Age-related Variation in Mechanical and Sensory Function of the Human Duodenum

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ABSTRACT

The aim was to investigate biomechanical properties and sensory function of the duodenum in young and old volunteers using a previously developed impedance planimetric probe. A volume-controlled ramp distension protocol was used with subsequent evaluation of the circumferential wall tension and strain before and during administration of the relaxant drug butylscopolamine. Seven healthy young volunteers (mean age 26±2 years) and 5 healthy old volunteers (mean age 61±4 years) were studied. The pain threshold in the young group was significantly higher for most mechanical parameters than that in the old subjects. The luminal cross-sectional area (CSA) and strain of the young group were higher than those of the old group both without and with butylscopolamine administration (P<0.05 for all). In contrast, the pressure and tension of these 2 groups both without and with butylscopolamine administration did not differ. Isometric length-tension diagrams in terms of tension-strain relations were computed. In both groups the total and passive tension increased exponentially as function of strain or normalized volume. The passive tension curve was translated to the left for the old subjects when compared with the young subjects. The active tension increased until a maximum (L_{max}) at a strain of 0.96±0.13 in the young group and 0.64±0.07 in the old group was achieved. L_{max} in the old group was significantly lower than that of the young group (P<0.05). Active tension decreased after the maximum was reached in both groups. The pain threshold appeared approximately at a normalized volume of 0.88 in the young group and of 0.77 in the old group. In conclusion, aging resulted in increased passive stiffness of the human duodenum in vivo, whereas the muscle function was preserved. The pain threshold to a controlled mechanical load differed between the two groups, a finding that may be explained by resetting of the intestinal mechanoreceptors. The

increased sensation to mechanical stimuli may explain why diseases characterized by pain related to the gut are prevalent in old age groups.

INTRODUCTION

The function of the duodenum is mechanical to a large degree. Contents received from the stomach are propelled further down the intestine and mixed with secreted fluids to digest and absorb the food constituents. A decline of function and an increased rate of pathological conditions usually characterize the aging process in multicellular organisms.[1] In humans, decreased intestinal motility and dysfunction of visceral sensation are commonly associated with aging. Studies have shown that the total number of neurons in the myenteric plexus decrease with a concomitant increase in the fibrous components of the myenteric ganglia.[2,3] Animal studies suggest that senescent GI muscle responds less to excitatory factors in vitro, and neural injury in old animals may result from apoptosis, defects of mitochondrial metabolism, and inadequate levels or response to neurotrophines.[4,5] Changes in the structure and functional integrity of the GI tract depend on collagen content and the degree of collagen cross-linkage. Accumulation of collagenous proteins was found in old rats compared with middle-aged rats and this may deteriorate the functional integrity of the GI tract with age.[6,7] Furthermore, collagen deposits increase with age in humans.[1] Thus, most evidence points towards an age-related alteration in the morphology of collagen and neuromuscular properties. Consequently, the sensory function and biomechanical properties in the GI tract may also change.

In this study, we aimed to investigate the difference between young and old volunteers in biomechanical properties and sensory function of the duodenum using a previously developed impedance planimetric technique. A ramp distension protocol was used to derive isometric length-tension data in vivo with subsequent evaluation of the circumferential wall tension, strain and sensory intensity. This length-tension test provides data on the passive nature of the tissue, on the maximum force generated by the smooth muscle, and the strain corresponding to the maximum force.

MATERIALS AND METHODS

Seven healthy young volunteers, 5 men and 2 women (mean age 26±2 years) and 5 healthy old volunteers, 2 men and 3 women (mean age 61±4 years) were studied. The volunteers were healthy, 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.

Experiment Probe Design

A four-electrode impedance measuring system located inside a balloon on a 120-cm probe (GMC Aps., Hornslet, Denmark) was used for measurements of luminal cross-sectional area (CSA) in the duodenum. Briefly, the impedance planimetry system consisted of 2 outer ring electrodes for excitation. They were placed at an interelectrode 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 grooves to create a smooth

surface. The CSA was recorded from measurement of electrical impedance inside the bag as described in detail previously.[8-10] The attached balloon was 40 mm and was made of 50-µm, non-conducting polyurethane. The balloon was connected via an infusion channel (2.5 mm in diameter) to a pump (see below) 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 mm^2 (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 mm^2. 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 37° C using 10 PVC tubes with lumens of known CSAs. Multiple calibration points were used because of non-linearity between the real and measured CSAs. Non-linearity was corrected for up to CSA of approximately 2000 mm^2 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 pressures were 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

An electromechanical pump (type 111, Ole Dich Instrumentmakers Aps, Hvidovre, Denmark) 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.

Study Protocol

The subjects fasted at least for 8 hours. A questionnaire was administered to all participants to assess the characteristics of visceral perception before the study started. After calibrating the equipment, the probe was passed into the duodenum via the nostrils. 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/kg body weight of a meal (Nutridrink, Nutricia A/S, Allerød, Denmark) containing 6.3 calories mL^{-1} was given to the subjects. A fed motility pattern was induced in all subjects. Ramp-controlled distensions were then initiated. The subjects assessed the sensation on the visual analogue scale (VAS). The balloon was deflated at VAS = 7 (moderate pain) using the same rate as during inflation until it was empty. The distensions were performed at a speed of 25 mL/min^{-1} 4 times to precondition the tissue and to teach the volunteer to use the VAS. Afterwards distensions at the same speed 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 abolishment of contractions and by the development of classic anticholinergic side effects.

Sensory Assessment

Before the distension test started, the subjects were trained how to use a 0-10 electronic 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.[8] 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. A VAS for combined evaluation of non-painful perception and pain was selected as we previously have demonstrated the usefulness of this instrument to assess painful visceral stimuli in the stomach, small and large intestine in healthy subjects and in patients with visceral hyperalgesia.[8,11-14] This is in accordance with pilot experiments in the current study, where increasing pressure in the duodenal balloon resulted in a smooth continuum from non-painful to painful sensations.

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 computed from the CSA under the assumption that the geometry was circular, and ΔP is the transmural pressure. The total tension (T_{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 ($T_{passive}$) that results from passive components such as the extracellular collagen was obtained from the test with butylscopolamine. The active tension (T_{active}) contributed by smooth muscle activity was computed using the equation:

$$T_{total} = T_{active} + T_{passive}$$

Strain is a unit-less measure of deformation that facilitates comparison between groups. The circumferential strain is thus the fractional change in radius computed as

$$\varepsilon = \frac{r - r_0}{r_0}$$

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 (determined from curve-fitting the tension-radius curve[8]). At the reference tension, it was easy to determine r_0 for each subject. The active and passive tension was plotted as function of the circumferential strain to reveal an in vivo tension-strain diagram (somewhat similar to isometric length-tension curves obtained 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 set-up we were primarily interested in evaluation of smooth muscle tone.

The volume, pressure, strain and tension were determined at the pain threshold (VAS = 5) without or with administration of butylscopolamine.

Statistics

The results are expressed as mean and SEM. At VAS 1, 2, and 3 we determined the corresponding pressure, CSA, tension, and strain in both young and old groups. Two-way ANOVA and t-test were used to compare the difference between these two groups. Difference were considered significant if $P<0.05$.

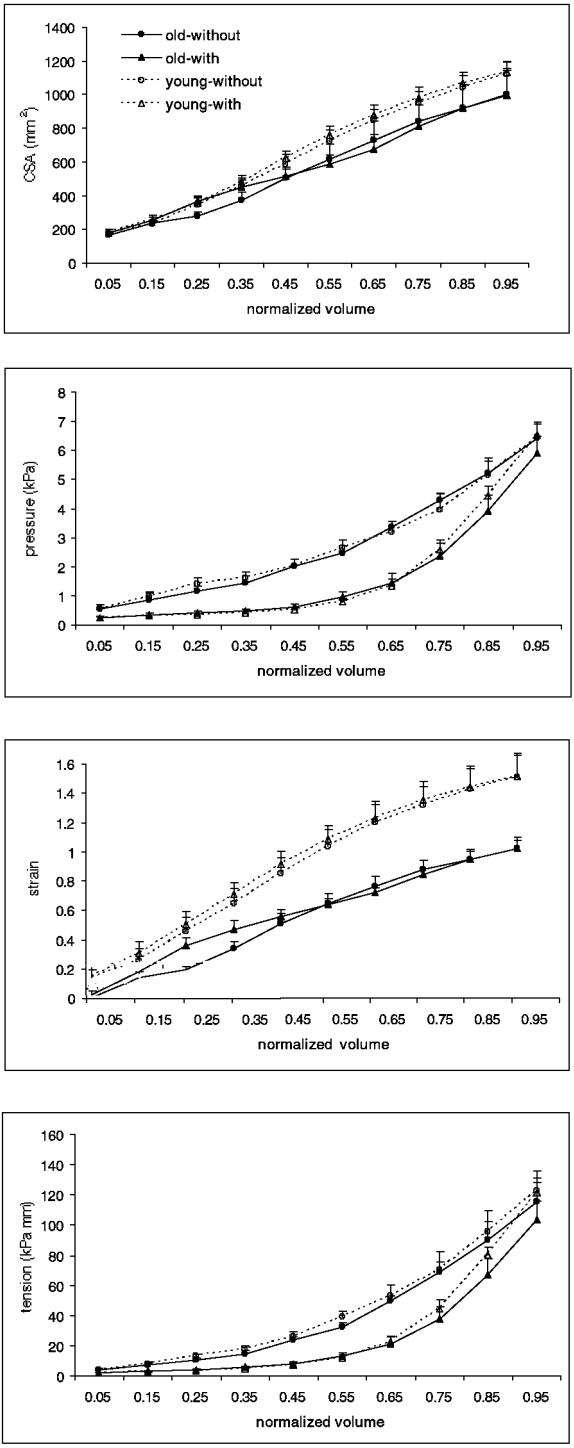


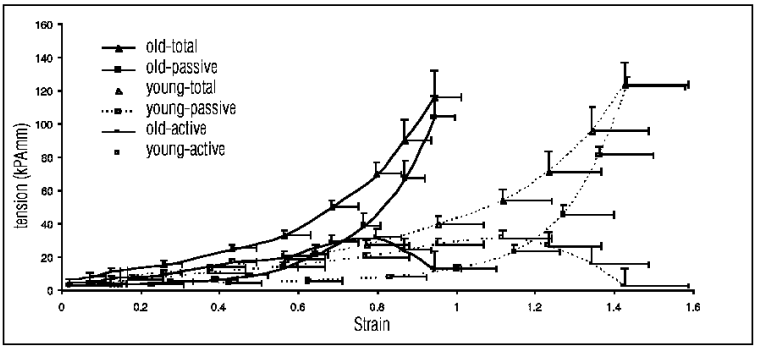
Figure 1. The CSA, pressure, strain and tension both with and without butylscopolamine administration as function of the normalized volume (volume/maximum volume) in the young and old group. Mean and SEM are shown.

RESULTS

Except for the 4 preconditioning distensions in each subject, our results are based on 28 distension profiles in the 7 young subjects and 20 in the 5 old subjects. Half of the distensions were 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 obtaining reproducible results regarding evaluation of visceral pain and biomechanical properties in the GI tract. All subjects reported that it was easier to use the VAS after they had at least once reached the pain level. There appeared not to be differences in the preconditioning behavior between young and old subjects.

Figure 1 illustrates that the CSA, pressure, strain, and tension both without and with butylscopolamine administration increased as function of the normalized volume (volume/maximum volume) in the young and old group, respectively. The CSA and strain of the young group both without (CSA: F=6.0, $P<0.05$; Strain: F=60.1, $P<0.001$) and with (CSA: F=10.2, $P<0.005$; Strain: F=72.6, $P<0.001$) butylscopolamine administration were higher than that of the old group. However, the pressure and tension of these two groups both without (Pressure: F=0.009, $P>0.5$; Tension: F=0.91, $P>0.2$) and with (Pressure: F=0.40, $P>0.5$; Tension: F=2.85, $P>0.05$) butylscopolamine administration did not differ.

Length-tension diagrams expressed in terms of tension-strain (top) and tension-normal-



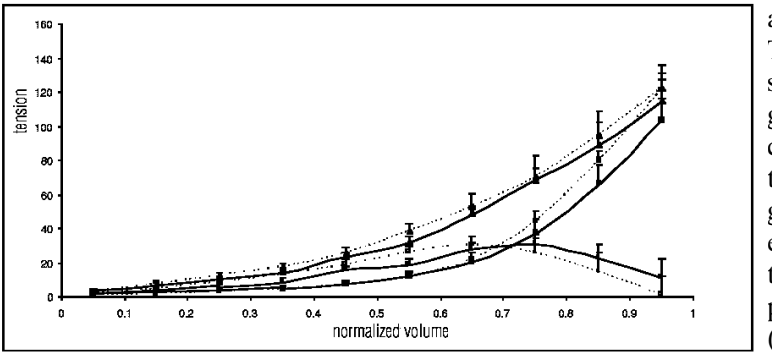


Figure 2. Length-tension diagrams expressed in terms of tension-strain and tension-normalized volume. Mean and SEM are shown. The active, passive, and total tensions are illustrated.

ized volume (bottom) are shown in Figure 2. In both groups 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 0.96±0.13 in the young group and of 0.64±0.07 in the old group was achieved. The strain of the old group corresponding to the maximum active tension was significantly lower than that of the young group ($P<0.05$). This corresponds with a normalized volume of 0.75 in the young group and 0.65 in the old group. In both groups the active tension decreased after the maximum was reached (the descending leg). The pain threshold appeared approximately at a normalized volume of 0.88 in the young group and 0.77 in the old group, ie, at a higher strain that that of the maximum tension (in the beginning or mid of the descending leg).

Figure 3 shows that the perception score without and with butylscopolamine administration increased as function of the normalized volume, CSA, pressure, strain, and tension in both the young and the old group. The perception score of the old group was significantly higher than that of the young group, when expressed as function of each of the parameters above (all F values above 52.4 and all *P* values below 0.001).

The volume, pressure, tension and strain both without and with butylscopolamine administration at the pain threshold (VAS = 5) are shown in Table I. The pain threshold of the above parameters was significantly higher for most parameters in the young group than those in the old subjects (see *P* values in Table I).

DISCUSSION

Methodological Aspects

The mechanical properties of the GI 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 increasing interest in motility research. Data in the literature pertaining to the mechanical aspects of duodenal function are concerned with the contraction patterns,[15-17] the length-tension relationship in circular and longitudinal tissue strips in vitro,[18] flow

Table 1. Mechanical Parameters at the Pain Threshold.

	Volume	Pressure	Tension	Strain
Young without butylscopolamine	58.3±7.4	62.1±4.1	110.2±12.8	1.1±0.2
Old without butylscopolamine	45.2±5.7	41.5±3.4	64.8±6.8	0.6±0.1
***P* value**	*P*>0.1	*P*<0.001	*P*<0.005	*P*<0.02
Young with butylscopolamine	63.7±7.6	61.9±7.4	111.2±13.8	1.2±0.2
Old with butylscopolamine	57.4±4.5	43.0±5.6	70.5±9.2	0.7±0.0
***P* value**	*P*>0.4	*P*>0.05	*P*<0.05	*P*<0.05

Volume, pressure, tension, and strain obtained at the pain threshold (VAS 5) in young and old subjects without and with administration of butylscopolamine. *P* values indicate differences between the young and old group

patterns,[19] the compliance and the tension-strain relationship.[20] 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 (because air rather than liquids is often used). During the past 2 decades, impedance planimetry was used in gastroenterology to determine wall tension and strain in animal experiments and human studies.[8-10,20] To gain a better understanding of these aspects of intestinal function, we recently developed a new ramp distension protocol with concomitant pressure-CSA-VAS measurements (Gao, et al, unpublished paper). Impedance planimetry provides a measure of balloon cross-sectional area and is therefore a better basis than volume measurements for determination of mechanical parameters such as tension and strain in cylindrical organs.[10] The distension protocols included experiments before and during administration of the antimuscarinic drug butylscopolamine. Hereby, active and passive properties could be studied. In this study, we introduced an experimental model using ramp-controlled distension in young and old people to identify more precisely the biomechanical and sensory functional properties of duodenum during aging. The data were expressed as function of strain or normalized volume in order to compensate for any difference in size of the intestine between the groups and used for isometric evaluation of active and passive tissue properties.

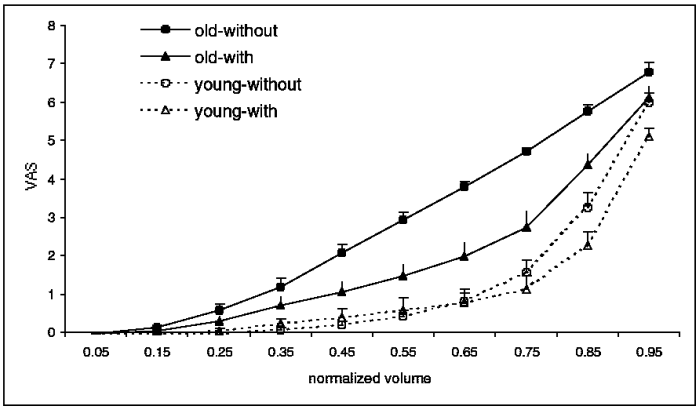
Biomechanical Aspects

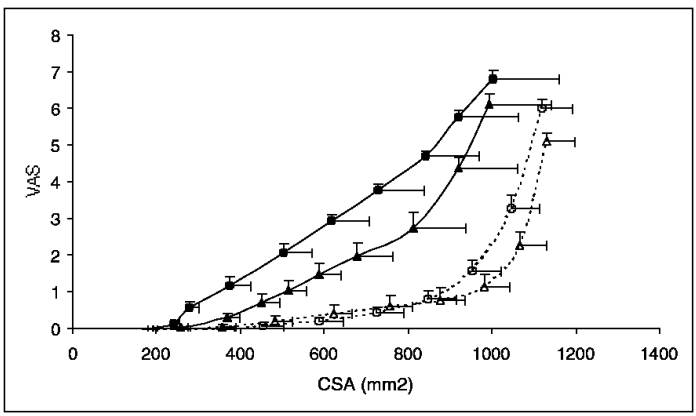
It is well known that the passive elastic behavior of biological tissues is exponential.[8,20,21] This mechanical feature protects the tissue against over-distension and damage at high luminal pressure loads while distending easily and facilitating flow in the physiological pressure range. In arteries, it was demonstrated that collagen bears circumferential loads at high stress levels.[22,23] As GI tissue is rich in collagen, it is likely that collagen is a major determinant of the curve shape.[4] This study demonstrated that the passive elastic behavior of duodenum in both young and old people are exponential and hence can play a role in protecting tissue against high stress. At high loads the tissue elastic behavior is contributed mainly by the passive tension curve, whereas at low stress levels, ie, in the physiological range, the active tension curve dominates the tissue elastic

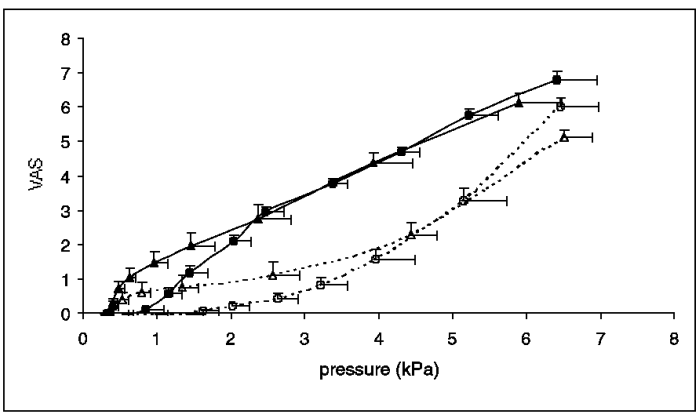
behavior, facilitating bolus transport. Thus, the distensibility in vivo depends not only on the passive properties, but also on the physiological state of smooth muscle. This finding is in line with our previous study based on the stepwise distension protocol.[8]

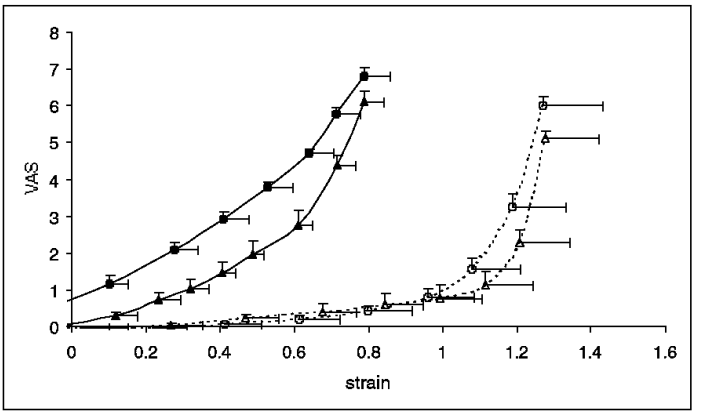
The data obtained in this study showed differences in the sensory-motor and biomechanical properties of the duodenum between young and old normal volunteers. The unloaded size of the duodenum did not differ between young and old subjects. At higher loads, it was seen that the old group had lower CSA than the young volunteers, indicating that the duodenal wall is stiffer in old people. This could also be seen in the strain-normalized volume graph. The increase in stiffness was clearly confirmed in the tension-strain graph (by comparing the passive curves in the tension-strain graph), because a translation to the left in the coordinate system and higher slope are consistent with a higher elastic modulus.[10] The increased stiffness in old subjects may be associated with previous findings of an accumulation of collagen in the intestine in old animal and human subjects, because collagen has a high elastic modulus.[1,6,7]

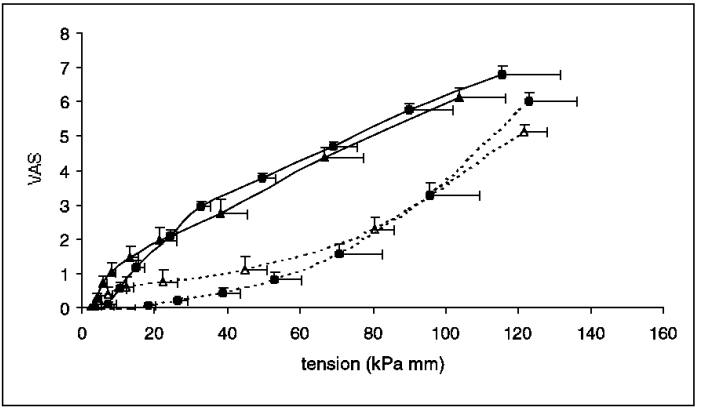
Figure 3. The perception score without and with butylscopolamine administration as a function of the normalized volume, CSA, pressure, strain, and tension. Mean and SEM are shown.











strain curve. The maximum tension is a measure of the ability of the muscle to generate force. In the classical sense it represents the degree of cross-bridges between filaments in the muscle. The tension obtained at the local maximum did not differ between the 2 groups. This indicates that smooth muscle function is preserved in the old subjects because the muscle is capable of generating a force similar to that in young subjects. However, the maximum active tension, which is correlated with the smooth muscle contractile function, appeared at lower strain (0.64) in the old subjects compared with the young individuals (where the strain at maximal active tension was 0.96). The mechanism for the shift of the maximum towards a low strain in old subjects is unknown from the present data, but it can be explained by resetting of the mechanosensitive receptors in the intestinal wall. Because the wall becomes stiffer, the strain-sensitivity of the mechanoreceptors may reset as part of the structural and mechanical remodeling of the tissue. Whether this is a primary or secondary

Another important finding in the present study relates to the position of the local maximum in the active tension-

phenomenon is yet unknown, though the stiffening points in the direction of a secondary phenomenon. Because the muscle function is preserved, the intestine apparently does not need to compensate for lack of muscle contractile force. However, the present study does not give information about the coordination of the contractility in the two groups. The tendency to more dys-coordination of motility in old subjects may require a resetting of the mechanoreceptors to reach the same functional level as in young subjects. The data indicate that alterations appear in the receptor-neuro-muscular pathway in the intestinal wall (intrinsic reflex). This is consistent with animal studies showing that aging resulted in a decreased number of neurons in the myenteric plexus and that the GI muscle responds less to excitatory factors in vitro.[4,5]

Sensory Aspects

Most clinical studies have shown an age-related decrease in pain perception in visceral diseases.[24] Clinical pain due to diseases of the gut, however, is difficult to observe and characterize. The patients typically describe the pain as very diffuse with autonomic reactions such as nausea and sweating. Fear, anxiety, and cognitive reactions may also blur the observation of pain as part of an illness. Finally, visceral pain is most often part of a multi-organ syndrome with systemic reactions such as fever and malaise. In old subjects, age-related degenerative changes and central differences in plastic neuronal responsiveness may also change the perception to nociceptive stimuli.[25] Hence, the physiological and psychological response to pain is most likely changed in old subjects, although it cannot be excluded that observational bias due to the complexity of assessment in visceral pain may explain the clinical findings. Experimental pain models are tools for better characterization and understanding of pain mechanisms. In such models the investigator is able to control the input, ie, the stimulus site, intensity, duration, and modality. Furthermore, the output can be assessed quantitatively or qualitatively.[11] Experimental studies of the pain response to controlled stimuli have given more equivocal results with respect to aging.[24] In the gut, however, no studies have addressed the effect of aging with a controlled mechanical stimulus.

The perception score as function of all the biomechanical variables was highest in the old volunteers. Strain is probably the best stimulus parameter for studying perception and mechanoreceptor responses. Strain is a non-dimensional parameter that is independent of the geometry of the organ and directly associated with tissue deformation.[26] In contrast volume, pressure and tension all depend on geometry and the initial size of the organ. Correspondingly, in previous studies (Gao, et al, unpublished paper), strain was the most reliable measurement for the degree of deformation necessary to activate the receptors, and correlated best with the sensory response during distension of the duodenum. In the current study, the sensory response to increasing strain was identical in the old and young subjects, but in the young group the curve was displaced to the right in the coordinate system. The similarities in curve form suggest that the receptor properties, eg, encoding high and low intensity stimuli are preserved, but that increased sensation to a given mechanical stimulus of the gut is a characteristic finding in old subjects. Although central neuronal changes may influence the findings, receptor kinematics and tissue properties (increased stiffness, but preserved muscle function) can contribute. Though it is difficult to differentiate between these mechanisms, we find it most likely that

resetting of the intestinal mechanoreceptors as discussed previously is the main factor. This resetting would tend to increase the afferent activity at lower strain levels and thus increase the sensation to a mechanical stimulus. One argument speaking in favor of this hypothesis is the fact that both intrinsic and extrinsic changes were observed and that the mechanoreceptors are part of both systems.

CONCLUSION

Aging resulted in increased stiffness of the human duodenum in vivo whereas the muscle function was preserved. The sensation to a controlled mechanical load was increased in the old subjects, and probably resetting of the intestinal mechanoreceptors is the main factor to explain these findings. The increased sensation to mechanical stimuli may explain why diseases characterized by pain related to the gut are prevalent in old age groups. The results also indicate that age matching is important in studies where mechanical stimuli are used to assess the effects of aging, eg, pharmacological interventions on the sensation of the gut.

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