain perception at 30 seconds from the start of the distension. Prior to the study, participants were instructed that the sensation of gas is a non-noxious sensation of distension, as opposed to pain which is a noxious sensation that limits a person's tolerance and could lead participants to request cessation of the stimulus. The performance characteristics of such colonic sensation studies have been published elsewhere (18). Participants' distinctions of sensations of gas and pain are illustrated by differences observed in the sensory thresholds for first sensation of gas and pain, and for the different sensation ratings in response to the same distension pressures in 72 participants (38 males and 34 females [18]).

Compliance was measured by a computer-based linear interpolation method as previously validated by Floyd et al. (19). This estimated the pressure corresponding to specific volumes at 10% and 50% of maximum distension. Thus, for example, a higher value of Pr50 indicates lower compliance. Increase in colonic compliance using this method documented with clonidine (20) was associated with reduced sensations of gas and pain in response to

distension; however, clonidine has analgesic properties, and the influence of colonic compliance per se on sensations could not be assessed in those prior studies.

Statistical Analysis

Analysis of covariance (ANCOVA) models were used to assess overall treatment effects (differences among the three treatment groups) on compliance, sensation VAS ratings at 36mmHg, the overall (distension level) mean VAS scores, and stress-arousal scores in all randomized subjects [intent to treat (ITT) analysis]. The covariates included in these analyses were sex, the corresponding baseline (pretreatment) response value and, in addition, for compliance, BMI.

Associations between gas and pain sensations and between colonic compliance and sensation ratings were assessed using Pearson correlation coefficients, as the data were normally distributed.

RESULTS

Demographics

Among the healthy participants in this study, 46 were female; for the entire group, the mean age was 32.1 ± 1.4 years (SEM) and BMI was 26.3 ± 4.8 kg/m².

Relationship of Colonic Sensation Ratings for Gas and Pain during Random-Order Phasic Distensions

There were positive associations of sensations of gas and pain in response to distension. Individual plots of the gas and pain sensations, analyzed by Pearson correlation coefficients (n=60), are shown in Figure 2. All the correlations are significant ($p < 0.001$).

Colonic Compliance and Relationship to Mean Gas and Pain Ratings

Figure 3 shows the inverse relationship between high sensation ratings and low Pr_{50%} which suggests that sensation ratings are highest with the highest colonic compliance. Though significant, the correlations suggest that compliance accounts for a small proportion (~25%) of the variation in sensation.

DISCUSSION

Two important observations from our study in 60 healthy adults are: the correlation of gas and pain sensation; and the relationship of sensations during distension and colonic compliance.

There was a significant positive correlation between scores of gas and pain in response to a range of pressure distensions in the colon in vivo. These data may be considered consistent with the observations of Sengupta and Gephart (9) that the same mechanotransducers mediate noxious and non-noxious events, and with the concept of Cervero (10) that the colon senses only pain. However, our experience with these studies indicates that the symptoms of gas and pain are easily discerned when distension is applied to the colon. In addition, a prior assessment of the performance characteristics of colonic sensation testing using these same methods (18) showed the threshold pressures for gas and pain were different (18), and the current study shows sensation ratings of gas and pain in response to different distension pressures fall some distance from the line of identity (Figure 2).

The literature suggests that there are different mechanotransduction mechanisms that may mediate different sensations. Specialized endings in visceral afferents (intraganglionic

laminar endings and intramuscular arrays) are low-threshold mechanoreceptors and, therefore, are less likely to be involved in detecting noxious events. However, both types of endings have limited distributions (e.g., near sphincters) and are specific to vagal or pelvic innervation in muscle layers (21,22). Mechanotransduction may also be transmitted by naked nerve endings of visceral afferents located in non-sphincteric viscera, as in the colonic distensions conducted in our experiments.

The literature documents five different types of afferent fiber, each with specific response criteria and functional role, in the colon: serosal, mesenteric, muscular, mucosal, and muscular/mucosal (23). Serosal afferents are mechanosensitive and signal short, sharp events (e.g., muscle contraction). Mesenteric afferents are closely associated with blood vessels and may signal twisting of the colon wall. Muscular afferents respond directly to circumferential stretch with a low threshold of activation (though they can also code into the noxious range) and contribute to sensations of sustained filling, bloating, or distending sensations. Mucosal afferents are stretch-insensitive and respond to fine probing and stroking of the mucosa, providing feedback from physiological stimuli such as the normal passing of fecal material through the gastrointestinal tract. The fifth type of afferents, found only in the pelvic innervation (in mouse colon), projects from muscular/mucosal layer and detects both circular stretch and fine mucosal stroking.

Given this array of receptors and innervations, our second aim was to explore the hypothesis that, in the distended human colon *in vivo*, increased sensations of gas and pain are associated with lower colonic compliance, consistent with the hypothesis that the mechanotransduction arises *in series* with circular muscle.

The classical literature suggests that nociception results from the activation of *in series* receptors (20) that convey action potentials through dorsal root afferents and overcome the input resistance of the dorsal root ganglion neuron to enter the dorsal horn of the spinal cord and stimulate the second order neuron which ascends toward conscious perception. These *in series* receptors were attributed the role of mediating human colonic sensation in response to distension in the presence of parenteral neostigmine (7). On the other hand, mechanosensory cholinergic afferents function as length or stretch detectors *in parallel* to the circular muscle and activate superior mesenteric ganglia neurons to induce short (peripheral) reflex responses that relax the colon (24,25).

Contrary to our expectation, our second observation is that there are higher sensations of gas and pain with higher colonic compliance. Increase in compliance is usually reflected by a left shift in the pressure-volume curve, as previously observed with clonidine (20,26,27). Clonidine reduced sensations while it increased compliance; however, α_2 -adrenergic agonists have independent visceral analgesic effects, and therefore the increase in compliance may be unrelated to the decrease in sensation in the presence of clonidine treatment.

Our observations are consistent with the hypothesis that colonic receptors stimulated during distension and mediating gas and pain may be arranged *in parallel* to the muscle layer (Figure 1), rather than *in series* as we had initially hypothesized. In contrast, in the model proposed by Corsetti et al (7), isovolumetric distension in the presence of neostigmine-induced colonic contractions is thought to activate *in series* receptors (Figure 1). It is also likely that distension results in elongation of smooth muscle cells which would potentially offload, and inactivate *in series* transducers. This inactivation would be expected to result in reduced afferent action potentials conducting sensation towards the central nervous system.

Our current data regarding the relationship of colonic compliance to sensation in response to distension are consistent with those published previously by Sun et al. (28), even though the

methods used were quite different. Thus, studies of mechanoreceptors in 12 male volunteers by Sun et al. were based on volume-based (not pressure-based) stimuli, used a latex balloon of unknown compliance, and were primarily focused on effects of different inflation rates (ramp versus rapid). In contrast, our study used a polyethylene balloon of infinite compliance and pressure-based, stepwise (ramp) distensions delivered by colonic barostat. Sun et al. observed that, with both ramp and rapid inflation rates, there were lower volume thresholds (suggesting higher sensation) with higher compliance. Similarly, our current study showed that higher compliance is associated with higher sensation and vice versa. Sun et al. speculated that their findings were consistent with stimulation of mechanosensitive afferents, but no definite mechanisms or orientation of the mechanoreceptors were identified in their study. Their suggestion was that the receptor triggering rectal sensation is not a simple volume or pressure receptor, but is more likely to be a slowly adapting mechanoreceptor lying parallel to the circular muscle of the rectal wall (28), as we suggested from our observations.

More recently, Song et al. identified medium/high threshold extrinsic mechanosensitive afferent nerves that are characterized by varicose branching axons on intramural blood vessels. These submucosal endings have relatively high thresholds to stretch (29).

Advances in the study of human colonic afferents based on direct recordings from resected colonic or appendiceal specimens have the potential to provide further mechanistic insights regarding mechanotransduction (30,31). With such preparations, mechanical stimuli could be applied in series or in parallel to the muscle fibers in the colon. Alternatively, diverse transmitters or mucosal perturbations could be applied at the same time to appraise the mechanisms and mediators of these mechanoreceptors located within or on the rectal wall. Such direct measurements from colonic afferents are eagerly awaited, though the consistent success and reproducibility of this new methodology require further work, as the method could only be established in 50% of preparations by one group (30) and in 4 of 27 preparations by the second group (31).

Limitations of our study include the lack of information of whether pelvic or splanchnic afferents are conveying sensations. On the other hand, from a methodological perspective, the assessment of sensations during distensions of the descending colon is not confounded by the potential concern encountered during rectal sensation studies in which patients cannot easily distinguish sensations of gas, pain and desire to defecate (32), and where the study of rectal compliance may be often confounded by the location of the balloon relative to the bony pelvis and the uterus in its antegrade or retrograde positions.

In summary, gas and pain sensations were significantly correlated across a range of distension pressures. A significant inverse correlation between $Pr_{50\%}$ and sensations of gas and pain suggests that higher compliance was associated with higher sensations. These data are consistent with the hypothesis that, if mechanoreceptors are stimulated by distension to mediate gas and pain in humans, they may be partly arranged *in parallel* to the muscle layer. Nevertheless, we acknowledge that the conditions of the current study did not appraise tension receptors, which would be activated under conditions of passive distension and active contraction.

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Figure 1.

Scheme representing the activation and inactivation of mechanotransducers *in series* and *in parallel* to muscle fibers in the colon (adapted from Corsetti et al., reference 7). Note that relaxation associated with increased colonic compliance activates *in parallel* receptors. Whereas, distension is thought to activate both *in series* and *in parallel* receptors, it is also likely that distension results in elongation of smooth muscle cells which would potentially offload and inactivate *in series* transducers.

Figure 2.

Relationship of sensation ratings for gas and pain averaged at each distension level. The Pearson correlations are provided with each plot and all are highly significant ($p<0.001$).

Figure 3.

Relationship of colonic compliance and mean sensation ratings for gas and pain (averaged over 4 distension levels). Note the significant inverse relationship, suggesting that sensation ratings are lower with decreased compliance (higher Pr50 is associated with lower compliance).