Sensory and Biomechanical Responses to Ramp-Controlled Distension of the human duodenum

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Short title: mechano-sensory duodenal function

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Abstract

The aim of this study was to develop a new method for investigation of the relation between the mechanical stimulus, the biomechanical properties and the visceral perception evoked by volume-ramp-controlled distension in the human duodenum in vivo. An impedance planimetric probe for balloon distension was placed in the third part of the duodenum in seven healthy volunteers. Distension of the duodenum was done at infusion rates of 10, 25 and 50 ml min\(^{-1}\), respectively. The pump was reversed when level 7 was reached on a visual analog scale (VAS) ranging from 0-10. Distensions were done with and without the administration of the antimuscarinic drug butylscopolamine. The total circumferential tension (T\(_{\text{total}}\)) and the passive circumferential tension (T\(_{\text{passive}}\)) were determined from the distension tests without and with administration of butylscopolamine, respectively. T\(_{\text{total}}\) and T\(_{\text{passive}}\) showed an exponential behavior as function of strain (a measure of deformation). The active circumferential tension (T\(_{\text{active}}\)) was computed as T\(_{\text{total}}\) - T\(_{\text{passive}}\) and showed a bell-shaped behavior as function of strain. At low distension intensities, the intensity of sensation at 10 ml min\(^{-1}\) was significantly higher than that obtained at 25 and 50 ml min\(^{-1}\). The coefficient of variation at the pain threshold for circumferential strain (average 4.34) was closer to zero compared to those for volume (8.72), pressure (31.22), and circumferential tension (31.55). This suggests that the mechanoreceptors in the gastrointestinal wall depend primarily on circumferential strain. The stimulus-response functions provided evidence for the existence of low and high threshold mechanoreceptors in the human duodenum. Furthermore, the data suggest that high threshold receptors are non-adapting.

Keywords: Cross-sectional area; Distensibility; Duodenum; Pain; Length-tension relation.
INTRODUCTION

Visceral pain is one of the most frequent reasons why patients seek medical attention. It is well known that distension of the gastrointestinal tract elicits reflex-mediated inhibition and stimulation of motility via intrinsic or extrinsic neural circuits and induces visceral perception such as pain. Previous studies demonstrate that mechanoreceptors located in the intestinal wall play an important role in the sensory stimulus-response function (17,18,37). From animal studies it seems evident that some receptors have a high threshold to mechanical stimuli and an encoding function that is evoked by stimuli within the noxious range. Other receptors have a low threshold to mechanical stimuli and an encoding function that spans the range of stimulation intensity from innocuous to noxious (3). Furthermore, some evidence obtained in animal studies indicates that the mucosal nerve endings act as rapidly-adapting mechanoreceptors, whereas the intramuscular endings act as a slowly-adapting mechanoreceptors (35). This suggests that rapid distension evokes the mucosal mechanoreceptor, whereas slow distension primarily evokes the muscular mechanoreceptors. Whether low and high threshold receptors exist in the human small intestine and how the receptors adapt to the velocity of mechanical stimulation still remain to be studied.

It is a misconception to believe that mechanoreceptors are sensitive to variation in pressure or volume. A large variation in the peristaltic reflex and perception have been found in various studies and species (13,14,36) suggesting that pressure and volume are not the direct stimuli. Instead, the receptors may be activated by mechanical forces and deformations in the gastrointestinal (GI) wall secondary to changes in the transmural pressure (9). Thus, the mechanical distension stimulus and the biomechanical tissue properties must be taken into account in studies of the sensory-motor function in the gastrointestinal tract. Circumferential tension and strain are likely candidates as the direct receptor stimulus because in distensible biological tubes the tensile circumferential wall tension and strain are largest in that direction during distension. It is well known that stepwise balloon distension evokes non-painful and painful sensations in humans and nociception in animals (11,30). However, a ramp distension protocol may be more optimal than a stepwise distension protocol for determining which
biomechanical parameter perception depends on and whether the sensory responses depend on the rate of distension.

The aim of this study was to develop a new method for investigation of the relation between the mechanical stimulus, the biomechanical properties and the visceral perception evoked by volume-ramp-controlled distension in the human duodenum in vivo and to differentiate between active and passive tissue properties by making distension without and with administration of butylscopolamine. Continuous balloon distension and monitoring of the cross-sectional area (CSA) provide the possibility to investigate what stimulus the mechanoreceptors in the human gastrointestinal wall depend on and whether the biomechanical properties depend on the speed of distension, i.e. the strain rate.
MATERIALS AND METHODS

We studied seven healthy volunteers, 5 men and 2 women (mean age 26±1 years), who were recruited among students. The volunteers were asymptomatic, did not take any medication and had no previous gastrointestinal surgery. All had normal physical examination. The participants gave written informed consent to their participation and the local Ethics Committee approved the protocol.

Experimental Probe Design

A four-electrode impedance measuring system located inside a balloon on a 120-cm-long probe (Gatehouse Medical, Nørresundby, Denmark) was used for measurements of luminal CSA in the duodenum. Briefly, the impedance planimetry system consisted of two outer ring electrodes for excitation. They were placed at an inter-electrode distance of 38 mm and were connected to a constant current generator in the impedance planimeter (Gatehouse Medical, Nørresundby, Denmark) yielding 100 µA at 5 kHz. Two ring electrodes for detection were placed at an inter-electrode distance of 2 mm midway between the excitation electrodes and were connected to an impedance detection unit in the impedance planimeter. The electrodes were made of thin stainless steel wire and were wound around the probe in 0.2-mm-wide grooves to create a smooth face. The CSA was recorded from measurement of electrical impedance inside the balloon as described in detail previously (10,14,15). The attached balloon was 40 mm long and was made of 50-µm-thick non-conducting polyurethane. The balloon was connected via an infusion channel (2.5 mm in diameter) to a pump (type 111, Ole Dich Instrumentmakers Aps, Hvidovre, Denmark) that pumped electrically conducting fluid (0.0045% NaCl) in and out of the balloon at a controlled flow rate. The balloon could be inflated to a maximum CSA of approximately 2000 mm² (diameter 50 mm) without stretching the balloon wall. The size of the balloon was chosen on the basis of pilot studies on healthy volunteers that showed the luminal CSA of duodenum at maximum applied balloon volume never exceeded 2000 mm². Thus, reliable measurements could be carried out in the physiological range without stretching the balloon wall. Calibration of the CSA measuring system was done at 37ºC using 10 PVC tubes with lumens of known
Multiple calibration points were used because of non-linearity between the real and measured CSAs. Non-linearity was corrected for up to approximately 2000 mm² by means of a software feature (Openlab, Gatehouse, Nørresundby, Denmark).

The probe contained one channel for pressure measurement. A side hole was located inside the balloon between the detection electrodes. The diameter of the pressure channel and side hole was 0.5 mm. The pressure was measured by means of a low-compliance perfusion system connected to external transducers. The perfusion rate for the pressure channel was 0.1 ml min⁻¹. The pressure transducer was calibrated using 0 and 10 kPa as the minimum and maximum. Records of CSA and pressure were amplified, analog-to-digital converted, and stored on a computer for later analysis.

**Infusion system**

The electromechanical pump could fill or empty the balloon with fluid continuously at various flow rates. The connecting tube between the pump and the probe was heated to 37°C and contained 150 ml of fluid. A safety valve was placed on the tube so that the volunteer could deflate the balloon at any time. The fluid reservoir only contained 125 ml of fluid as a safety precaution.

**Sensory assessment**

Before the distension test started, the subjects were trained how to use a 0-10 electronic visual analog scale (VAS) where 0 = no perception; 1 = vague perception of mild sensation; 2 = definite perception of mild sensation; 3 = vague perception of moderate sensation; 4 = definite perception of moderate perception; 5 = pain (pain detection threshold); 6 = mild pain; 7 = moderate pain; 8 = pain of medium intensity; 9 = intense pain; and 10 = unbearable pain. First, they were asked to report the sensation to somatic stimuli (increasing pressure applied to the right forearm) and second, they scored visceral symptoms during a few balloon distensions. We selected a VAS for evaluation of perception as we previously have demonstrated the usefulness of this parameter to assess painful visceral stimuli in the stomach, small and large intestine in healthy subjects and in patients with visceral hyperalgesia (1,5,26).
The rationale for combining the non-painful and painful scores is based on recent studies showing that, apart from being polymodal, both low and high intensity receptors in the gut encode stimuli from the innocuous to the noxious range (30). This is different from the skin where non-painful and painful stimuli are at least partly encoded by specific classes of receptors (2) and where different pain qualities (such as burning and stinging pain) are transmitted by selective classes of afferents. Accordingly, the sensations encoded via individual and groups of visceral afferents probably constitute a continuing sensation from non-painful such as mild fullness/pressure to unpleasantness and pain. This corresponds with our previous experiments with electrical stimuli (5,26,30) and pilot experiments in the current study, where increasing pressure in the duodenal balloon resulted in a smooth continuum from non-painful to painful sensations.

**Study protocol**

The subjects fasted at least for 8 hours. The probe was passed into the duodenum via the nostrils after calibration of the equipment. The balloon was positioned under fluoroscopic guidance into the third portion of the duodenum. The subjects were asked to lie on the bed at the same level as the pressure transducer and to relax for 10 minutes. Four ml/kilo body weight of a meal (Nutridrink, Nutricia A/S, Allerød, Denmark) containing 6.3 calories ml⁻¹ was given to the subjects. The motility pattern changed from a fasting pattern to a fed pattern in all subjects. Ramp-controlled distensions were then initiated. The subjects scored the sensation intensity from zero to seven on the visual analog scale. At VAS = 7 the balloon was deflated using the same rate as during inflation until it was empty (figure 1). The distensions were performed at a speed of 25 ml min⁻¹ four times to precondition the tissue and the volunteer. Afterwards distensions at 25, 50 and 10 ml min⁻¹ were performed twice. Ten minutes after finishing these distensions, they were repeated during administration of the antimuscarinic drug butylscopolamine in order to relax the smooth muscle. The total butylscopolamine dose was guided by the degree of inhibition of contractions and by the development of classic anticholinergic side effects. Finally, in the last 5 of the 7 volunteers an extra distension at 25 ml min⁻¹ was done where the inflation
stopped at the pain threshold. The volume was kept constant for two minutes or until the volunteers requested the balloon to be emptied.

**Data analysis**

The circumferential wall tension was calculated according to the law of Laplace for cylindrical structures as

\[ T = \Delta P r \]

where \( T \) is the circumferential wall tension, \( r \) is the balloon radius under the assumption that the geometry was circular, and ?\( P \) is the transmural pressure. ?\( P \) was computed as the difference between the distension pressure and the intraabdominal pressure where the latter was estimated from the initial part of the volume-pressure curves obtained during butylscopolamine infusion (12). The total tension (\( T_{\text{total}} \)) during distension (due to both active and passive tissue properties) was determined from the distension test without the administration of butylscopolamine. The passive tension (\( T_{\text{passive}} \)) that results from passive components such as the extracellular collagen was obtained from the test with butylscopolamine. The active tension (\( T_{\text{active}} \)) contributed by smooth muscle activity was computed using the equation:

\[ T_{\text{total}} = T_{\text{active}} + T_{\text{passive}} \]

Strain is a unitless measure of deformation. The circumferential strain (\( \varepsilon \)) is thus the fractional change in radius computed as
where $r$ is the radius at a given distension and $r_0$ is the reference radius at a wall tension of 2 kPa mm under the assumption that the geometry was circular (12). At the reference tension, it was easy to determine $r_0$ for the different subjects. The active and passive tensions were plotted as function of the circumferential strain to reveal an *in vivo* tension-strain diagram (somewhat similar to the isometric length-tension curves obtained in muscle strips *in vitro*). The active tension-strain curve examines how changes in the initial length of a muscle affect the ability of the muscle to develop force (tension). In this setup we were primarily interested in evaluation of smooth muscle tone.

The volume, pressure, strain and tension were determined at the pain threshold (VAS = 5). As a statistical measure showing the relative variability of a trait, the coefficient of variation (CV, defined as the standard deviation divided by the mean in percent) was computed for determination of which parameter the mechanoreceptors depend on at the pain threshold. Furthermore, for some analyses, the normalized volume was computed as the volume divided by the maximum volume where the pump was reversed (VAS = 7). The CSA, pressure, circumferential strain, circumferential tension and perception score could be calculated for each interval of the normalized volume.

**Statistics**

The results are expressed as mean and SEM. One- and two-way ANOVAs were used to compare the difference between the values at different distension rates. F and P values are reported from the ANOVA. When the data were not normal distributed, Kruskall-Wallis test was used and H and P values reported. Difference were considered significant if P<0.05.
RESULTS

Preconditioning behavior

Except for the 4 preconditioning distensions made in each subject, our results are based on 84 distension profiles in seven subjects. Of these distensions, half was done during butylscopolamine administration. During the preconditioning distensions, we noticed some variability in the perception score and biomechanical parameters before the responses became repeatable in each subject. It demonstrates that preconditioning is important for investigation of both visceral pain and biomechanics in the GI tract. All subjects admitted that it was easier to report the perception score after they had at least once reached the pain level.

Mechanical data

The CSA (figure 2, left) and pressure (figure 2, right) both with and without butylscopolamine administration increased as function of volume at distension rates of 10 (figure 2, top), 25 (figure 2, middle) and 50 ml min⁻¹ (figure 2, bottom). Increasing the distension rate resulted in fewer contractions when the distension was performed without butylscopolamine administration. Butylscopolamine administration abolished the contractions. This pattern was found in all subjects.

The volume, pressure, total tension, passive tension and strain at the pain threshold (VAS = 5) were at the distension rate of 25 ml min⁻¹ without butylscopolamine administration (except for the data for the passive tension obtained during butylscopolamine administration) 61.0±7.0 ml, 6.2±0.5 kPa, 110.2±12.8 kPa mm, 111.2±13.8 kPa mm and 1.1±0.2, respectively. The coefficients of variation of volume, pressure, tension and strain were 9.74±0.89%, 23.60±1.93%, 25.5±1.63 % and 7.50±1.25 % without butylscopolamine and 8.72±1.40%, 31.22±6.01%, 31.55±6.36% and 4.34±0.86 during butylscopolamine administration, respectively. The comparison of these parameters is shown in Figure 3. The coefficient of variation for strain was the smallest one both without and with butylscopolamine administration, indicating that the sensation receptors are strain-dependent.
The CSA, pressure, strain and tension (figure 4, from top to bottom) both with (figure 4, right) and without (figure 4, left) butylscopolamine administration increased as function of the normalized volume (volume/maximum volume) at 10, 25 and 50 ml min\(^{-1}\), respectively. Both the pressure and tension were inversely proportional with the distension rate, especially at high loads (pressure without and with butylscopolamine administration H=8.48, P<0.02 and F=4.1, P<0.02; tension without and with butylscopolamine F=0.47, P<0.01 and F=3.39, P<0.05). The CSA and strain did not depend on the distension rate (CSA without and with butylscopolamine administration H=0.67, P>0.5 and H=0.24, P>0.5; strain without and with butylscopolamine administration H=0.35, P>0.5 and H=0.25; P>0.5).

In vivo tension-strain diagrams

The length-tension properties were expressed in terms of tension-strain (figure 5, left) and tension-normalized volume (figure 5, right) with distension rates of 10 (figure 5, top), 25 (figure 5, middle) and 50 ml min\(^{-1}\) (figure 5, bottom). The total and passive tension increased exponentially as function of strain or normalized volume, whereas the active tension increased until a maximum at a strain of 1.0 or at a normalized volume of 0.65. The active tension decreased at higher loads. The pain threshold appeared approximately at a normalized volume of 0.88.

Perception

The perception score (PS) during balloon distension with 25 ml min\(^{-1}\) in the volunteers with and without butylscopolamine administration is shown in figure 6. A very large variation among the volunteers was found. Most curves demonstrated that the sensation increased slowly in the beginning. After reaching a mean of approximately 1 on the VAS, the perception increased exponentially. Butylscopolamine shifted the curves to the right but it did not change the shape of the curve (figure 6).

The perception score both without (figure 7, left) and during (figure 7, right) butylscopolamine administration increased as function of the normalized volume (figure 7, top), pressure (figure 7, middle top), CSA (figure 7, middle), strain (figure 7, middle bottom) and tension (figure 7 bottom) at 10, 25 and
50 ml min\(^{-1}\), respectively. The perception score obtained at 10 ml min\(^{-1}\) was higher than the score obtained at the other distension rates at low loads (corresponding to strains less than 1.0) when expressed as function of the normalized volume, CSA and strain (e.g. for volume without and with butylscopolamine administration \(H=14.19, P<0.001\) and \(H = 25.0, P<0.001\)). The difference also appeared at high loads when expressed as function of pressure and tension.

In some experiments the volume was kept constant at VAS 5 (figure 8). The perception intensity continued to increase when the infusion was stopped, whereas the CSA was fixed and pressure decreased (due to a mechanical phenomenon called stress relaxation). This pattern was found in four of the five subjects.
DISCUSSION

The main findings of this study were that; the ramp-controlled balloon distension was applicable in intestinal studies in humans; in the physiological range, the active tension curve influences the tissue behavior whereas the passive properties dominates at high degrees of distension; the biomechanical parameters did not depend on the distension speed; and the mechano-sensitive receptors in the duodenal wall depend on circumferential wall strain rather than on volume, pressure and tension.

Mechanical aspects

Methodological considerations. The mechanical properties of the gastrointestinal tract are important for its function as a digestive organ. Hence, in the last decade biomechanical data obtained by balloon distension or bolus injection have gained increasingly interest in motility research. Data in the literature pertaining to the mechanical aspects of duodenal function are concerned with the contraction patterns (6,19,27), the length-tension relationship in circular and longitudinal tissue strips in vitro (36), flow patterns (33), the compliance and the tension-strain relationship (29). Conventional methods such as manometry and radiology do not provide exact assessment of CSA and distensibility during luminal balloon distension; volume-based systems suffer from errors due to elongation of the balloon, contraction-induced volume variations and compressibility of the air; and ultrasound systems are quite expensive. During the past two decades, impedance planimetry was used in gastroenterology to determine compliance, hysteresis, tone, and wall tension in animal experiments and human studies (10,13,14). In a previous study based on a stepwise distension protocol, impedance planimetry enabled us to characterize the luminal dimension and wall tension in the human duodenum along with the secondary peristalsis (Gao et al. Yet unpublished data). The administration of the antimuscarinic drug butylscopolamine allowed us to investigate active and passive tissue behavior, though it in human studies can be difficult to completely relax the muscle contractions (11,17). In this study, we introduce an experimental model using ramp-controlled distension with different distension rates, i.e. we could not
only identify the pain threshold concerning biomechanical parameters more precisely, but also the rate dependency of both perception and biomechanical properties in the gastrointestinal tract.

**Tension-strain diagrams.** Several studies have been done *in vitro* for investigation of the active and passive mechanical properties of gastrointestinal smooth muscle (20,32), but no studies have been performed *in vivo*. In the current study we quantified the active and passive length-tension components in the human intestine *in vivo*. It is well known that the passive elastic behavior of biological tissues is exponential (15,16,29). The exponential behavior protects the organs including the intestine against overdistension and damage at high luminal pressure loads and allows the intestine to distend easily to facilitate flow in the physiological pressure range. In arteries, it has been demonstrated that collagen bears circumferential loads at high stress levels (4,25). Since gastrointestinal tissue is rich in collagen (8), it is likely that collagen is a major determinant of the curve shape. This study demonstrated that the passive elastic behavior (tension-strain relation) of duodenum *in vivo* is exponential (figure 5) and hence can play a role in protecting tissue against high stress. At high loads the mechanical behavior is contributed mainly by the passive tension curve, whereas at low stress levels, that is in the physiological range, the active tension curve also affects the tissue behavior. Thus, the distensibility *in vivo* depends not only on the passive properties but also on the physiological state of smooth muscle. The maximum active tension always appeared before the pain threshold and before overstretching the intestinal wall. This maximum active tension is presumably reached at a level of optimum overlap between the sliding filaments in the intestinal muscle cells (23,32). When the intestinal wall was stretched to a degree where pain appeared, the passive tension predominated. Thus, we conclude that the gut wall can contribute its largest active force to transport the bolus within the physiological range.

**Effect of strain rate.** The effect of strain rate on the biomechanical parameters was also investigated in this study. Three volume rates varying by a factor 5 was used. Tension only depended on the strain rate at large volumes (figure 4). This effect was due to a change in the pressure during distension. The
relatively minor effect of strain rate on the mechanical parameters is consistent with studies on other soft tissues (7).

**Perception**

Our results may shed some light on the discussion regarding the visceral sensory receptors in man. For many years gastroenterologists believed that the mechanoreceptors in the afferent pathways were pressure receptors. The current concept is that the mechanoreceptors are tension-sensitive receptors that lie in-series or in-parallel with the muscle cells (31). This concept is borrowed from striated muscle physiologists and should yet be regarded as a working hypothesis since no clear evidences support it in gastrointestinal smooth muscle studies. It is basically an uni-axial model that does not account for complex biomechanical properties such as the distribution of the deformation field and for the existence of different receptor populations. Furthermore, no evidence seems to support that the in-series receptor respond to tension rather than to strain. In contrast, our result demonstrated that mechanoreceptors with high thresholds evoked by high intensity stimuli directly depended on wall strain rather than on pressure and tension (figure 3).

Several arguments support the hypothesis that strain is the best stimulus parameter for studying perception and mechanoreceptor responses. From a theoretical point of view strain is a non-dimensional parameter that is independent of the geometry of the organ and directly associated with tissue deformation. In contrast, volume, pressure and tension all depend on the geometry and the initial size of the organ, for example according to Laplace's law pressure imposes a higher force on the tissue in a large organ than in a small organ (12). Furthermore, the CV for strain at the pain threshold was low (Figure 3). This suggests that strain is the most reliable parameter for activation of the receptors. Volume is in a way related to strain and also showed a rather low CV in this study. Whether volume can be used in general as a proxy for strain needs further studies with control of the balloon length and with distension protocols that are not volume-controlled.
The curves in figure 7 provide some information about the receptor properties in the gut. In the strain-VAS diagram the curves for 10 ml min\(^{-1}\) were higher than those obtained at 25 and 50 ml/min approximately until strain reached 1 (corresponding with a VAS of 2). Beyond this strain level a similar exponential curve form was found for the three distension rates. The higher VAS obtained at the lowest distension rate (10 ml min\(^{-1}\)) in the low intensity range suggests that temporal summation may play a role for the perception during balloon distension. Temporal summation in the dorsal horn neurones to visceral stimuli has been demonstrated in the non-painful range, whereas for somatic tissues this is only a feature of painful stimuli under normal conditions (39). The linear curve form found in the low intensity range in this study is comparable to the characteristics of low threshold mechanosensitive dorsal horn neurons in somatic tissues (38). It is likely that fibers specific for low and high threshold stimuli with similar characteristics also exist in the gut (28). When the circumferential strain exceeds 1, the curve increases exponentially for all distension rates and the characteristics are similar to the stimulus-response function found for high threshold dorsal horn neurons (38). The biomechanical properties of the tissues can, however, influence the curve. If the receptors are in-series with the muscle cells and only one receptor type exist, the receptors may only be stretched to a certain degree in the low strain range (0.2-1), thus encoding a VAS of 1. This could be due to relaxation of the smooth muscle in this strain range. At high strains the smooth muscle cannot relax more and further deformation of the tissue results in high VAS. The curves where the muscle is relaxed by butylscopolamine does not, however, support this assumption as no decrease in VAS rating was seen in the low load range. The exponential form of the curves could also be explained by temporal summation of second order neurons. However, this mechanism is unlikely because the curves obtained at the different distension rates all start to increase at the same strain level (where the time for summation by sustained afferent discharge is 5 times as long for the lowest infusion rate compared to the highest). Therefore, we believe that the stimulus-response curve is best explained by activation of at least two different receptor populations.
Previously it has been suggested that tonic stimuli activate receptors in the mucosa and phasic stimuli are more likely to stimulate receptors in the muscle tissue (21). Although phasic ramps were not used in our study, it cannot be excluded that the different infusion speeds may have influenced our results, i.e., the 10 ml min^{-1} infusion rates activates mucosal receptors more than the stimuli using faster infusion rates, where deep receptors may predominantly be activated. The curves for the different infusion rates were, however, comparable with characteristics suggesting that low and high threshold receptors are activated independently of the eventual different tissue distribution. The curves where the muscle is relaxed by butylscopolamine show a minor decrease in VAS in the high load range (above 1 in strain). It can be postulated that it is only the high intensity receptor that responds to smooth muscle relaxation. Therefore, this receptor may be in-series with the smooth muscle, whereas the low intensity receptor is maybe organized in a completely different way. The current model may be suitable to investigate this in man, but need a design especially for this purpose.

The intensity of pain continued to increase when loading was stopped and the same CSA withhold at the pain threshold. Because of stress relaxation in the intestine (figure 8), pressure and tension decreases. Animal experiments in the cat small intestine (24) have shown that the output from the peripheral receptors during constant load is either constant or decreases (so-called non-adapting and adapting receptor populations). Thus, the mechanoreceptors in the human duodenum are probably non-adapting at the peripheral level and when the load is held constant, central summation of the sustained input results in increasing pain.

Conclusions

The ramp-controlled balloon distension model could safely and effectively be applied for studying experimental pain and the mechanical behavior in the gastrointestinal tract. At high loads the tissue elastic behavior is controlled by the passive tension curve, whereas at low stress levels, i.e. in the physiological range, the active tension curve also affects the tissue behavior. The biomechanical parameters did not depend on the distension rate within the physiological strain range. The CV data
support that the receptors located in the gastrointestinal wall depend on wall circumferential strain rather than on volume, pressure and tension. Some evidence point in the direction several mechanoreceptor populations exist and that the mechanoreceptors are non-adapting at the peripheral level.
LEGENDS

Figure 1
Sketch of pump controlled balloon distension. For each subject, ten distensions without butylscopolamine administration (top) and six distensions with butylscopolamine administration (bottom) were done. Of these, the first four distensions were done for preconditioning.

Figure 2
Representative data obtained in one of the volunteers participating in this study. The CSA and pressure both with (dotted line) and without (solid line) butylscopolamine administration increased as function of the volume infused at rates of 10 ml min⁻¹ (top), 25 ml min⁻¹ (middle) and 50 ml min⁻¹ (bottom), respectively.

Figure 3
The coefficients of variation at the pain detection threshold of volume, pressure, tension, and strain without (filled) and with (open) butylscopolamine administration. Mean and SEM values are shown.

Figure 4
The CSA (top), pressure (middle top), strain (middle bottom) and tension (bottom) both without and with butylscopolamine administration as function of the normalized volume (volume/maximum volume) at 10 ml/min (open circles), 25 ml/min (filled circles) and 50 ml/min (filled triangle), respectively. Mean and SEM values are shown.

Figure 5
Length-tension diagrams as tension-strain (left) and tension-normalized volume (volume/maximum volume, right) at 10 ml/min (top), 25 ml/min (middle) and 50 ml/min (bottom). The total, passive and
active tensions are indicated by filled circles, open circles (with dotted line) and triangles, respectively. Mean and SEM values are shown.

**Figure 6**
The sensation during infusion at 25 ml/min in the individual subjects both without (top) and with (bottom) butylscopolamine administration. The relative position of the curves did not change much between subjects when comparing the curves without and with butylscopolamine, e.g. the volunteers with the highest volume before butylscopolamine also had the highest volume during butylscopolamine administration.

**Figure 7**
The perception score (VAS) both without (left) and with (right) butylscopolamine administration as function of volume/maximum volume (A), pressure (B), CSA (C), strain (D) and tension (E) at 10 ml/min (open circles), 25 ml/min (filled circles) and 50 ml/min (triangles), respectively. Mean and SEM values are shown.

**Figure 8**
Pressure (top), CSA (middle) and VAS (bottom) from a distension in a subject where the distension was stopped at VAS = 5.
**Reference list**


**Figure 1**

Without Butylscopolamine administration

With Butylscopolamine administration
Figure 2
Figure 3
Figure 4

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Figure 5
Figure 6
Figure 8

![Graph showing changes in Pressure, CSA, and VAS over time.](image)