Oesophageal sensation assessed by electrical stimuli and brain evoked potentials – a new model for visceral nociception

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Abstract

Sensory thresholds and brain evoked potentials were determined in 12 healthy volunteers using electrical stimulation of the oesophagus 28 and 38 cm from the nares. The peaks of the evoked potentials were designated N for negative deflections and P for positive. Continuous electrical stimulation (40 Hz) at the 38 cm position resembled heartburn (five of 12 subjects) while non-specific ('electrical') sensations were provoked at 28 cm (10 of 12). Thresholds of sensation and of pain were lower at the initial than the second determination, but did not differ with respect to stimulation site. The pain summation threshold to repeated stimuli (2 Hz, 5 stimuli) was determined for the first time in a viscus. This threshold was lower than the pain threshold to single stimuli at 38 cm ($p < 0.02$). Evoked potential latencies did not change significantly over a six month period while the N1/P2 amplitude was higher at the first measurement ($p < 0.05$). P1 and N1 latencies were significantly shorter 38 cm (medians 100 and 141 ms) than 28 cm from the nares (102 and 148 ms) ($p = 0.04$ and $p = 0.008$). Electrical stimulation of the oesophagus may serve as a human experimental model for visceral pain. Longer evoked potential latencies from the proximal compared with distal stimulations provide new information about the sensory pathways of the oesophagus.

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Keywords: chest pain, afferent pathways physiology, electric stimulation, electroencephalography, evoked potentials, oesophagus innervation.

Several chronic pain syndromes may originate from visceral organs: the female reproductive tract in chronic pelvic pain; the colon in the irritable bowel syndrome; the heart in angina pectoris; the oesophagus in angina-like chest pain. Human visceral experimental pain models are few, however, compared with the number of models developed to study somatosensory pain.

Pain from the oesophagus has been provoked in chest pain patients and healthy persons by means of balloon distension^{1–6} and by electrical stimulation.⁷ In patients with chest pain several intravenously administered smooth muscle spasmogenics, for example, bethnechol,⁸ ergonovine,⁹ and edrophonium

chloride¹⁰ as well as direct installation of acid¹¹ have been used to reproduce chest pain of presumed oesophageal origin. Recent studies question whether provocative tests only elicit pain from the oesophagus or also affect the heart.^{12–15} Electrophysiological and psychophysical studies of sensations evoked from the human oesophagus represent new investigational methods. Both balloon distension^{16–18} and electrical stimulation^{7 19 20} have been shown to evoke brain potentials.

The mechanisms of perception related to the oesophagus need further assessment to understand the pathophysiology of oesophageal pain syndromes. The aim of this study was to investigate electrical oesophageal mucosal stimulation with respect to qualitative (sensations) and quantitative (brain evoked potentials) responses, regional differences, and reproducibility in healthy volunteers.

Methods

Subjects

Twelve healthy volunteers (six females and six males, median age 41 range 27 to 57 years) participated in the study. None of the subjects had a history of neurological, gastrointestinal, endocrinological, or cardiological diseases. None of the subjects were taking drugs at the time of the study.

Electrical stimulation

Oesophageal stimuli were delivered through a specially designed bipolar electrode (Fig 1). The two poles of 0.4 mm diameter made of platinum were situated 10 mm apart. Through a port hole between the poles the electrode was sucked to the mucosa with a syringe, mounted on the exterior end of the electrode catheter, to ensure contact. Two identical oesophageal electrodes with impedances of 2 kohm (measured at 1 kHz with the electrode in isotonic saline) were used. The electrode was passed transnasally and positioned in the oesophagus. Two positions were investigated: 28 and 38 cm from the nares. From previously performed oesophageal manometric studies these distances were known to be above the proximal border of the lower oesophageal sphincter in all subjects.

Oesophageal electrical stimuli were delivered as short trains of square wave pulses, 5 per train and each pulse of 1 ms duration, 4 ms apart from a computer controlled constant current stimulator. Firstly, the current was

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Figure 1: Bipolar electrode used for electrical stimulation in the oesophagus. The complete electrode is shown and a close up view of the tip. The two poles of 0.4 mm diameter are situated 10 mm from each other. Through a port hole between the poles the electrode is sucked to the mucosa with a syringe to ensure contact.

increased from zero in steps of 0.1 mA until the person perceived the stimulus (threshold of sensation). Secondly, the threshold reported as painful was determined (pain threshold) without respect to the modality of the pain perceived. Thirdly, we determined the 'pain threshold of summation' by applying 5 trains (each of 5 stimuli, 0.5 s between pulses with the same characteristics as above) during stepwise increments of 0.1 mA until the subjects felt that the repeated stimuli became increasingly painful through the series. All thresholds were measured twice at both positions. The level of oesophageal stimulation was randomised but the order of threshold determination was (a) perception, (b) pain, and (c) summation. An interval of at least three minutes separated threshold determinations. At the end of the stimulation series a continuous 40 Hz (1 ms duration of each pulse) stimulation was applied firstly at the 28 and secondly at the 38 cm position and the stimulus intensity was slowly increased until the subject asked for the procedure to stop because of discomfort. The subjects were asked to describe the sensations after single and continuous stimulation, without prompting from the investigators.

Evoked potentials. Experiment 1

Evoked vertex potentials were assessed by stimulating the oesophageal mucosa 28 and 38 cm from the nares at an amperage 1.3 times the previously determined pain threshold. The order of oesophageal positions was randomised between subjects. A 16 stimuli series was delivered at each level. The evoked potentials were recorded with a platinum needle electrode (Disa 25C04, Copenhagen, Denmark) inserted over the vertex (position Cz according to the international 10–20 system²¹) with reference to linked earlobes. The electroencephalogram was filtered by a second order filter (0.5–12 Hz), amplified (Disa Amplifier 5C01, Copenhagen, Denmark), and sampled by a computer at 64 Hz. Brain potentials with latencies between 100 and 300 ms are referred to as vertex potentials as they have the largest amplitude over the vertex.²² The average of 16 stimuli is sufficient to obtain an acceptable signal to noise ratio.²³ A test stimulus before each series was used to minimise variability of the evoked potentials.²⁴

The mean interval between stimuli was 10 seconds (range 8–12). About two seconds before each stimulus the subject received an auditory warning stimulus as this stimulus paradigm gives the smallest variability of the vertex potential.²⁵ The auditory stimulus itself generates a vertex potential with a negative peak (N1) latency of approximately 150 ms and lasts about 400 ms and does not directly affect the following electrically evoked potentials.²⁵ The subjects kept their eyes open, and eye movements that could contaminate the evoked potential were monitored continuously. The peaks of the evoked potential signal are designated N for negative deflections and P for positive. Numbers 1, 2, 3, and so on are given to the peaks in order of appearance after the stimulus. The P1, N1, and P2 peaks were determined independently by two observers who were blinded to the procedure. The peak to peak amplitudes (P1/N1 and N1/P2) in microvolts and latencies of P1, N1, and P2 in milliseconds with respect to stimulus onset were measured by computer.

Evoked potentials. Experiment 2

In one subject (female, 50 years) evoked potentials were determined again one month later. At this time stimulations were applied at 1 cm intervals in the oesophagus going from 38 to 28 cm from nares. Two stimulus intensities were used and determined 38 cm from the nares: one series was performed with a stimulus intensity corresponding to the threshold of pain. The other series used a strong but not painful sensation corresponding to 4 on a discrete scale where 0 represents no sensation, 5 the threshold of pain, and 10 the worst pain imaginable in the region.

Evoked potentials. Experiment 3

Seven of the participants in this study (4 females, 3 males, median age 49 range 29 to 57 years) had been investigated six months earlier. These subjects were investigated again (after

TABLE I Sensation after nociceptive electrical stimulation of the oesophageal mucosa in 12 healthy volunteers

Catheter distance from nares (cm)	Stimulus type	Non-specific ('electric') sensation	Heartburn	'Warm' sensation	Projection
28	Single	12	0	0	0
28	Continuous	10	1	1	2
38	Single	8	4	0	0
38	Continuous	7	5	0	6

Results from stimulation 28 and 38 cm from nares with single and continuous stimulation. The most pronounced sensation is shown for each person in both positions and for single and continuous stimulation respectively. Projection was only to local areas. Projection was not considered an independent sensation, but if present ticked in addition to the primary sensation.

experiment 1) with nociceptive stimulus intensities identical to the initial study. Stimuli were applied at the 38 cm position. The results were evaluated graphically by plotting the difference between the two measurements against their mean as recommended by Bland and Altman²⁶ and by testing whether the first and second measurement differed statistically.

Statistics

Wilcoxon (signed rank sum) and Mann-Whitney tests were used for comparisons between thresholds and evoked potential parameters. Bivariate associations were evaluated by least square regression. A *p* value <0.05 was considered significant.

Ethics and safety

The study was conducted in accordance with the Helsinki Declaration and approved by the local ethical committee. Written informed consent was obtained from each volunteer. A pre-defined upper stimulus intensity of 70 mA was chosen. The length of stimulus and size of the electrode were considerably less than that known to affect the ventricular myocardium^{27,28} or to damage the oesophageal mucosa.²⁹ Nevertheless the entire study was carried out in a cardiac clinic with continuous electrocardiographic monitoring, intravenous access established, and resuscitation stand by.

Results

Sensation

All persons were able to describe sensations after nociceptive single and continuous stimulation (Table I). The most pronounced sensations could be categorised as non-specific, 'electrical' (like touching an electric

fence), heartburn, or warmth. In two subjects at 28 cm and in six at 38 cm projection to local areas were reported during continuous electrical stimulation. This projection was towards the neck in six, the throat in one, and to the back in one. No person described projection to the arms, left or right side of the chest, or to jaw or teeth.

After continuous stimulation at 38 cm from the nares heartburn (five of 12 subjects) and projection (six of 12) were more likely to occur than at 28 cm from nares (one and two of 12, respectively) (Table I).

Threshold determination

One 34 year old man had an excessive production of saliva, which made assessment of threshold difficult probably because of distorted contact between electrode and oesophageal mucosa. Values for this subject were therefore excluded. Later the salivary production decreased and evoked potentials could be determined. Because of severe discomfort pain thresholds of summation could only be determined in seven subjects at four conditions (double determinations at the two levels). At stimuli below this summation threshold subjects reported that the last stimuli in the series decreased in intensity. When approaching the pain summation threshold, every single stimulus in the series was perceived equally in intensity. At higher stimulus intensities the last stimuli in the series were perceived stronger than the first ones and the pain summation threshold was reached.

For the thresholds of sensation and of pain the first determination was significantly lower than the second determination at both 28 and 38 cm from the nares (Table II) whereas there were no differences between the two determinations of threshold of summation (Table II). The thresholds of pain were significantly higher than the thresholds of summation at 38 cm (*p*=0.02) while there was no difference at 28 cm (*p*=0.12). Threshold of sensation, pain, and summation at 28 compared with 38 cm from the nares were not statistically different.

Evoked potentials. Experiment 1

Latencies of the P1 and N1 peaks of the evoked potentials were longer for stimulation at 28 cm (median 102 and 148 ms, respectively) than at 38 cm (median 100 and 141 ms) (*p*=0.04 and *p*=0.008, Table III). Figure 2 shows individual values of N1. The difference was not statistically significant for the P2 peaks. There was no difference between amplitudes at the two positions (Table III).

Evoked potentials. Experiment 2

In one subject re-examined after one month the N1 latencies decreased with increasing distance from the nares although reaching significance only for nociceptive stimuli (*r*=−0.66, *p*=0.04) and not for strong nor painful stimuli (*r*=−0.57, *p*=0.06, Fig 3).

TABLE II Two determinations of sensation, pain, and temporal summation in 11 healthy volunteers in the oesophagus 28 and 38 cm from the nares after electrical stimulation

Thresholds (mA)	First	Second	<i>p</i> Value
Sensation			
28 cm from nares	4.0 (4.0–5.5)	6.0 (4.0–7.3)	0.005
38 cm from nares	4.0 (3.5–4.5)	5.0 (4.0–6.5)	0.04
Pain			
28 cm from nares	18.0 (8.0–23.0)	25.0 (8.5–27.5)	0.005
38 cm from nares	13.0 (9.2–20.0)	17.0 (11.3–21.5)	0.04
Summation			
28 cm from nares	10.0 (5.1–19.5)	12.0 (6.0–20.0)	0.06
38 cm from nares	10.0 (7.8–13.5)	10.0 (7.5–12.0)	0.30

First: first determination; second: second determination. Values are median and (interquartile ranges).

TABLE III Latencies and interpeak amplitudes of vertex evoked potentials (measurements taken at C₂) in 12 healthy volunteers after nociceptive electrical stimulation in the oesophagus 28 and 38 cm from the nares

	28 cm from nares	38 cm from nares	p Value
Latency (ms)			
P1	102 (87–113)	100 (70–102)	0.04
N1	148 (141–159)	141 (125–146)	0.008
P2	234 (215–246)	227 (211–237)	0.08
Amplitude (μV)			
P1/N1	31.0 (18.0–45.0)	29.0 (17.0–39.0)	1.00
N1/P2	68.0 (43.5–103.0)	66.0 (54.0–72.5)	0.30

N: negative, P: positive. Values are median and (interquartile ranges).

Evoked potentials. Experiment 3

Figure 4 shows the reproducibility of P1 and N1 latencies, and N1/P2 amplitudes of the seven re-examined subjects. The change (mean (2 SD)) in latency for the P1 peak was -10 (27) ms ($p=0.13$) and for the N1 peak it was 13 (43) ms ($p=0.16$). For the N1/P2 amplitude the change was 5 (32) μV ($p<0.05$).

Discussion

Investigation of nociception from the oesophagus is of importance to clarify the oesophageal contribution to various syndromes accompanied by thoracic pain: angina-like chest pain,³⁰ non-cardiac chest pain,^{31 32} diffuse oesophageal spasm,^{33 34} and nutcracker oesophagus.³⁵

Sensations described by the subjects in this study resembled heartburn after continuous electrical stimulation in the oesophagus more often than after single stimuli. Furthermore heartburn almost exclusively occurred in the distal oesophagus. This is in accordance with the early experience that balloon distension elicits a feeling of pressure in the upper part of the oesophagus in contrast with a burning sensation in the lower oesophagus.^{6 36} Referred pain was more likely to occur after the continuous stimulation. This is in line with the general assumption that projection of visceral pain depends on intensity and duration of the nociceptive stimulus.³⁷ As in previous studies using balloon distension^{3 38} the sensations projected to local areas, which is considered a

Figure 2: Individual latency values of the N1 peak of the evoked potentials for oesophageal stimulation at 28 cm (median 148, range 141 to 159 ms) and at 38 cm (median 141, range 125 to 146 ms) from the nares in 12 healthy volunteers ($p=0.008$). ms=Milliseconds.

Figure 3: Latencies of the N1 peaks of vertex evoked potentials in one healthy volunteer after nociceptive (filled symbols, $r=-0.66$, $p=0.04$) and strong, non-painful (open symbols, $r=-0.57$, $p=0.06$) electrical stimulation in the oesophagus. Stimuli were applied in 11 positions 1 cm apart at distances 28 to 38 cm from the nares.

general characteristic of referred pain.³⁹

Thresholds of sensation and of pain were significantly higher at the second compared with the first determination. This could result from adaptation, as found after consecutive cutaneous electrical stimulations.⁴⁰ The period of time, however, between the first and second determination was several minutes in this study, and varied between patients. To have a catheter in the oesophagus is an unfamiliar experience. It is possible that subjects were more aroused at the first determinations than at the following ones as increased arousal is known to decrease the pain threshold.⁴¹ It is unlikely that the stimulus regimen caused sensitisation of the sensory nerves, which requires 20 minutes of high intensity stimulation at a strength that excites C-fibres.⁴² Electrical stimulation bypasses the receptor and is therefore independent of a possible receptor sensitisation.

Repeated nociceptive stimuli increased in intensity during a stimulus series and hence this study showed temporal summation of experimental pain in the oesophagus. The neural mechanisms behind temporal summation are not clarified but a combination of local and central integration and neuron recruitment (increased stimulus area increases the total number of nociceptive neurons activated) has been suggested.⁴³ Temporal and spatial summation of pain may help to explain why patients with angina-like chest pain can be disabled by repetitive episodes of gastro-oesophageal reflux and oesophageal motility disturbances if these act together or even in concert with a decrease in coronary blood flow.^{12 14 15}

In a previous study⁷ using electrical stimulation of the oesophagus it was shown that latencies of evoked vertex potentials were inversely related to intensity of the stimulus. This was confirmed in this study (experiment 2) and has also been shown in investigations of electrically elicited somatosensory evoked potentials.^{44 45} Subtraction of latencies of brain

Figure 4: Reproducibility of evoked potentials after nociceptive electrical stimulation in the oesophagus six months apart. P1 and N1 latencies, and N1/P2 amplitudes of seven re-examined subjects. The solid horizontal lines are means while the dotted lines represent (2 SD). Latencies did not differ from the first to the second determination (Wilcoxon, P1: $p=0.13$, N1: $p=0.16$). N1/P2 amplitudes were higher at the first compared with the second determination ($p<0.05$).

evoked potentials after balloon distension in two oesophageal positions have been used for estimates of nerve conduction velocities.^{46 47} This implies two reasons for erroneous results. Firstly, stimulus intensity is difficult to standardise with balloon distension. In the study by Devault *et al*⁴⁷ median stimulus intensity was 16 ml at the distant position versus 13 ml at the proximal. Secondly, increasing stimulus duration increases N1 and N2 latencies of the evoked vertex potential.⁴⁸ Devault *et al* used a pump with an inflation rate of 170 ml/sec. Inflation time therefore comprised a median of 94 ms distally versus 76 ms proximally and although the evoked potential recorder was not started until 90% inflation was obtained it is probable that a systematic error in the calculation of latencies was introduced. Estimation of nerve conduction velocities on the basis of evoked potential latencies after oesophageal

balloon distension must therefore, with the previously applied techniques,^{18 46 47} be regarded as speculative.

In two earlier studies^{19 20} using non-nociceptive oesophageal electrical stimulation to evoke brain potentials, the stimulus intensities were the same at two levels. Frieling *et al*¹⁹ found that N1, P1, N2, and P2 latencies were significantly shorter proximally than distally. Although not reported in the paper²⁰ this was also the case for the N1 latencies in the study by Tougas *et al* (personal communication). In this study stimulus intensity was also equal at the two different stimulation positions and it was found that latencies of the P1 and N1 peaks after stimulation at the distal position were shorter than latencies from stimulation of the more proximal part of the oesophagus. The only obvious difference between our study and the two studies previously mentioned is our use of painful stimuli. We showed that the increase in latency apparently took place gradually the more rostrally the stimulus was applied and that it was statistically significant for high intensity nociceptive stimuli but not for lower non-noxious stimulation. There could be several explanations for our findings.

Firstly, different afferents may supply different parts of the oesophagus. Physiological studies in the opossum show that sympathetic pathways may carry nociceptive information.⁴⁹ The vagus nerve and its branches may also play a part in oesophageal sensations,²⁰ while its role in oesophageal nociceptive is disputed.^{50 51} The superior laryngeal nerve runs to the cervical oesophagus, while the thoracic and abdominal oesophagus are innervated by the recurrent laryngeal nerves and by oesophageal branches of the vagus.⁵² Conduction velocities are faster proximally as the superior laryngeal nerve is myelinated. Also the thoracic vagus contains small diameter myelinated fibres while the abdominal vagus contains only unmyelinated fibres.⁵³ The distribution of afferent output, however, from the oesophagus between sympathetic and parasympathetic nerves is unknown, which may explain why latency findings are not only a question of conduction velocity.

Secondly, a distal entrance of many or all afferents to the oesophagus. This explanation is in accordance with the regions innervated by the recurrent laryngeal nerves resulting in longer afferent pathways in the proximal part of the oesophagus than in the distal.

Thirdly, latencies of brain evoked potentials are dependent on recruitment of nerve fibres. As suggested previously⁵⁴ a possible more dense afferent nerve supply in the distal oesophagus could result in more intense recruitment here than proximally and hence shorter latencies distally than proximally.

Limitations of this study include the limited number of subjects. Measurements in the oesophagus were carried out at the same distances from the nares in all subjects irrespective of subject height. This results in the same absolute length of the nervous pathways that signals should travel in all subjects but means that not exactly the same oesophageal regions

were stimulated. When describing the sensations elicited after oesophageal stimulation subjects were not provided with help in the description or a list of words. This was to avoid bias from the investigators. It may be argued that categorisation of the patients' description after the study into three classes introduces bias at another level. Over a six month period a variation in latency values for the individual subject similar to that previously reported in other anatomical areas⁵⁵ was shown while there were no systematic differences between the first and second measurement. This emphasises the importance of controlled conditions when measuring evoked potentials by stimulating the oesophagus. Whether the change in latencies over time after proximal and distal stimulation shows covariance must be considered in a future study. The significantly higher amplitude in the first compared with the second measurement could reflect that subjects were more aroused at their first session. Evoked potential amplitudes have previously been found to depend on the level of arousal.⁵⁵

In conclusion, this study has shown that electrical stimulation in the oesophagus may serve as a human experimental model for visceral pain. Longer latency of evoked potentials after proximal oesophageal stimulation compared with stimulation in the distal part of the oesophagus provides new information about the afferent nerve innervation of the human oesophagus.

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- 1 Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 1986; **91**: 845-52.
- 2 Kramer P, Hollander W. Comparison of experimental esophageal pain with clinical pain of angina pectoris and esophageal disease. *Gastroenterology* 1955; **29**: 713-43.
- 3 De Caestecker JS, Pryde A, Heading RC. Site and mechanism of pain perception with oesophageal balloon distension and intravenous edrophonium in patients with oesophageal chest pain. *Gut* 1992; **33**: 580-6.
- 4 Barish CF, Castell DO, Richter JE. Graded esophageal balloon distension. A new provocative test for noncardiac chest pain. *Dig Dis Sci* 1986; **31**: 1292-8.
- 5 Clouse RE, McCord GS, Lustman PJ, Edmundowicz SA. Clinical correlates of abnormal sensitivity to intra-esophageal balloon distension. *Dig Dis Sci* 1991; **36**: 1040-5.
- 6 Chapman WP, Jones CM. Variations in cutaneous and visceral pain sensitivity in normal subjects. *J Clin Invest* 1944; **23**: 81-91.
- 7 Frøbert O, Arendt-Nielsen L, Bak P, Andersen OK, Funch-Jensen P, Bagger JP. Electrical stimulation of the esophageal mucosa: perception and brain evoked potentials. *Scand J Gastroenterol* 1994; **29**: 776-81.
- 8 Deschner WK, Maher KA, Cattau ELJ, Benjamin SB. Prospective evaluation of high-dose bethanechol in investigation of oesophageal chest pain. *Dig Dis Sci* 1989; **34**: 1656-61.
- 9 London R, Ouyang A, Snape WJ, Goldberg S, Hirshfield J, Cohen S. Provocation of oesophageal pain by ergonovine or edrophonium. *Gastroenterology* 1981; **81**: 10-5.
- 10 Hewson EG, Dalton CB, Richter JE. Comparison of esophageal manometry, provocative testing, and ambulatory monitoring in patients with unexplained chest pain. *Dig Dis Sci* 1990; **35**: 302-9.
- 11 De Caestecker JS, Pryde A, Heading RC. Comparison of intravenous edrophonium and oesophageal acid perfusion during esophageal manometry in patients with noncardiac chest pain. *Gut* 1988; **29**: 1029-34.
- 12 Mellow MH, Simpson AG, Watt L, Schoolmeester L, Haye OL. Esophageal acid perfusion in coronary artery disease. Induction of myocardial ischemia. *Gastroenterology* 1983; **85**: 306-12.
- 13 Cannon RO, Cattau ELJ, Yakashe PN, Maher K, Schenke WH, Benjamin SB, et al. Coronary flow reserve, esophageal motility, and chest pain in patients with angiographically normal coronary arteries. *Am J Med* 1990; **88**: 217-22.
- 14 Chauhan A, Petch MC, Schofield PM. Effect of oesophageal acid instillation on coronary blood flow. *Lancet* 1993; **341**: 1309-10.
- 15 Gayheart PA, Gwitz PA, Bravenec JS, Longlet N, Jones CE. An alpha-adrenergic coronary constriction during esophageal distention in the dog. *J Cardiovasc Pharmacol* 1991; **17**: 747-53.
- 16 Castell DO, Wood JD, Frieling T, Wright FS, Vieth RF. Cerebral electrical potentials evoked by balloon distention of the human esophagus. *Gastroenterology* 1990; **98**: 662-6.
- 17 Smouth AJ, DeVore MS, Dalton CB, Castell DO. Cerebral potentials evoked by oesophageal distension in patients with non-cardiac chest pain. *Gut* 1992; **33**: 298-302.
- 18 Smout AJ, DeVore MS, Castell DO. Cerebral potentials evoked by esophageal distension in humans. *Am J Physiol* 1990; **259**: G955-9.
- 19 Frieling T, Enck P, Wienbeck M. Cerebral responses evoked by electrical stimulation of the esophagus in normal subjects. *Gastroenterology* 1989; **97**: 475-8.
- 20 Tougas G, Hudoba P, Fitzpatrick D, Hunt RH, Upton RM. Cerebral-evoked potential responses following direct vagal and esophageal electrical stimulation in humans. *Am J Physiol* 1993; **264**: G486-91.
- 21 Jasper HH. The ten twenty electrode system of the international federation. *Electroencephalogr Clin Neurophysiol* 1958; **10**: 371-5.
- 22 Regan D. Human brain electrophysiology. *Evoked potentials and evoked magnetic fields in science and medicine*. New York: Elsevier, 1989.
- 23 Arendt-Nielsen L. First pain event related potentials to argon laser stimuli: recording and quantification. *J Neurol Neurosurg Psychiatry* 1990; **53**: 398-404.
- 24 Arendt-Nielsen L, Bjerring P. Selective averaging of argon laser induced pre-pain and pain related cortical responses. *Neurosci Meth* 1988; **24**: 117-23.
- 25 Svensson P, Arendt-Nielsen L, Kaaber S, Bjerring P. Vertex potentials evoked by nociceptive laser stimulation of oral mucosa: a comparison of four stimulation paradigms. *Anesthesia and Pain Control in Dentistry* 1992; **4**: 222-8.
- 26 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i**: 307-10.
- 27 Shafiroff BGP, Linder J. Effects of external electrical pacemaker stimuli on the human heart. *Journal of Thoracic Surgery* 1957; **33**: 544-50.
- 28 Burack B, Furman S. Transesophageal cardiac pacing. *Am J Cardiol* 1969; **23**: 469-72.
- 29 McNally EM, Meyer EC, Langendorf R. Elective counter-shock in unanesthetized patients with use of an esophageal electrode. *Circulation* 1966; **33**: 124-7.
- 30 Davies HA. Anginal pain of esophageal origin: clinical presentation, prevalence, and prognosis. *Am J Med* 1992; **92**: 5-10S.
- 31 Breumelhof R, Nadorp JH, Akkermans LM, Smout AJ. Analysis of 24-hour esophageal pressure and pH data in unselected patients with noncardiac chest pain. *Gastroenterology* 1990; **99**: 1257-64.
- 32 Ward B, Wu W, Richter JE, Hackshaw BT, Catell DO. Long term follow-up of symptomatic status of patients with noncardiac chest pain: Is diagnosis of esophageal etiology helpful? *Am J Gastroenterol* 1987; **82**: 215-8.
- 33 Stein HJ, DeMeester TR, Eypasch EP, Klingman RR. Ambulatory 24-hour esophageal manometry in the evaluation of esophageal motor disorders and noncardiac chest pain. *Surgery* 1991; **110**: 753-61.
- 34 Eypasch EP, DeMeester TR, Klingman RR, Stein HJ. Physiologic assessment and surgical management of diffuse esophageal spasm. *J Thorac Cardiovasc Surg* 1992; **104**: 859-68.
- 35 Valori RM. Nutcracker, neurosis, or sampling bias? *Gut* 1990; **31**: 736-7.
- 36 Stürup GK. Visceral pain. *Plethysmographic 'pain reactions'. Dilatation of the oesophagus*. London: HK Lewis, 1940.
- 37 Ness TJ, Gebhart GF. Visceral pain: a review of experimental studies. *Pain* 1990; **41**: 167-234.
- 38 Pollard WS, Bloomfield AL. Experimental referred pain from the gastrointestinal tract. Part I. The esophagus. *J Clin Invest* 1931; **10**: 435-52.
- 39 Foreman RD. Spinal mechanisms of referred pain. In: Vecchiet L, Albe-Fessard D, Lindblom U, Giamberardino MA, eds. *New trends in referred pain and hyperalgesia*. Amsterdam: Elsevier Science, 1993: 47-57.
- 40 Price DC, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain* 1977; **3**: 57-68.
- 41 Willer JC. Influence de l'Anticipation de la Douleur sur les Fréquences Cardiaque et Respiratoire et sur le Réflexe Nociceptif chez l'Homme. *Physiol Behav* 1975; **15**: 411-5.
- 42 Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *J Physiol (Lond)* 1984; **356**: 443-58.
- 43 Price DD, McHaffie JG, Larson MA. Spatial summation of heat-induced pain: influence of stimulus area and spatial separation of stimuli on perceived pain sensation intensity and unpleasantness. *J Neurophysiol* 1989; **62**: 1270-9.
- 44 Buchsbaum MS, Davis GC, Bunney Jr. Naloxone alters pain perception and somatosensory evoked potentials in normal subjects. *Nature* 1977; **270**: 620-2.
- 45 Debecker J, Desmedt JE. Les potentiels évoqués cérébraux et les potentiels de nerf sensible chez l'Homme. *Acta Neurol Psychiatr Belg* 1965; **64**: 1212-48.
- 46 DeVault KR, Castell DO. Esophageal balloon distention and cerebral evoked potential recording in the evaluation of unexplained chest pain. *Am J Med* 1992; **92**: 20-6S.

- 47 DeVault KR, Beacham S, Streletz LJ, Castell DO. Cerebral evoked potentials. A method of quantification of central nervous system response to esophageal pain. *Dig Dis Sci* 1994; **38**: 2241–6.
- 48 Ardnt-Nielsen L, Bjerring P. Cortical response characteristics to painful argon laser stimulation. *Clinical Evoked Potentials* 1988; **6**: 13–8.
- 49 Sengupta JN, Saha JK, Goyal RK. Stimulus-response function studies of esophageal mechanosensitive nociceptors in sympathetic afferents of opossum. *J Neurophysiol* 1990; **64**: 796–812.
- 50 Lynn RB. Mechanisms of esophageal pain. *Am J Med* 1992; **92**: 11–9S.
- 51 Grimson KS, Hesser FH, Kitchin WW, Durham NC. Early clinical results of transabdominal celiac and superior mesenteric ganglionectomy, vagotomy, or transthoracic splanchnicectomy in patients with chronic abdominal visceral pain. *Surgery* 1947; **22**: 230–8.
- 52 Roman C, Gonella J. Extrinsic control of digestive tract motility. In: Johnson LR, ed. *Physiology of the gastrointestinal tract*. 2nd ed. New York: Raven Press, 1987: 507–19.
- 53 Andrews PL. Vagal afferent innervation of the gastrointestinal tract. *Prog Brain Res* 1986; **67**: 65–86.
- 54 Rodrigo J, Hernandez CJ, Vidal MA, Pedrose JA. Vegetative innervation of the esophagus. II. Intraganglionic laminar endings. *Acta Anat* 1975; **92**: 79–100.
- 55 Arendt-Nielsen L. Characteristics, detection, and modulation of laser-evoked potentials. *Acta Anaesthesiol Scand* 1994; **38** (suppl): 101.