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Multimodal assessment of pain in the esophagus: a new experimental model

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Mohr Drewes, Asbjørn, Klaus-Peter Schipper, Georg Dimcevski, Poul Petersen, Ole Kæselær Andersen, Hans Gregersen, and Lars Arendt-Nielsen. Multimodal assessment of pain in the esophagus: a new experimental model. *Am J Physiol Gastrointest Liver Physiol* 283: G95–G103, 2002. First published March 6, 2002; 10.1152/ajpgi.00496.2001.—A new multimodal pain assessment model was developed integrating electrical, mechanical, cold, and warmth stimuli into the same device. The device, with a bag and electrodes for electrical stimulation, was positioned in the lower part of the esophagus in 11 healthy subjects. Mechanical stimuli were delivered with an impedance planimetric system. Thermal stimuli were performed by circulating water of different temperatures (5–50°C) inside the bag. All subjects reported both nonpainful and painful local and referred sensations to all stimuli. Temporal summation to repeated electrical stimuli could be studied. For all stimuli, there was a relationship between stimulus intensity and pain intensity. The referred pain area increased with increasing intensity of the electrical and mechanical stimuli. There were several differences between the sensations evoked by the four stimulus modalities, indicating activation of different visceral nerve pathways. This model offers the possibility for controlled multimodal stimuli activating the superficial and deeper layers of the human gut and should be used in basic, clinical, and pharmacological pain studies.

experimental pain; gastrointestinal pain; gut; electrical stimuli; mechanical stimuli; thermal stimuli

VISCERAL PAIN IS AMONG THE most common forms of pain experienced in medical practice. Despite its greater clinical importance, visceral pain is less well understood and treated than pain from the skin and other somatic tissues (23). This is mainly due to the difficulties of characterizing the pain, typically described in terms of unpleasant and diffuse sensations with autonomic reactions such as nausea and sweating. In the clinic, fear, anxiety, and cognitive reactions may also blur the observation of pain as part of an illness. Finally, visceral pain is often part of a multiorgan

syndrome with systemic reactions such as fever and malaise.

To overcome such problems, experimental pain assessment models have been developed to explore pain mechanisms. Most experimental studies in the gut have been performed in anesthetized animals, with the nociceptive response based on neurophysiological or behavioral reactions. Because human pain is a multimodal experience composed of sensory, psychological, and physiological aspects, results from animal experiments can, however, only partly be extrapolated to humans. Hence, several human models have been developed to stimulate somatic structures. In such models, the investigator can control the stimulus with respect to localization, intensity, and duration. The response can be assessed quantitatively and qualitatively (1). However, only few models for visceral experimental pain stimuli exist, mainly due to the difficulties of complicated testing equipment coming into contact with the internal organs. The major limitation of the existing human models is that they may not mimic clinical pain because they are based on single, short-lasting stimuli only partly involving the many mechanisms typically activated during diseases (1, 23). Thus experimental visceral models mimicking more closely the clinical situation are needed. Such a model should be based on multimodal testing regimens in which different receptors and central nervous system mechanisms are activated. Multimodal sensory assessment has been shown to be valid for testing somatic pain, where, e.g., single-modality models have been inadequate for clinical assessment and for drug testing (1, 7, 13). Hence, a test battery in which different stimuli are used will increase the probability for activation of a range of relevant involved nervous mechanisms. Especially if the stimulation is relatively long-lasting and includes modalities known to evoke peripheral as well as central sensitization of the nervous system, the likelihood that part of the model will mimic clinical pain is high despite the nonharmful

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nature of the stimulation. In the viscera, technical limitations of the currently available experimental models have until now made such a multimodal stimulation approach impossible.

The aims of the current study were: 1) to develop a multimodal pain model to stimulate the human esophagus with electrical, mechanical, cold, and warmth stimuli and 2) to characterize and compare the evoked responses on pain intensity, pain quality, and referred pain patterns.

METHODS

Subjects

Eleven healthy subjects (7 male and 4 female, mean age 40 ± 10.4 yr) were included. None had any previous or current visceral diseases. Specifically, they denied any chest pain, heartburn, dyspepsia, or irritable bowel syndrome-like symptoms. They received no medication and had no somatic pain complaints. The local Ethics Committee approved the protocol. The experiment was carried out at the Gastrointestinal Research Laboratory at Aalborg Hospital a short distance from the Intensive Care Unit, where personnel and equipment for rescue operations were available.

Intubation of Stimulation Device

A probe designed for multimodal stimulation (TensioMed, Hornslet, Denmark) with modifications performed at the Technical Department at Aalborg University included a bag for impedance planimetry, temperature stimuli, and electrodes for electrical stimuli (Fig. 1). The subjects fasted for at least 4 h before the experiment. After receiving a small amount of local anesthetic spray (Xylocaine, AstraZenica) in the nose, the participants were intubated. The bag was carefully folded and lubricated, and the probe was inserted through the nostrils. The bag was first inserted into the stomach and then retracted to identify the location of the

lower esophageal sphincter as a zone of high resting pressure that decreased with swallowing. Then the bag was placed 8 cm proximal to the sphincter, and the probe was taped to the nose. After intubation, the subjects were asked to lie down with their heads tilted at 30°. After 30 min of rest, the experiment was performed in that position.

Sensory Assessment

The assessment parameters were 1) quantitative sensation intensity, 2) qualitative sensation, and 3) referred pain size. The sensory intensity was assessed continuously by using an electronic visual analog scale (VAS) (Gatehouse, Aalborg, Denmark). Sensory assessment on a VAS can be complex, because visceral pain is diffuse and difficult to characterize. Therefore, the patients were trained in assessment of sensation to deep pressure at the muscles on the right forearm several times before the visceral stimuli were given. Although still debated, most sensory afferents in the gut are probably polymodal and encode both nonpainful and painful sensations (31). We therefore decided to use the scale for both nonpainful and painful sensations. The intensities of the nonpainful sensations were scored on the VAS up to 5, and the following descriptors were used to characterize the sensations: 1 = vague perception of mild sensation; 2 = definite perception of mild sensation; 3 = vague perception of moderate sensation; and 4 = definite perception of moderate perception. A descriptor of 5 was the discomfort/pain threshold. A qualitative scale was added to the nonpainful intensity scores, as the subjects were asked to assign the feeling to one of the following seven sensations: pressure, burning/warm, stinging, colicky/cramping, fullness/nausea, cold, and other. The method and descriptors were chosen according to earlier studies using bag distension in the gut (29). For the painful sensations, the patients used the scale from 5 to 10 anchored at 5 = discomfort/slight pain to 10 = unbearable pain, with anchor words selected from the intensity scale in the Danish version of the McGill Pain Questionnaire (MPQ) (10). Accordingly, when the subject reported that the stimuli resulted in pain and/or severe discomfort (>5 on the nonpainful scale) they were asked to score the intensity from 5–10 on the VAS. The VAS has previously been demonstrated to be useful to assess painful stimuli to electrical current and distension in the stomach and small and large intestine (2, 8, 11). After the experiment, the MPQ was used to assess the painful sensations qualitatively.

Referred Pain

After the stimulation, the patients were asked about referred pain, and, if present, the area was marked with a pen and transferred to a transparent paper. Later the area was digitized (ACECAD D900+ Digitizer), and its size was calculated (SigmaScan, Jandel Scientific).

Stimulation Device and Protocol

The stimulation protocol was composed of electrical stimuli followed by mechanical, cold, and warmth stimuli. During all stimuli, autonomic reactions were monitored and the result was displayed on screen using a Biopac MP100 system (Biopac Systems, Santa Barbara, CA) including sensors and recording system. An electrocardiogram was recorded by using a multilead electrocardiography cable record with the following leads: I, II, III, AVR, AVL, and AVF. A pulseoxymeter was connected to one finger of the subject's right hand, allowing monitoring of oxygen saturation along with changes in pulse rate. Respiration was monitored by using a chest belt, adjusted for inspiration and expiration movements.

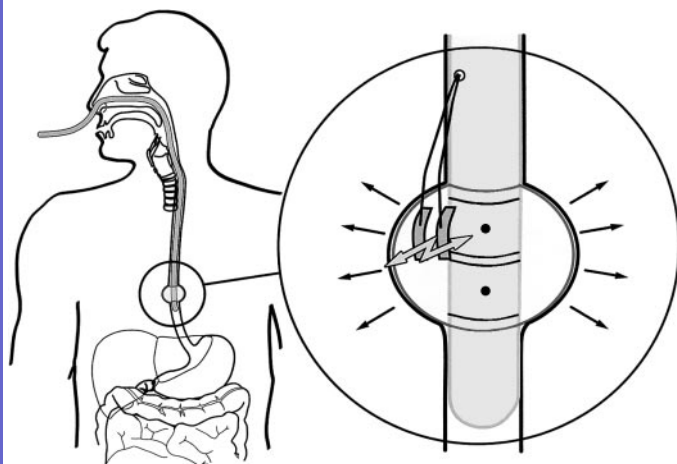


Fig. 1. Schematic illustration of the multimodal device for electrical, mechanical, cold, and warmth stimuli. The probe has a distal bag for impedance planimetry. Electrodes for electrical stimuli are mounted on the outer surface of the bag. The thermal stimuli are given by a pump system that recirculates water through 2 channels in the probe. The infusion channels end inside the bag, where a probe monitors the temperature. For details, see METHODS. The system allowed sequential stimulation of individual stimuli with control of site, duration, electrical intensity, mechanical forces and motility, and temperature inside the bag.

Electrical stimuli. Two flexible silver-chloride stimulation electrodes (2×4 mm) were glued to the bag (Fig. 1). The electrodes were connected to a computer-controlled constant-current stimulator (NoxiTest, Aalborg, Denmark). The maximum intensity of the current was limited to 80 mA. Previous systems were capable of inducing atrial capturing when parts of the esophagus near the heart were stimulated (14). Hence, to increase the distance between the electrodes and the heart, the electrodes were placed on the dorsal side of the bag, which was inflated with 10 ml of water corresponding to a diameter of 15 mm. This inflation was not felt by any of the subjects. The construction of the probe made twisting impossible, and a mark on the catheter ensured that the electrodes were placed at the dorsal site. Thus the bipolar stimuli secured a maximal electrical field opposite to the heart with a distance of at least ~ 20 mm from the heart. Two other safety procedures were included in the protocol: 1) for electrical stimuli, a special computer was activated first (and was disconnected after the stimulation was completed) and 2) the wires connecting the patient to the electrical stimulator were removed after the electrical stimulation. Electrical stimuli were given as single or repeated bursts. Single-burst stimuli were defined as five rectangular constant-current pulses with duration of 1 ms at 200 Hz. Repeated-burst stimuli were defined as five single-burst stimuli delivered at 2 Hz. These stimulus sequences have previously been shown to be suitable for evoking pain in the esophagus (14, 27) stomach, duodenum, and colon (9, 11). The stimulus intensity was blinded for the subjects. The current intensity was gradually increased in steps of 0.5 mA with an interval of 15 s until the pain detection threshold was found. We used a protocol with pseudorandom sequences including lower-intensity stimuli interspersed with the ascending stimulus intensities. Such series have proven to be valuable in our previous studies using both electrical and mechanical stimuli (8, 11, 25). Thus intermittent sham stimuli with either no current or the same current as in the previous step were given to ensure that the subject did not automatically increase the sensory rating. The sensory and pain detection thresholds, corresponding to 1 and 5 on the VAS, were found for the single and repeated stimuli. The subject rated the most intense of the train of five repeated stimuli. For the repeated stimuli, a stimulus-response function was made at baseline, where the current intensities corresponding with 1, 3, 5, 6, and 7 on the VAS scale were found.

Mechanical stimuli. The bag contained a four-electrode impedance planimetry system as described previously (12, 20, 26). The electrodes were located inside a cylindrical bag on a 70-cm long probe with a diameter of 4.5 mm (Fig. 1). Two outer ring electrodes for excitation were placed on the probe with an interelectrode distance of 38 mm. A constant alternating current of $100 \mu\text{A}$ at 5 kHz was delivered to the electrodes from a current generator (Gatehouse Medical A/S, Nørresundby, Denmark). Two ring electrodes for detection of potential differences were placed 2 mm apart and midway between the excitation electrodes. The detection electrodes were connected to an impedance-measuring system. The cylindrical bag was 40 mm in length and was made of 35- μm , nonconducting polyurethane. It completely enclosed the electrodes and a sidehole used for measurement of pressure within the bag. The bag could be inflated with electrically conducting fluid (0.009% saline) through a pair of infusion channels, each with a diameter of 2 mm. It could be inflated to a cross-sectional area (CSA) of $\sim 2,000 \text{ mm}^2$ (diameter = 50 mm) without stretching the wall of the bag. The infusion channels were connected to an infusion pump (Type 111; Ole Dich Instrument Makers Aps, Hvidovre, Denmark) that was

able to fill or empty the bag continuously at varying flow rates. A safety valve was connected to the pump, allowing the subjects to stop the infusion at any time. The system was calibrated before the probe was inserted into the esophagus. The CSA of the bag was measured from the impedance of the fluid inside the bag. Hence, when a current is induced in a uniform cylinder by two excitation electrodes, the voltage difference between the detection electrodes is related to the impedance of the fluid and thus the CSA of the bag. Details of the calculations have been described previously (19). All data were digitized and stored electronically for later display and processing on the computer system (Gatehouse Medical). A few test stimuli were done for preconditioning the tissue and to teach the subjects to score the sensation intensity. These were followed by three baseline distensions with a constant infusion rate of 25 ml/min until the subject reported pain (5 on the VAS). After these stimuli, a stimulus-response function was made in which the volume, pressure, and CSA were recorded at intensities corresponding with 1, 3, 5, 6, and 7 on the VAS scale.

Temperature stimuli. Recirculating water was infused into the same bag as used for the mechanical stimuli (Fig. 1). The infusion channels in the catheter were attached to a manual pump system in which 50 ml of water was infused into one channel and simultaneously sucked out through the other channel with a speed of ~ 300 ml/min. A temperature probe (PR Electronics, Roende, Denmark) monitored the water temperature inside the bag. The time elapsing from one temperature level to the next was 60 s. First, the system was filled with 10 ml water at the desired temperature. In the range of 25–40°C, this could not be felt by any of the subjects, excluding the possibility that the distension contributed to the sensation. Immediately after filling of the bag, 50 ml of water at the desired temperature was recirculated without changing the volume or pressure in the bag. In pilot experiments, it was found that, during perfusion of the esophagus, temperatures inside the bag of $\sim 5, 10, 15, 20, 25, 30, 35, 40, 45,$ and 50°C corresponded with water temperatures of 0, 5, 10, 16, 22, 30, 35, 44, 52, and 60°C in the pump system. Similar to the electrical stimuli, we used a pseudorandom, blinded sequence with lower-intensity stimuli interspersed with the ascending stimulus intensities. In each series, the stimuli were given with expected intrabag temperatures of 10, 5, 15, 20, 30, 35, 40, 25 (sham), 45, and 50°C , with 2–3 additional sham stimuli having the same temperature as the previous stimulus interposed randomly.

Statistics

Results were expressed as means \pm SD. Data were analyzed by using paired-sample *t*-tests, and for multiple comparisons ANOVA was used. Because the referred pain areas were not normally distributed, a Wilcoxon test and Friedman's nonparametric ANOVA were used to describe these data. $P < 0.05$ was considered significant. For software, SPSS v.10.0 was used.

RESULTS

All subjects completed the experiment. One subject reported slight soreness on swallowing the following day, but otherwise no adverse effects were observed.

Electrical Stimulation

In one subject, there were technical problems with the electrodes and the electrical stimulation was not performed. The word most frequently used to describe

the nonpainful sensations was “stinging” ($n = 10$). The most frequent words selected from the MPQ for the painful sensations were “pricking” ($n = 7$) and “warm” ($n = 4$), but several other words such as “shooting,” “cold,” and “pressing” were also used (Table 1).

The thresholds for the sensation and pain detection were lower for repeated compared with single electrical stimuli (sensation threshold: 10.4 ± 4.8 vs. 13.9 ± 6.9 mA; pain threshold: 16.9 ± 7.8 vs. 25.3 ± 10.1 mA; $P < 0.05$ and $P < 0.001$, respectively). The stimulus-response relationship for the first stimulation is seen in Fig. 2. An increasing VAS rating to the increasing stimulus intensities was seen ($F = 3.0$; $P = 0.03$). All subjects reported referred pain to the repeated stimuli (Fig. 3). The spread was to the chest in six subjects. One subject had spread pain to the back together with the chest pain. One subject experienced only referred pain to the back, and two had spread pain only to the neck. The referred pain areas increased as a function of pain intensity and were 11.4 ± 12.8 , 20.7 ± 28.5 , and 35.1 ± 53.4 cm² at VAS ratings of 5, 6, and 7 ($P < 0.001$) (Fig. 4).

Mechanical Stimulation

All subjects completed the distension series. Several words were used to describe the nonpainful distensions, but the most frequent was pressing ($n = 5$). The most frequent words selected from the MPQ for the painful sensations were pressing ($n = 7$), pricking ($n = 4$), and warm ($n = 4$) (Table 1).

The CSA increased with increasing volume, although the association was not linear. The pressure typically increased at the start of the distension but was very variable at higher CSAs. An example is shown in Fig. 5. The stimulus-response relationship for the first stimulation is seen in Fig. 6. The VAS rating increased for the increasing stimulus intensities: CSA ($F = 10.2$, $P < 0.001$) and pressure ($F = 3.5$, $P = 0.015$). All subjects reported referred pain (Fig. 3). The spread was to the chest in 10 subjects and to the abdomen in 1. Two subjects had referred pain to both the chest and the back and neck. The referred pain areas increased as a function of pain intensity and were 21.9 ± 23.6 ,

Table 1. Words used to characterize the nonpainful and painful sensations during the different visceral stimuli

Stimulus	Nonpain descriptors	Pain descriptors
Electrical	Stinging	Pricking Warm
Mechanical	Pressing	Pressing Pricking, warm
Cold	Cold	Cold Squeezing, pricking
Warmth	Warm/Burning	Hot/Burning Pricking, pressing

The words used by most subjects (>50%) are shown in the upper line. Pain descriptors less frequently used are shown in italics below. For further details, see text.

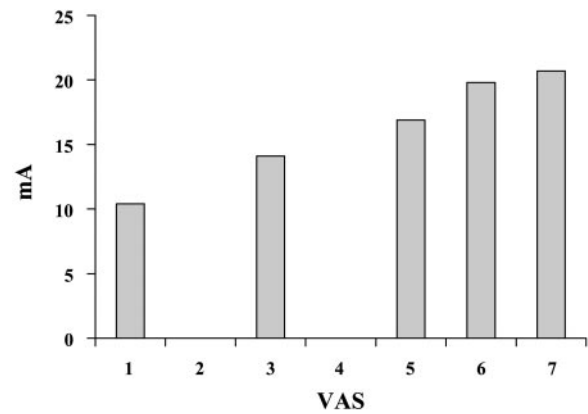


Fig. 2. Stimulus-response function for the bipolar electrical stimuli in the esophagus. Pain intensity was rated on a visual analog scale (VAS), with 5 as the pain threshold. There was a significant relationship between the stimulus intensities (mA) and the VAS ratings.

52.0 ± 64.4 , and 81.1 ± 86.9 cm² at VAS ratings of 5, 6, and 7 ($P < 0.001$) (Fig. 4).

Thermal Stimulation

Two subjects did not tolerate the highest and/or lowest temperatures; otherwise, all subjects completed the experiment. At temperatures in the pump system of 0, 5, 10, 16, 25, 30, 35, 44, 52, and 60°C, the corresponding temperatures inside the bag were 7.1, 10.7, 14.7, 19.4, 25.0, 30.4, 35.4, 40.9, 44.9, and 50.0°C, corresponding with the original pilot experiments.

For the nonpainful stimuli, all subjects used the word cold for the cold stimuli and warm/burning for the warmth stimuli. For the painful stimuli, several words were selected from the MPQ. For the cold stimuli, the most often used were cold ($n = 6$), squeezing ($n = 3$), and pricking ($n = 2$). For the warmth stimuli, the most often used were hot/burning ($n = 8$), pricking ($n = 4$), and pressing ($n = 2$) (Table 1). Figure 7 shows the stimulus-response relationship for the thermal stimuli. There was an increasing VAS rating to either decreasing or increasing temperatures (cold stimuli: $F = 16.5$, $P < 0.001$; warmth stimuli: $F = 28.8$, $P < 0.001$). All subjects reported referred pain to the thermal stimuli (Fig. 3). In 10 subjects, both cold (7°C) and warmth (50°C) stimuli resulted in pain to the chest. In those subjects, one also had referral pain to the neck and another had back pain. One subject had only referred pain to the back following the temperature stimuli. The referred pain area to the coldest stimulus was $35.5-36.5$ cm² at a mean temperature of 7.1 ± 2.4 °C (mean VAS 4.6). At the warmest stimulus of 49.8 ± 3.5 °C (mean 5.5 on the VAS), the referred area was 52.5 ± 40.0 cm². There was no difference between the sizes of these areas ($P = 0.24$).

Comparison Between the Stimuli

There were several differences between the reported sensations to the four stimuli. First, the descriptive words chosen for both the nonpainful and painful sensations were different for the electrical, mechanical,

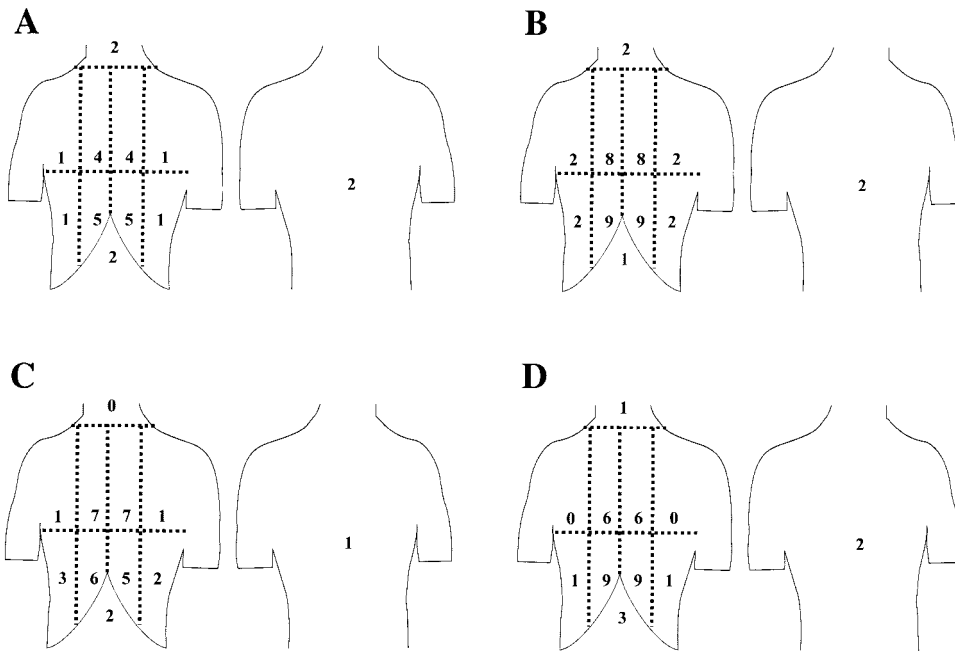


Fig. 3. Schematic illustration of the anatomic regions where the referred somatic pain was reported at the maximal intensity of the experimental visceral stimuli. On the VAS (see METHODS), the mean stimulus intensity was 7 for the electrical (A) and mechanical (B) stimuli and 4.6 and 5.5 for the cold (C) and warmth (D) stimuli, respectively. The figure shows the front (left) and back (right) for all stimulus modalities. The front of the chest was divided into 8 areas by a horizontal line 5 cm above the xiphoid process and 2 vertical lines 5 cm lateral to the midline. The neck, abdomen, and back were considered separate areas. The numbers on the figure refer to the number of subjects reporting pain to that particular region of the chest.

cold, and warmth stimuli. The location of the referred areas to mechanical, electrical, and temperature stimuli at the pain-detection threshold differed within the same anatomic area (chest, abdomen, neck, and back) in all subjects. The chest was divided into four regions at the same size, with the neck, abdomen, and back as other regions. In this division, the referred area at the pain threshold was reported to different anatomic regions for one or more of the four stimulus modalities in eight subjects. At the pain threshold, there were no differences between the size of the referred pain areas to the electrical, mechanical, minimum, and maximum temperatures ($F = 1.8$, $P = 0.17$). However, as seen in Fig. 4, the referred areas to VAS ratings of 5, 6, and 7 combined were greater for the mechanical stimuli compared with the electrical stimuli ($P < 0.001$).

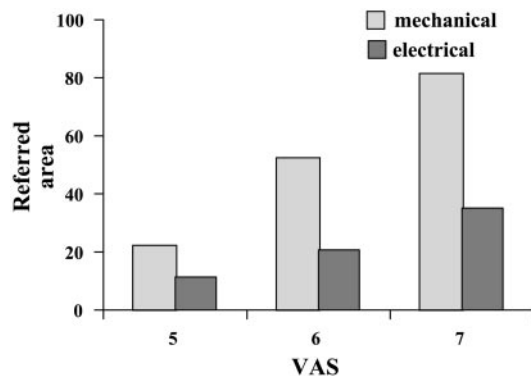


Fig. 4. The somatic referred pain areas (cm^2) during repeated electrical (5 pulses, 2 Hz) and mechanical stimulation of the esophagus at pain intensities of 5, 6, and 7 on the VAS, with 5 as the pain threshold. There was an increase in referred pain area to increasing stimulus intensities. The mechanical stimuli resulted in greater referred pain than electrical current.

DISCUSSION

A multimodal experimental model to evoke pain from the human esophagus was developed by using electrical, mechanical, cold, and warmth stimuli. The various stimulus modalities were all technically improved compared with previous studies and, for the first time, integrated into the same stimulation device. The system allowed sequential activation of the individual stimuli with control of site, duration, electrical intensity, mechanical forces, motility, and temperature inside the bag, hence fulfilling the demands for a comprehensive experimental pain model. The stimuli are most likely able to activate receptors in superficial (thermal), deep (mechanical), or combined (electrical) layers of the esophagus. All subjects reported nonpainful and painful sensations, with referred pain to somatic structures. The responses were stimulus dependent, reflecting the differentiated activation of the involved receptors and pathways. Hence, the model may be adequate for further clinical and pharmacological studies.

Experimental Design

The safety of the electrical stimuli was improved compared with previous methods, because the bipolar electrodes with the direction pointing backward in the esophagus ensured that the electrical field was maximal contralateral to the heart. Thus (in the subjects in whom the probe was in the correct position) no arrhythmias were observed, in contrast to previous studies, in which atrial capture was reported (9). Compared with our model using an endoscope (8, 9, 11), the current method did not allow visual inspection of the mucosa. On the other hand, the unpleasantness associated with the much thicker endoscope was avoided.

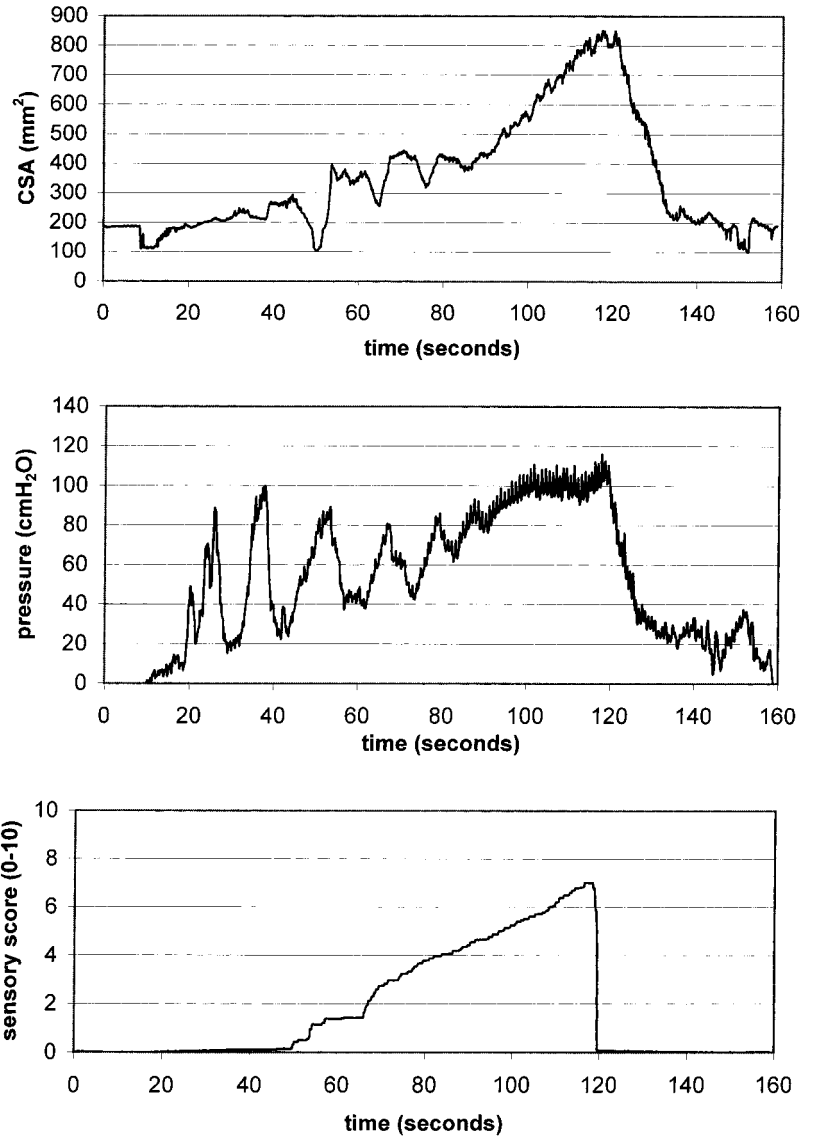


Fig. 5. Example of mechanical stimulation of the esophagus in which the bag was filled at an infusion speed of 25 ml/min. The pain intensity was rated on a VAS, with 5 as the pain threshold. During the distension, pressure and cross-sectional area (CSA) were recorded online. Contractions in the esophagus are seen as an increase in pressure with a simultaneous decrease in CSA. The increase in CSA corresponded with increasing stimulus intensity after the bag was filled with 20 ml water.

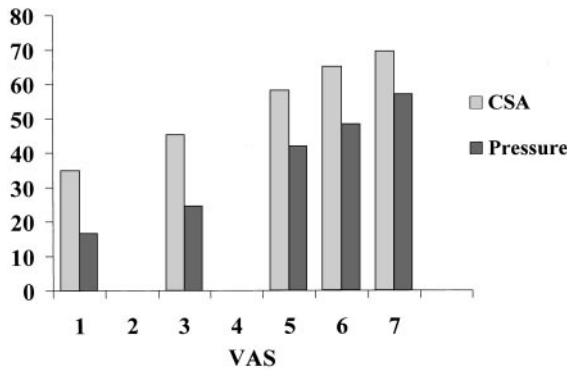


Fig. 6. The stimulus-response function for the mechanical stimuli in the esophagus. Pain intensity was rated on a VAS, with 5 as the pain threshold. The CSA (mm² × 10; y-axis) and pressure (cmH₂O; y-axis) increased with the increasing pain ratings.

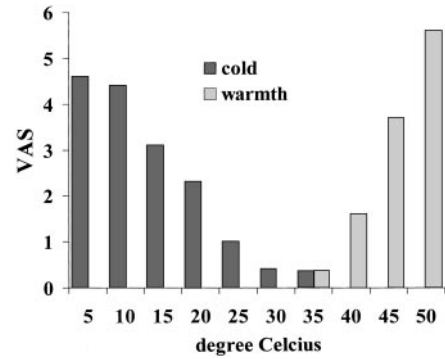


Fig. 7. The stimulus-response function for the cold and warmth stimuli of the esophagus. Pain intensity was rated on a VAS, with 5 as the pain threshold. There were significant relationships between decreasing (cold stimuli) or increasing (warmth stimuli) temperatures, respectively, and the VAS ratings.



Therefore, the sensation to the experimental electrical stimuli could be differentiated from the unpleasantness related to the inserted probe. The filling of the bag during the electrical stimuli, however, induced contractions in the esophagus, although they decreased after initiation of the experiment. These were unpleasant for some subjects, but after a short time the unpleasantness disappeared and the slight filling of the bag could not be felt by any of the subjects.

For the mechanical stimuli, a large polyurethane bag was used, providing no resistance to the distension compared with many earlier studies that used latex balloons. Newer methods, such as the barostat, provide the possibility for control of volume and pressure during the distension, allowing calculations of compliance. This system, however, suffers from methodological limitations due to, e.g., intrinsic compliance, which may not represent the “true” compliance of the organ (18). Moreover, the length of the bag will influence the shape of the curves and have to be taken into account (15, 16, 35). Geometric and time-dependent mechanical behavior of the tissue also influence the measurements (20), and volume and pressure are not valid measures of the deformation and forces applied at the gut wall. The impedance planimetry provided exact measurement of the CSA. In the esophagus, the tension and strain are related to the CSA (20), and in the current study, any data for the CSA will also be valid for these parameters. The CSA, tension, and strain are probably more directly responsible for activation of the mechanoreceptors and hence of more interest than pressure and volume in the bag (16, 20). In the current study, the CSA was variable due to the contractions evoked by the distensions. Relaxation of the esophagus with pharmacological substances such as continuous infusion of butylscopolamine will ease the interpretation of CSA and pressure data (17). However, because we did not know the eventual influence of butylscopolamine on the other stimuli, we decided not to give any muscle-relaxing drugs.

Only few previous studies have used temperature stimuli, although Hertz (21) reported temperature sensation in the esophagus in 1911. Recently, Villanova et al. (34) created controlled thermal stimuli in the stomach and small intestine by using recirculating water. This method did not, however, allow measurement of the temperature inside the bag. Because there was a significant change in the intrabag temperature during the 10-s perfusion, only methods allowing online recording of the temperature inside the bag are controllable. The temperature inside the bag is supposed to be somewhat different from that at the receptors, which probably are situated below the mucosal lining (28, 34). On the other hand, the insulation due to the 35- μm polyurethane material in the bag is negligible and the measured temperature must be comparable to that applied at the mucosal surface. It was not possible to insulate the probe completely. Hence, the subjects were able to discriminate cold and hot water in the pharynx but were not able to rate the different tem-

perature steps in the throat. Therefore, the selected method with a pseudorandom ascending sequence, including interposed lower-intensity stimuli, seemed sufficient as blinding procedure for the temperature steps.

Characteristics of the Different Stimuli

Electrical stimuli. In the current study, the different stimuli provided the possibility for stimulation of different neural pathways and mechanisms in the same experiment. The bipolar electrical stimuli bypass the receptors and stimulate the afferent nerves directly (11). Although this can be regarded as a nonspecific activation, the electrical stimuli at lower intensities activate the myelinated afferents (A δ -fibers in the gut) and, for higher intensities, nonmyelinated C-fibers as well (5, 17) and may give some differentiation between the afferent nerve populations. The electrical field will invariably activate receptors at mucosa, submucosa, and muscle layers depending on the intensity and thus represent a broad activation of the gut wall. The well-defined stimulation area and unique possibility for control of the time sequence give these stimuli several advantages (8, 9). Hence, we showed an increased response to stepwise increments together with demonstration of temporal summation to repeated electrical stimuli.

Mechanical stimuli. The mechanical stimuli activate receptors in different layers of the gut. Although mucosal afferents are sensitive to movements across the surface, the main response probably comes from afferent fibers located in series with the esophageal muscle layer (6, 28). Our distension protocol took advantage of a pump-controlled ramp distension, in which the rate of discharge is most likely related to the strain applied to the smooth muscle layers (20, 28, 32). In the current study, we found that the increase in perception intensity was nearly linearly related to the magnitude of the stimulus, measured as CSA of the esophagus. Because the CSA is related to the strain of the gut wall (20), we believe that the mechanical stimulus mainly activates deep receptors in the smooth muscular layers.

Thermal stimuli. Thermosensitive mucosal afferents have previously been demonstrated in animal studies as well as in the human esophagus, stomach, and rectum (20, 23, 28, 30, 34). Animal studies suggest that thermoreceptors with specific responses are widely distributed throughout the gut. Accordingly, in humans, Villanova et al. (34) observed uniform perception of thermal stimuli from the stomach down to the jejunum with different reflex responses evoked by the stimuli. Although cold and warm were the words most frequently used to describe the painful thermal stimuli, other descriptors were also used, demonstrating the lesser specificity of the receptors compared with skin stimuli. The temperature stimuli showed a stimulus-response relationship, demonstrating the validity of the receptor activation. With respect to stimulus-response function, there were no differences between the cold and warmth stimuli, although the project was not

designed for direct comparison of the thermal energy. The subjects were able to sense the first temperature stimuli in the chest within a few seconds, before the thermal energy could be conducted to deeper layers. Hence, we believe that the afferents activated by the temperature stimuli must be located superficially. Thus the model provides the possibility for activation of superficial receptors with stepwise thermal stimuli that can be controlled with respect to site, intensity, and duration.

Most evidence points toward polymodality of the visceral receptors (31), and thus the different classes of specific afferents known in the skin encoding, e.g., mechanical and thermal stimuli are not found. Therefore, the same receptors may encode the different stimuli given in the current study. However, although the receptors are polymodal, characterization of the responses to different sensations is important to develop a comprehensive sensory evaluation of the gut in health and disease (4, 22, 34). In previous studies (24, 30) some subjects reported paradox sensations to different stimuli, e.g., cold was reported warm, but such adverse sensations were not found in our study. Especially for the painful sensations, many different descriptions were reported. For example, in some subjects electrical and mechanical stimuli were reported as warm and cold, among other sensations, but such feelings were reported together with more typical sensations such as pricking and pressing. Thus the subjects were able to discriminate between the stimuli with different qualitative sensations, and although the receptors may be polymodal, the peripheral activation and subsequent central processing resulted in a robust differentiation of the stimuli. The differentiation between the stimuli was not, however, as distinct as for cutaneous stimuli, and obviously the visceral nervous system is less specific than the somatic counterpart.

Central Responses and Possibility for Pharmacological Modulation

Temporal summation, being a human correlate to the early phase of the “wind-up” process, is a potent mechanism for generation of referred visceral pain (3, 9, 24). Summation was demonstrated in response to the electrical stimuli, to which the threshold to repetitive stimuli was lower than for single stimuli. Thus the model is usable for testing basic central mechanisms and pharmacological substances targeted to modulate central temporal summation mechanisms (such as those with action on the *N*-methyl-D-aspartate receptor) (1). Referred somatic pain to visceral stimuli is a central phenomenon due to visceral nerves terminating in the same area of the spinal cord as somatic afferents (for review, see Ref. 3). During increasing stimulus intensities, the referred area to mechanical stimuli was greater than for electrical stimuli. Spatial summation mechanisms at the central level may explain this finding, because the stimulation area was greater during mechanical activation compared with the size of the electrical field created by the bipolar

stimulation. Such spatial stimulation has also been demonstrated in the jejunum (29). At the pain threshold, the size of the referred pain areas to the four different stimuli was comparable but the anatomic area differed for most subjects. Although this may be related to the different areas and depths of activation for the stimuli, there were also differences between the cold and warmth stimuli in the same subjects. Hence, the possibility for evoking and modulating central mechanisms makes this model highly suitable to study basic visceral pain mechanisms.

Previous experimental gut studies in which pharmacological modulation has been assessed were based on distension models. Most of these models are based on simple pressure and volume recordings with limitations as discussed above. Such technical flaws may explain why the results are often not consistent (15, 20) or insensitive to the pharmacological interventions. In the current model, we used impedance planimetry, encompassing many of the limitations associated with previous mechanical systems (12, 18, 20). However, because the effect of a certain drug in experimental skin models is often only seen when multiple stimuli are used (1, 7), distension of the gut may be invalid as a single instrument under experimental circumstances. The presented new multimodal model offers the possibility of assessing the characteristics and central reactions after modulation of four different stimuli believed to activate different afferent pathways. Therefore, this model will probably be a sensitive instrument for pharmacological testing.

In conclusion, the present new visceral pain model offers the possibility for controlled multimodal stimulation, in which different stimulus modalities are integrated into one stimulus device. The stimuli activate superficial and deeper layers of the gut and therefore resemble the polysensorial experiences present in painful visceral diseases. The distinct responses to the individual stimuli, together with robust stimulus-response relations, offer the possibility of comparative studies of different visceral sensations. Central phenomena such as temporal summation and viscerosomatic projections can be studied in the same experiment. This may provide new possibilities to evaluate patients and to screen/test pharmacological interventions.

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