Hypoalgesia to pressure pain in referred pain areas triggered by spatial summation of experimental muscle pain from unilateral or bilateral trapezius muscles

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Abstract

Animal and human experimental studies have suggested the importance of spatial summation in the nociception processing and in the activation of descending inhibition. However, the relationship between the areas (size) of muscles simulated and the recruitment of descending inhibition has not been addressed. Consequently, we tested whether bilateral versus unilateral injection of hypertonic saline into trapezius muscles caused hypoalgesia to pressure pain (pressure pain thresholds, PPTs) in the local pain areas (the trapezius muscles) and the referred pain areas (the posterolateral neck muscles). Two groups of volunteers participated. One group received a unilateral injection (one injection) and the other group bilateral injections (two injections). In the bilateral group, hypertonic saline was injected in one trapezius first, and 45 s later, while pain was still present from the first injection, a second injection was performed into the contralateral trapezius muscle. The saline-evoked time to maximal pain was significantly shorter after the second injection than after the first injection. More subjects developed referred pain after the bilateral compared with the unilateral injection. In the referred pain areas, the PPTs 7.5 and 15 min after the second injection were significantly increased compared with the first injection, while no changes in the PPT were observed in local and referred pain areas after unilateral injection. This suggests that the induction of descending inhibition was triggered by spatial summation during the later phase of experimentally induced muscle pain. The present experimental model might be used for further investigation of descending inhibition related to the spatial characteristics of nociceptive stimuli in humans.

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Keywords: Referred muscle pain; Spatial summation; Descending inhibition; Hyperalgesia; Hypoalgesia

1. Introduction

From a clinical point of view, multiple painful foci, for example in work-related musculoskeletal disorders, involve a large number of peripheral afferent fibres and central neurones. Thus, spatial summation may be important for the processing of nociceptive information (Arendt-Nielsen et al., 1996; Coghill et al., 1993; Graven-Nielsen et al., 1997). Descending inhibitory mechanisms such as descending nocuous inhibitory controls (DNIC) (Le Bars et al., 1979) have been found to be a potent pain-relieving mechanism (Carlsson, 2002; Kosek and Ordeberg, 2000; Murase and Kawakita, 2000; Willer et al., 1984). Three factors have been shown to be important for the recruitment of DNIC: (1) the intensity of the stimulus (Willer et al., 1984, 1989), (2) the duration of the stimulation (Graven-Nielsen et al., 1998), and (3) the size of the area stimulated (Bouhassira et al., 1995; Gall et al., 1998–2000). A number of studies have been undertaken to explore the relationship between the skin areas stimulated and the pain intensity perceived. However, these studies have mainly employed cutaneous thermal pain (Bouhassira et al., 1995; Gall et al., 1998, 2000; Marchand and Arsenault, 2002; Price and McHaffie, 1988) as a
conditioning stimulus. In view of the high incidence of musculoskeletal disorders, it is of importance to obtain further insights into the relationship between the areas (size) of muscles stimulated and the recruitment of descending inhibition. Intra-muscular injection of hypertonic saline, a well-documented method for inducing experimental muscle pain, evokes local and referred muscle pain with cutaneous and muscular sensitivity changes in the referred pain areas (Arendt-Nielsen and Svensson, 2001). Further, the homogeneously innervated trapezius muscles provide an optimal anatomic substrate to evaluate the influence of spatial summation of muscle pain on the descending inhibition. Previous studies have shown that unilateral injection of hypertonic saline into trapezius muscle induces somatosensory changes, but without manifestations of hypoaesthesia in either local and referred pain areas in healthy subjects (Madeleine et al., 1998). While workers with neck–shoulder pain after six months of employment express both hyperalgiesia manifested as decreased pressure pain thresholds (PPTs) compared with workers without neck–shoulder pain and hypoaesthesia manifested as increased PPTs compared to the beginning of employment (Madeleine et al., 2003). Lack of pressure pain modulation is also reported in patients with fibromyalgia (Kosek and Hansson, 1997) and patients with painful osteoarthritis before, but not following, surgical pain relief (Kosek and Ordeberg, 2000). These studies indicate a possible involvement of descending inhibition in chronic musculoskeletal pain conditions.

The aim of the present study was to investigate spatial summation of experimentally induced muscle pain and its impact on recruitment of descending inhibitory control in healthy volunteers.

2. Materials and methods

2.1. Subjects

Fifteen healthy volunteers (14 males, one female) participated in the first session with injection of hypertonic saline into unilateral trapezius muscle (unilateral group). Sixteen healthy volunteers (15 males, one female) participated in the second session in which two identical bolus injections of hypertonic saline were given into bilateral trapezius muscles (bilateral group). The two groups were not significantly different (unpaired t test, \( P > 0.05 \) for age and weight) in age (25 ± 3 versus 26 ± 1 years old) and weight (73 ± 1 versus 76 ± 3 kg). Manual palpation of the bilateral trapezius and postero-lateral neck muscles was carried out to exclude subjects with tender points and active trigger points. Informed consent was obtained from each subject. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

2.2. Experimental procedure

The subjects were seated upright in a comfortable chair with backrest and their arms placed at their sides. After the skin had been cleaned with alcohol, a single bolus of hypertonic saline (6%, 0.5 ml) was injected into the belly of each trapezius muscle with a 27 G × 3/4 in. cannula over 15 s at a point 2 cm lateral to the halfway point between the spinous process of the seventh cervical vertebra (C7) and the lateral edge of the acromion. For the unilateral group, only right trapezius muscle was injected. For the bilateral group, the second injection was made 45 s after the first injection. The order of injection was randomised with respect to whether the first injection was made into the dominant or non-dominant side. The intensity of muscle pain from each injection was continuously scored with two electronic visual analogue scales (VAS, Aalborg University, Denmark) by each hand of the subjects. PPTs were measured bilaterally before, 7.5 min, and 15 min after injection at the local pain areas (the trapezius muscle injection sites) and the referred pain areas (the postero-lateral neck muscles). The latter is the most commonly referred pain area from upper trapezius muscle pain (Simons et al., 1999). The subjects were asked to describe the quality of pain with the Danish version of the McGill pain questionnaire (MPQ) (Drewes et al., 1993) and to draw the distribution of pain in the neck and shoulder region after each session (see Fig. 2).

2.3. Assessment of muscle pain intensity, quality, referred pain pattern, and PPTs

The muscle pain intensity was assessed with a VAS scale. The lower extreme of the VAS scale was marked "no pain" and the upper extreme was marked "most pain imaginable". The pain intensities were sampled at 20 Hz and recorded for a period of 7.5 min. The time taken from the onset of pain to the maximal pain, mean, and maximal pain intensities were extracted from the VAS data.

The pain rating index (PRI) from the MPQ (Melzack, 1975) was calculated for the sensory, affective, evaluative, and miscellaneous categories. Words from the MPQ chosen by at least one-third of the subjects were used to describe the quality of hypertonic saline induced muscle pain.

The subjects were asked to draw areas of pain on an anatomical map at the end of the experiment. A pressure algometer (Somedic® Algometer type 2, Sollentuna, Sweden) with a 1 cm² rubber tipped plunger mounted on a force transducer was used to measure the PPTs. Pressure was applied at a rate of 30 kPa/s. The PPTs were measured bilaterally around the trapezius muscle injection sites and at the postero-lateral neck muscles (levator scapulae muscles: 4 cm lateral and 2 cm rostral of the C7 cervical vertebra). The PPT was calculated as the mean of two measurements separated by at least 10 s at each site.
2.4. Statistical analysis

The Friedman repeated measures analysis of variance on ranks (Friedman) was used to analyse the PPTs over time after injections within each group, and the Student–Newman–Keuls (SNK) method was followed for post-hoc comparisons. The two-way ANOVA was applied to compare PPTs between the unilateral and the bilateral group, the SNK method was followed for post-hoc comparisons. VAS data, weight, age, and the time to maximal pain were compared between the two groups with the use of the unpaired t test. A paired t test or non-parametric Wilcoxon test was used to compare the time to maximal pain after the first and second injections within the bilateral group. Chi-square test was used to compare incidence of referred pain and PRI between the unilateral and the bilateral group. Values are reported as means ± standard error (SE) in the text and figures. The significant level was set at P < 0.05.

3. Results

3.1. Pain intensity

Muscle pain was evoked in all subjects by injection of hypertonic saline into the trapezius muscles. There was no statistically significant difference in mean pain and maximal pain intensities either between the bilateral and the unilateral group or between the first and the second injections within the bilateral group (Fig. 1). The time to maximal pain after the second injection was significantly shorter than both after the first injection in the bilateral group (Table 1; Wilcoxon signed rank test, P < 0.001) and the unilateral group (unpaired t test, P < 0.01). No significant difference in the time to maximal pain was found between the first injection in the bilateral group and the injection in the unilateral group (unpaired t test, P > 0.05).

3.2. Referred pain patterns

Referred pain developed in 11 out of 16 subjects (70%) in bilateral group and four out of 15 subjects

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<tr>
<th>Bilateral group (n = 16)</th>
<th>Unilateral group (n = 15)</th>
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<tr>
<td>Pain intensity (cm)</td>
<td>Pain intensity (cm)</td>
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<tr>
<td>Bilateral first injection</td>
<td>3.6 ± 0.2</td>
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<td>Bilateral second injection</td>
<td>3.8 ± 0.3</td>
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<tr>
<td>Unilateral injection</td>
<td>3.2 ± 0.3</td>
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*P < 0.001 (Wilcoxon signed rank test).

![Graphs](https://via.placeholder.com/150)

Fig. 1. Visual analogue scales (VAS) (mean ± SE) profiles following unilateral injection (A) of 0.5 ml hypertonic saline (6%) into right trapezius muscle and both the first (B) and the second (C) injection of 0.5 ml hypertonic saline (6%) into trapezius muscles separated by 45 s in the bilateral group.
(27%) in unilateral group (Chi-square test, P < 0.001). The unilateral injection evoked unilateral local pain and referred pain, while the bilateral injection evoked symmetrically right–left distributed referred pain pattern (Fig. 2). In the bilateral group, the subjects reported referred pain (Fig. 2) to the posterolateral aspects of the neck ipsilateral to the injection site (11/16), 7% to the chest (1/16), 7% to the temporomandibular region (1/16), and 7% to the posterolateral upper arms (1/16). While in the unilateral injection group, referred pain areas were confined only to the posterolateral aspects of the neck.

3.3. Pain quality

The qualitative words mostly chosen were pressing (8/16), drilling (5/16) by the bilateral group, and pressing (9/15), annoying (7/15), throbbing (6/15), and sore (5/15) by the unilateral group. The mean PRI calculated for the sensory, affective, evaluative, and miscellaneous were 56.6 ± 4.1%, 11.7 ± 5.3%, 40.9 ± 7.0%, and 27 ± 6.0% for the bilateral group and 49.63 ± 4%, 10 ± 5.4%, 29.3 ± 6.7%, and 18.7 ± 6.5% for unilateral group, respectively (Chi-square, P > 0.05 for all categories between the bilateral and unilateral group).

Fig. 2. Local and referred muscle pain patterns of unilateral injection of 0.5 ml hypertonic saline (6%) into right trapezius muscle and bilateral injections into trapezius muscles.

Fig. 3. Pressure pain thresholds (PPTs) (mean ± SE) of unilateral (A) injection of 0.5 ml hypertonic saline (6%) into right trapezius muscle, bilateral (B) injections of 0.5 ml of hypertonic saline (6%) into trapezius muscles over time in the trapezius injection sites (local pain areas) and posterolateral neck muscles (referred pain areas). * indicates significant difference compared with pre-injection (P < 0.05). # indicates significant difference as compared with first injection (P < 0.05).


Multi-modal induction and assessment of allodynia and hyperalgesia in the human oesophagus

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Abstract

Background and aims. Experimental pain models based on single stimuli have to some degree limited visceral pain studies in humans. Hence, the aim of this study was to investigate the effect of multi-modal visceral pain stimuli of the oesophagus in healthy subjects before and after induction of visceral hyperalgesia. We used a multi-modal psychophysical assessment regime and a neurophysiological method (nociceptive reflex) for the characterisation of the experimentally induced hyperalgesia.

Methods. A probe for multi-modal (cold, warm, electrical, and mechanical) visceral stimulation was positioned in the lower part of the oesophagus in eleven healthy subjects. Mechanical stimuli were applied as distensions with a bag, which also had electrodes mounted for electrical stimulation. Thermal stimulation with temperatures from 0 to 60 °C was applied with re-circulating water in the bag. To assess the interaction between visceral and somatic pathways, the nociceptive withdrawal reflex to electrical stimuli at the ankle was measured with and without simultaneous mechanical oesophageal distension to painful levels. Finally, the oesophageal sensitisation was induced by perfusion with hydrochloric acid. Multimodal responses (pain threshold, stimulus response function, size of nociceptive reflex, and referred pain areas) were assessed before and after the induced hyperalgesia.

Results. The multi-modal psychophysical responses and reflex sizes were assessed twice before sensitisation, and the parameters were reproducible. Sensitisation of the oesophagus resulted in hyperalgesia to electrical and mechanical stimuli (29 and 35% decrease in pain threshold) and allodynia to cold and warm stimuli (11% increase in sensory rating). After sensitisation, the referred pain area to mechanical stimuli increased more than 300% with a change in the localisation of the referred pain to all stimuli, and the amplitude of nociceptive reflex increased 100%, all indicating the presence of central hyperexcitability.

Conclusions. Visceral hyperalgesia/allodynia can be induced experimentally and assessed quantitatively by the newly introduced multi-modal psychophysical assessment approach. The significant changes of the experimentally evoked referred pain patterns and of the nociceptive reflex evoked from a distant somatic structure indicate that even short-lasting visceral hyperalgesia can generate generalised sensitisation.

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Keywords: Pain, Gut; Experimental; Hyperalgesia; Nociceptive reflex

1. Introduction

Due to the difficulties in characterising clinical pain, human experimental pain models have been developed as a way to induce pain in a standardised way. These models provide the possibility to control the stimulus and to assess the response quantitatively by physio-

physical and/or electrophysiological methods. The experimental pain models have predominantly been developed for the study of somatic pain. For these structures multi-modal sensory assessment regimes can be applied to investigate in more details the differentiated responses to the activation of different receptor populations and afferent pathways. Only very recently
the multi-modal sensory assessment approach has been developed for visceral structures due to methodological difficulties (Drewes et al., 2002). This facilitates combination of different stimuli and investigation of as well the non-nociceptive and nociceptive processing of different pathways which are involved in vivo (Arendt-Nielsen, 1997; Ness and Gebhart, 1990).

To mimic clinical pain, the experimental methods should involve sensitisation of the nervous system. Central sensitisation is characterised by neuronal changes such as increased spontaneous activity, decreased firing threshold, and expansion of the receptive fields of spinal neurons (Coderre et al., 1993; Laird et al., 1995). In humans we cannot assess the neuronal changes directly, but experimental phenomena which reflect such changes can be observed indirectly. Chronic or recurrent visceral pain seems to induce long-lasting sensitisation of somatic or other visceral structures (Bajaj et al., 2001; Giamberardino, 1999). This sensitisation is manifested by muscle hyperalgesia to pressure or electrical stimuli, or as increased pain reactions from adjacent visceral structures (Giamberardino, 1999). Another manifestation of sensitisation evoked by visceral pain is enlarged referred pain areas to clinical pain symptoms (Mayer and Gebhart, 1994; Sanger, 1999) as well as to experimental visceral stimuli such as electrical stimuli of the gut (Arendt-Nielsen et al., 1997). These manifestations are very similar to what is observed in patients suffering from chronic musculoskeletal pain (Johansen et al., 2001). In muscle pain syndromes the sensitisation is projected to other muscles and the skin, but interestingly never to visceral structures. Therefore the mechanisms involved in visceral and muscle sensitisation are not "bi-directional".

In the past, most models of experimentally induced sensitisation have used the skin or muscles (Andersen et al., 1995; Babenko et al., 1999; Curatolo et al., 2000). Such models show sign of central sensitisation manifested by, e.g., allodynia and hyperalgesia (pain produced by normally innocuous stimuli and increased response to normally painful stimuli, respectively). However, the models may only indirectly provide better knowledge of the mechanisms involved in visceral pain (Arendt-Nielsen, 1997; Curatolo et al., 2000; Yaksh, 1999). An optimal situation would be to study true experimental induced visceral sensitisation, and from such models infer to mechanisms involved in clinical visceral pain conditions. In human pain research chemical stimulation of the oesophagus with acid have been used previously to sensitise the mucosa to mechanical stimuli (Mehta et al., 1995; Sarkar et al., 2000). However, these previous studies have not been consistent with respect to the evoked hyperalgesia probably due to methodological problems (Hu et al., 2000), and systematic responses to multi-modal stimuli following sensitisation have never been investigated. Thus, a human model, where experimental induction and multi-modal assessment of visceral allodynia and hyperalgesia can be studied, may contribute to a better understanding of the mechanisms involved in painful visceral pathologies.

The aims of the current study were: (1) to apply a multi-modal visceral pain approach to assess modality specific allodynia and hyperalgesia after experimentally induced sensitisation of the human oesophagus, (2) to evaluate the referred pain areas to experimental visceral stimuli before and after sensitisation, and (3) to utilise the human nociceptive reflex elicited form the splanchnic nerve to investigate if short-lasting sensitisation of the esophagus may cause a stage of generalised hyperexcitability to nociceptive stimuli.

2. Methods

2.1. Subjects

Eleven healthy subjects, seven males and four females, mean age 40 years ±10.4 were included. They were all healthy and did not suffer from any kind of chronic or recurrent pain. Especially were subjects with chest pain, heartburn, dyspepsia, or irritable bowel syndrome-like symptoms excluded. The subjects were recruited among the hospital and university staff as well as their acquaintances and relatives. They were compensated for their participation corresponding to their normal salary on an hourly basis. All subjects gave informed consent prior to the study. The experiment was carried out at the Visceral Pain and Biomechanics Laboratory at Aalborg Hospital. The experiment was approved by the Ethics Committee in North Jutland, which is a local department of the Danish Ethical Committee system. The experiment was assigned the following case number: VN 97/134.

2.2. Stimulation device

The subjects fasted for at least 4 h prior to the experiment. A probe designed for multi-modal stimulation included a non-conducting polyurethane bag for mechanical and thermal stimuli as well as electrodes for electrical stimuli. A side-hole for acid perfusion was placed 5 mm above the bag. The probe was 60 cm long with a diameter of 4.5 mm. The bag on the tip had a length of 40 mm (Fig. 1). Detailed information of the probe and stimulation system have recently been described (Drewes et al., 2002). For electrical stimulation two Ag–AgCl stimulation electrodes (2 × 4 mm) were glued to the bag. The electrodes were connected to a computer-controlled constant-current stimulator (Nocistim Test A/S, Aalborg, Denmark). The intensity of the current was limited to 80 mA. During the stimulation the bag was inflated with 10 ml of water corresponding to a diameter of 15 mm. For mechanical stimuli the perfusion
channels were connected to an infusion pump (Type 111, Ole Dih instrument Makers Aps, Hvidovre, Denmark), which was able to fill or empty the bag continuously at varying flow rates. The system recorded the infused volume and pressure during the perfusion (Gatehouse Medical A/S, Nørresundby, Denmark). A manual pump system circulated the water in the bag and provided cold and warmth stimuli. A temperature probe (PR Electronics, Rønde, Denmark) monitored the water temperature in the bag. The time elapsing from one temperature level to the next was 60 s. First, the system was filled with 10 ml of water with the pre-set temperature. In the range of 25–40 °C, this could be felt by any of the subjects, excluding the possibility of the distension to contribute to the sensation. Immediately after filling of the bag, 50 ml of water with the desired temperature was re-circulated in the bag. In previous experiments it was found that temperatures in the pump system of 0, 5, 10, 16, 25, 30, 35, 44, 52, and 60 °C corresponded with temperatures of 7.1, 10.7, 14.7, 19.4, 25.0, 30.4, 35.4, 40.9, 44.9, and 50.0 °C in the bag when placed in the oesophagus (Drewes et al., 2002).

After applying a small amount of local anaesthetic spray (Xylocaine, AstraZeneca, Sweden) in the nose, intubation was performed through the nostrils. The bag was first inserted into the stomach and then retracted to identify the location of the lower oesophageal sphincter as a zone of high resting pressure that decreased with swallowing. Then the bag was placed 7 cm proximal to the sphincter and the probe was taped to the nose. After intubation the subjects were asked to lie down with the head tilted by 30°. After 30 min of rest, the experiment was performed in the same position.

### 2.3. Protocol

The protocol design is schematically illustrated in Fig. 2. The experiment was composed of baseline electrical, mechanical, and thermal stimulation followed by assessment of the nociceptive reflex. After baseline recordings (after approximately 45 min of experiments) the electrical and mechanical stimuli were repeated to ensure the reliability (test re-test evaluation). The oesophagus was then sensitised by acid perfusion. During acid perfusion the electrical and mechanical stimuli were repeated every 10 min, and after the perfusion the stimulation battery was repeated. 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 for electrocardiogram, pulse rate, and respiration. A nurse cared for the subjects during the experiment.

### 2.4. Induction of hyperalgesia

After the first multi-modal stimulation series and recording of nociceptive reflexes, the subjects underwent a modified acid perfusion test. The test was basically similar to the Bernstein test used in the clinic (Bernstein, 1958). Hence, 100 ml of 0.1 N hydrochloric acid was infused through the perfusion channel in the bag at a rate of 4 ml/min for 30 min. The subjects were all able to taste the acid making blinding impossible, but neither the subjects nor the nurse, who assessed the pain responses, were aware that the acid perfusion could eventually result in changes of the assessment parameters. The perfusion was stopped every 10 min, and the pain thresholds to electrical and mechanical stimuli were
determined. Originally it was the intention to apply the stimulus intensity corresponding with the pain threshold before the sensitisation was induced, and then to assess the corresponding VAS rating. However, this stimulus intensity was too painful to be tolerated in most subjects due to the sensitisation. Alternatively, we determined the pain threshold and recorded the change in the stimulus intensity.

2.5. Stimulation

2.5.1. Electrical stimuli

Electrical stimuli were given as “repeated bursts” defined as five stimuli at 2 Hz. The individual stimulus consisted of five constant-current pulses with duration of 1 ms applied at 200 Hz. Previous studies (Drewes et al., 1999a,b; Frobert et al., 1994) have found the described stimulus sequence suitable for evoking visceral pain. The stimulus intensity was blinded for the subjects, but the intensity gradually increased in steps of 0.5 mA with an interval of 15 s, until the pain detection threshold corresponding to five on the visual analogue scale (VAS) was reached. Intermittent sham stimuli with either no current or the same current as in the previous step were given to further blind the subject. Such series have proven to be valuable in our previous studies using both electrical and mechanical stimuli (Drewes et al., 1997, 1999b; Petersen et al., 2001). To test the reliability before induction of allostynia/hyperalgesia, a stimulus-response experiment corresponding with one, three, and five on the VAS was performed at baseline and repeated just before the acid infusion was started.

2.5.2. Mechanical stimuli

Three distensions were carried out to precondition the tissue and to train the subjects in scoring the visceral sensation intensity (Drewes et al., 2003). These were followed by four distensions with a constant perfusion rate of 25 ml/min until the subject reported pain (five on the VAS). To test the reliability of the stimulations with simultaneous assessment of intensities corresponding to one, three, and five on the VAS was performed at baseline and repeated just before perfusion with acid.

2.5.3. Temperature stimuli

As for the electrical stimuli, we used a pseudo-random, blinded sequence with sham stimuli of lower or the same intensity interspersed with the ascending stimulus intensities. Hence, in each series the stimuli were applied with estimated intra-bag temperatures of 10, 5, 15, 20, 30, 35, 40, 25 (sham), 45, and 50 °C, with two to three additional sham stimuli having the same temperature as the previous stimulus interposed randomly. After the sensitisation with acid (see below), intra-bag temperatures of 5, 10, 35, and 50 °C were applied with two sham stimuli, as the sensitisation did not allow a full stimulation series due to the high pain ratings.

2.6. Sensory assessment and recording of the nociceptive reflex

The assessment parameters were: (1) perceived intensity and pain thresholds, (2) the size and localisation of the referred pain area, and (3) the size of the nociceptive reflex evoked from a somatic structure.

The evoked sensory intensity was assessed continuously using an electronic VAS (Gatehouse AS, Aalborg, Denmark). First the patients were trained in assessment on the VAS during somatic stimuli (pressure applied to the muscles on the right forearm). The scale was used for both non-painful and painful sensations. The intensities of the non-painful sensations were scored on the VAS up to five, where the following descriptors were used to characterise 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. Five was the discomfort/pain threshold (Serra et al., 1995). For the painful sensations the patients used the scale from 5 to 10 anchored at 5 = discomfort/pain threshold to 10 = unbearable pain, with anchor words equidistant on the intensity scale (Drewes et al., 1993). Accordingly, when the subject reported that the stimuli resulted in pain and/or severe discomfort (5 on the scale), they were asked to score the intensity from 5 to 10 on the VAS. The VAS has previously been demonstrated to be useful in assessing painful stimuli to electrical current and distension in the cesophagus, stomach, small, and large intestine (Arendt-Nielsen et al., 1997; Drewes et al., 1997, 1999b, 2002; Gao et al., 2003).

After 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 digitised (ACECAD D900+ Digitizer, Taiwan) and the size calculated (Sigma-Scan, Jandel Scientific, Canada). The relative change in referred area at the pain threshold was calculated as the area reported after acid perfusion divided by the area at baseline stimulation.

The lower extremity nociceptive withdrawal reflex (labelled “nociceptive reflex” in the text) was recorded to electrical painful stimuli at the sural nerve at the ankle. This reflex is normally denoted the RII-reflex (Hugon, 1973). The stimuli were delivered percutaneously by a constant current rectangular pulse train, consisting of five pulses with duration of 1 ms and delivered at 200 Hz. The EMG was recorded with Ag–AgCl surface electrodes placed parallel to the muscle fibre axis over the biceps muscle of the thigh. The inter-electrode distance was 2.5 cm. The skin was lightly abraded and cleaned with isopropyl alcohol before the electrode attachment. A reflex was defined as
an EMG activity above 20 µV for a period of at least 5 ms within a time window from 80 to 200 ms after stimulation. The stimulation intensity was above the subjects’ pain threshold and ensured a stable nociceptive reflex in all subjects throughout the experiment. The EMG signals were filtered (20–500 Hz), amplified 20,000 times, sampled (2000 Hz), shown on the computer screen, and stored on computer disk. The average of the root mean square (RMS) amplitude in the 80–200 ms post-stimulus time interval was used as a measure of the reflex size (Andersen et al., 2000). The reflex was recorded every 10 s and the mean reflex size was calculated. The baseline reflex was recorded for 1 min before intubation of the multi-modal stimulation probe in the oesophagus. During the experiment the reflex was measured during unfolding of the bag which was not sensed (level 1), and during distension at 10 ml/min until six was reported on the VAS (level 2). This intensity was then maintained for at least 60 s (level 3). Hence, the subject scored continuously on the VAS, and if the sensation changed, the volume was adjusted to reach six on the VAS. After sensitisation with acid, this experiment was repeated.

2.7. Statistics

The results are expressed as means ± SD. Data were analysed using paired samples t tests, and for multiple comparisons, analysis of variance (ANOVA) was used. As the reflexes were not normal distributed, Friedman’s non-parametric ANOVA and Wilcoxon’s rank-sum tests were used. P < 0.05 was considered significant. The software package SPSS v. 10.0 was used.

3. Results

3.1. Induction of hyperalgesia

All subjects could taste the acid after 15 min of infusion. Most had intermittent reflux-like symptoms, but only to a slight degree with non-painful ratings on the VAS. After the acid perfusion was stopped, none of the subjects had any spontaneously sensations, and hence, the chemical stimulus was not painful per se. After 10 min of acid perfusion, one male became too sensitised to the pain threshold determinations to tolerate further experiments, and the probe was removed.

3.2. Multi-modal pain stimulation

3.2.1. Electrical stimuli

In two subjects we experienced technical problems with the electrodes, and therefore electrical stimulation was not performed. In the test–re-test experiment no differences were seen between the current used to evoke one (10.3 ± 4.8 versus 11.1 ± 6.0 mA, three (14.1 ± 5.5 versus 13.5 ± 6.1 mA), or five (16.9 ± 7.8 versus 17.1 ± 6.1 mA) on the VAS (F = 0.008; P = 0.9). Hence, the responses were reproducible. Due to sensitisation already after 10 min of acid perfusion, five subjects were not able to tolerate the combined distension with 10 ml water into the bag together with the electrical stimuli. In the remaining four subjects, there was also a sensitisation with a fall in pain threshold from mean 23.3 ± 8.2 to 18.0 ± 12.2 mA after the acid perfusion.

3.2.2. Mechanical stimuli

The mechanical stimuli were reliable as no differences were seen between the test and re-test experiments performed before the acid perfusion. At VAS = 1, 3, and 5 the volumes were 12.1, 19.4, and 25.1 ml at the first experiment and 13.4, 20.3, and 25.5 ml at the re-test experiment (F = 0.25, P = 0.6). For the pressure the data were 16.5, 24.4, and 41.9 cm H2O at the first experiment and 15.9, 36.1, and 45.4 cm H2O at the re-test experiment (F = 0.46; P = 0.5). Comparing the baseline distension with the three distensions during acid perfusion, a significant decrease in pain threshold was found for volume (baseline: 26 ± 7.7 ml; acid perfusion at 10, 20, and 30 min: 20.2 ± 6.8 – 18.6 ± 7.3 – 19.2 ± 7.2 ml; F = 8.6, P = 0.005) – Fig. 3. The change in pressure was not significant (baseline: 42.6 ± 33.4 cm H2O; acid perfusion at 10, 20, and 30 min: 39.7 ± 30.1 – 36.8 ± 25.7 – 35.0 ± 20.2 cm H2O; F = 0.86, P = 0.4). For the final distension after the reflex investigation, the volume at the pain threshold was significantly lower compared to baseline before the acid infusion (volume: 15.7 ± 6.2 ml, P = 0.024; pressure: 29.0 ± 27.8 cm H2O, P = 0.2).

Constant mechanical stimuli corresponding to six on the VAS were given during the two reflex experiments. A

![Fig. 3 The pain detection thresholds (PDT) to mechanical stimuli in the oesophagus (mean and SD). The thresholds at baseline, during (0–30 min) and after (40 min) perfusion with acid in the oesophagus are shown.](image-url)
reduction in the mean volume from 17.7 ± 4.4 at the first experiment to 15.0 ± 3.7 ml after acid sensitisation was observed ($P = 0.01$). The corresponding reduction in mean pressure was from 25.6 ± 18.7 to 21.1 ± 20.4 cm H$_2$O ($P = 0.023$).

3.2.3. Thermal stimuli

Two males were unable to tolerate further experiments after the second reflex investigation. Hence, the final thermal experiment was not conducted in these two subjects due to nausea and vomiting. The VAS ratings to the lowest temperatures were higher after acid sensitisation (5°C: 4.6 ± 0.5 versus 5.2 ± 0.4; 10°C: 4.3 ± 1.8 versus 4.9 ± 1.0; $F = 6.9, P = 0.013$). Due to sensitisation four subjects were not able to tolerate the 50°C stimulation. Instead a temperature at 45°C was given in these subjects. This resulted in the same VAS rating to the two highest temperatures in the sessions before and after acid sensitisation (mean VAS 5.6 ± 0.9 versus 5.6 ± 0.5 in the two experiments). The mean temperatures to the highest VAS ratings were 50.0 and 46.6°C before and after sensitisation, but the difference was not significant ($P = 0.4$).

3.3. Referred pain areas

The referred pain area typically changed in localisation after the acid perfusion. A typical example from one of the experiments is shown in Fig. 4. The chest was divided in eight regions having approximately the same size, and the neck, abdomen, and back defined as other regions (Fig. 5). The referred areas to distension changed localisation after acid sensitisation in three subjects with a shift from the abdomen to the chest in two persons and from the chest to the neck in one subject. The referred areas to electrical (not illustrated due to the few subjects who accepted the electrical stimuli), cold, and warm stimuli changed within the same anatomic localisation in six, but they were localised in approximately the same area in three subjects. As shown in Fig. 6, the size of the referred pain areas to the different stimuli increased after acid sensitisation (mechanical stimuli: 21.9 ± 23.6 – 101 ± 90.7 cm$^2$, cold: 35.6 ± 36.5 – 36.6 ± 34.8 cm$^2$; warmth: 52.5 ± 40.0 – 59.0 ± 58.9 cm$^2$; $F = 11.6, P < 0.001$). The relative increase in size after sensitisation was highest for the mechanical stimuli (5.6 times baseline) compared to

![Warmth stimuli diagram](image1)

![Cold stimuli diagram](image2)

![Mechanical stimuli diagram](image3)

Fig. 5. A schematical illustration of the referred pain areas drawn by the subjects following mechanical, cold, and warmth stimuli of the oesophagus. The stimuli were given with an intensity corresponding to the pain threshold. The referred pain area to the stimulations were drawn before and after perfusion of the distal oesophagus with acid. The chest was divided into 8 areas by a horizontal line 5 cm above the xiphoïd process, a vertical midline and two vertical lines 5 cm lateral to the midline. The numbers on the figure refer to the number of subjects reporting pain to that particular region of the chest. Two subjects had additionally pain reported to the back both before and after induction of hyperalgesia (not shown).
Fig. 6. The referred pain areas (mean and SD) at the pain threshold during mechanical (light grey), cold (white), and warmth (dark grey) stimuli in the oesophagus before and after sensitisation with acid.

3.4. The nociceptive reflex

Only very small adjustments of the infused volume in three subjects were necessary to keep the constant VAS rating on six during elicitation of the nociceptive reflex. The mean stimulus intensity to evoke the reflex was 20 ± 5.4 mA. The mean reflex size was reproducible being 29.5 ± 14.8 μV at baseline before the intubation of the stimulation probe, and 29.5 ± 8.4 μV before the first period of the reflex modulation by mechanical stimulation (after approximately 1 h). As shown in Fig. 7 no changes in reflex size were visible during the first experiment with mechanical modulation (levels 1–3 before sensitisation, P = 0.9). After sensitisation with acid, the baseline reflex size increased dramatically to 60.1 ± 55.3 μV. The increase was significant compared to the baseline reflex before sensitisation (P = 0.03). During the evoked visceral pain after sensitisation (levels 2 and 3), there was a significant decrease in reflex size compared to the baseline value after sensitisation (level 1) (P = 0.02), although the reflex sizes were still larger than before sensitisation. An example of the EMG recorded from a typical subject is depicted in Fig. 8.

4. Discussion

Modality specific visceral allodynia (thermal stimuli) and hyperalgesia (mechanical stimuli) to stimulation of the human oesophagus were induced experimentally by acid perfusion of the organ. Major increases in the referred pain area to mechanical stimuli were observed. The sensitisation resulted in a strong facilitation of the human nociceptive withdrawal reflex indicating that localised short-lasting sensitisation of human oesophagus may lead to generalised central hyperexcitability.

4.1. Experimental design and methodological considerations

One of the purposes of the study was to demonstrate that it is possible to conduct a human study with a complicated design, allowing the many stimulus modalities and assessment parameters in the same experiment. The stimulation probe provided the possibility to
randomise many stimulus modalities and to include sham stimuli. The stimulation parameters were robust with reproducible reflex sizes and sensory responses when determined repeatedly before the acid perfusion. The patients thus served as their own controls. It cannot be excluded that the repeated stimuli could contribute to hyperalgesia. Therefore it would have been preferable to conduct a control experiment, and originally it was planned to perform a placebo series with saline infusion instead of acid. However, as all subjects could taste the acid, it was not possible to blind the infusion, and the only possibility was to let the test-re-test session replace the control experiment. The repeated stimuli with different modalities did not result in significant changes in the sensation, although the re-test experiment was performed after more than 1 h after intubation and several repeated stimuli. On the other hand, the pain threshold decreased immediately after the acid perfusion where the acid could not be tasted yet, and the subjects were not aware that any sensitisation could happen. We therefore believe that it was the sensitisation with acid, and not the long-lasting experimental procedure that resulted in lowering of the pain threshold. Correspondingly, in pilot series performed to design the current experiment, saline infusions did not change the pain thresholds.

The infused volume was used to determine the pain thresholds to the mechanical stimulus. In previous models we have used more sophisticated techniques to measure the cross-sectional area and biomechanical parameters such as the tension and strain of the gut wall (Drewes et al., 2000, 2002). Such models and systems like the “Barostat” may offer a better control of the mechanical stimulus, but for simple determination of pain thresholds the pump infusion system was more reliable. Furthermore, the ramp distension protocol allowed the time for accommodation of the tissue and, hence, to identify the pain thresholds with more accuracy.

4.2. Chemical stimuli and hyperalgesia

Chemical stimuli using various substances such as hypertonic saline, acidic, basic, and salt solutions, and more natural compounds such as bradykinin have been used for visceral nociceptive stimulation in animal studies (Ness and Gebhart, 1990). In contrast to electrical stimuli, chemical stimuli activate C-fibres more frequently than myelinated fibres (Longhurst, 1995) and are considered more “natural”. In human visceral experiments the potential harmful effects of chemical stimuli have limited their use. Acid stimulation of the oesophagus is, however, an established clinical method to be used, e.g., the diagnosis of functional chest pain disorders (Bernstein, 1998; Tack, 1999). Different modifications of the acid perfusion test have been used by several authors (de Vault, 1997; Fass et al., 1998; Hu et al., 2000; Mehta et al., 1995; Sarkar et al., 2000).

Acid-sensitive fibres have been demonstrated in animal studies and mucosal afferents are often sensitive to different chemical stimuli (for review see Ness and Gebhart, 1990; Sengupta and Gebhart, 1994). In recent human experiments, acid perfusion was shown to sensitise the oesophagus to distension (Hu et al., 2000; Mehta et al., 1995; Sarkar et al., 2000), although this sensitisation was not seen in many previous studies using latex balloons. This may be related to methodological problems with latex balloons where the distension data need to be corrected for the intrinsic mechanical properties of the balloons etc. (Hu et al., 2000; Gregersen and Kassab, 1996). As a consequence, a non-compliant polyurethane bag was used in our study, where the acid perfusion resulted in sensitisation of the receptors to mechanical, but also electrical and temperature stimuli.

The current study is the first to demonstrate visceral sensitisation to multiple stimulus modalities. Whether or not sensitisation of the same receptors or new activation of “silent receptors” (Koltzenburg, 1994; Sengupta and Gebhart, 1994) are responsible for the results is not possible to conclude from our experiment, as we cannot delineate how much is mediated by central sensitisation. After sensitisation with acid, allodynia as well as hyperalgesia were demonstrated to the local oesophageal stimuli. These phenomena are clinically relevant, as increased sensation to stimuli such as normal stools and air in the gut seem to contribute to many of the symptoms reported by patients with inflammation and functional disorders (Mayer et al., 1995; Yaksh, 1999). Therefore, a human visceral model with hypersensitivity to multi-modal stimulation has major impact with respect to assessing mechanisms possibly involved in painful visceral diseases.

4.3. Central mechanisms elucidated by multi-modal stimulation

In accordance with our results, Garrison et al. (1992) demonstrated that spinal neurones in the cat receiving input from the distal oesophagus also received convergent input from the thoracic wall. When the oesophagus was sensitised with turpentine, the neurones responded to a smaller mechanical stimulus. Compared to experiments in animals, it is not possible to give an exact definition of the neurophysiological changes observed in the nervous system following sensitisation in humans. What we observe in the oesophagus is most likely a combination of peripheral and central sensitisation. There was no pain evoked by the acid perfusion, and in the absence of stimulation no on-going pain after the perfusion. It therefore seemed as the acid only sensitised the receptors, but did not result in sufficient spontaneous activity to be felt as pain. The acid perfusion not only sensitised the superficial mucosal afferents encoding
electrical and temperature stimuli, but the pain threshold to the deeper mechanical stimuli also decreased. Furthermore, there was a marked increase in the referred area to mechanical stimuli, whereas there was nearly no increase in the referred area to thermal stimuli. As the acid perfusion most likely activates the superficial receptors in the mucosa (as does the thermal stimuli), the findings give evidence that the peripheral sensitisation also results in sensitisation of central neurones receiving convergent input from both somatic/visceral muscular and mucosal afferents. Hence, the increased referred pain area to mechanical visceral stimuli probably result from central sensitisation, although the receptors responding to the mechanical stimulus are most likely localised in the deeper muscle layers of the gut wall (Sengupta and Gebhart, 1994). The reason for the major increase in referred pain area to mechanical compared to superficial (thermal) stimuli is not clear.

We do not believe that spatial or temporal summation phenomena contribute, as the baseline referred pain area was larger to thermal stimuli than to pressure under the same experimental circumstances. The pain intensity was the same for different stimuli, and the incoming activity to the central level was probably comparable. Hence, the most plausible explanation may be that the afferents in the deeper layers of the gut activate second order neurones with convergent somatic input to a higher degree. This is in accordance with skin studies where secondary hyperalgesia to mechanical and electrical stimuli are consistent findings in the area surrounding the original lesion. However, secondary hyperalgesia to thermal stimuli of the skin is much more controversial and has been found in some studies (Arendt-Nielsen et al., 1996), but not in others (Ali et al., 1996; Dahl et al., 1993). Our findings therefore give evidence for the hypothesis that the referred area to visceral pain involves the same kind of central mechanisms which is active in secondary hyperalgesia to skin stimuli.

4.4. Central mechanisms elucidated by the nociceptive reflex

The modulation of the nociceptive reflex to mechanical stimuli is believed to be a central phenomenon. The connection from the primary afferents to the motor neurones is a polysynaptic pathway, which can be modulated by other afferent input, spinal neuronal excitability, and activity in descending control systems (Arendt-Nielsen, 1997). No change in reflex size was present during the first series before sensitisation. In the studies by Bouhassira et al. (1994, 1998), tonic distension of the stomach and rectum resulted in inhibition of the reflex. In other studies, however, painful stimuli resulted in either a decrease or an increase in reflex excitability depending on the conditioning site (Andersen et al., 2000). Correspondingly, in the paper by Bouhassira et al. (1998) phasic and tonic rectal stimulations resulted in differentiated effects on the reflex amplitude.

Therefore, the different stimulation sites and experimental situations may explain the discrepancies between the experiments.

The sensitisation to acid perfusion resulted in a significant increase in the baseline reflex excitability followed by a gradual inhibition during the visceral stimulus. The initial increased excitability may be explained by the chemical stimulation resulting in ongoing visceral input to the spinal cord. Nociceptive afferents are conveyed to the spinal cord, and the fibres from the lower part of the oesophagus terminate diffuse and broadly from the thoracic to the lumbar segments (Sengupta and Gebhart, 1994). This makes it possible that stimuli from the oesophagus may influence with the nociceptive reflex, which is integrated on the lumbar and sacral segments. The spinal termination from the visceral afferents is mainly in lamina I and V, where convergence with neurons receiving somatic input is seen (Cervero and Laird, 1999). Neurons within this area of the lumbar segments are also involved in the polysynaptic reflex (Schouenborg et al., 1995) opening for possible convergence between visceral and somatic afferents, thus resulting in facilitation of the reflex.

During the painful visceral stimulation after sensitisation, the decrease in reflex excitability could be a result of activation of descending inhibitory systems. Activation of descending systems and subsequent decreased excitability of dorsal horn neurons has been shown in animal (Fallon et al., 1994; Morgan et al., 1994) as well as human studies (Terkelsen et al., 2001; Willer et al., 1984). Hence, the most likely explanation is that the slight, but relatively long-lasting sensitisation by acid resulted in a general facilitation of the nociceptive reflex via convergent dorsal horn neurons in the reflex pathway. Subsequent mechanical activation of the viscera resulted in widespread and rather strong pain and hence activation of inhibitory pathways from the brainstem (Gjerstad et al., 1999), although the size of the reflex was still larger than before sensitisation. A similar pattern (initial facilitation followed by inhibition) has been observed after electrical conditioning stimuli in spinally intact rats, whereas the latter inhibition was not found if the descending inhibition was interrupted (Gozariu et al., 1997). Hence, the possibility for evoking and modulating central mechanisms makes the model highly suitable for basic and pharmacological experiments.

4.5. Clinical implications for the model

The experiment was performed in healthy controls and we have not yet studied patient groups. Central hyperexcitability is assumed to give major contribution to the pain related symptoms reported in chronic visceral dis-
cases (Giamberardino, 1999; Mayer and Gebhart, 1994; van der Schaar et al., 1999). The current model could investigate these central phenomena. Thus, mechanical hyperalgesia during swallowing may be the predominant stimuli to evoke pain and discomfort in patients where the oesophagus is sensitised by reflux disease.

In patients with functional gut disorders, most studies have observed a lowering in pain threshold to mechanical and electrical stimuli (Drewes et al., 2000; Lembo et al., 1994). It has been suggested that changes in descending control systems arising in the brainstem are responsible for the increased pain experience (Mayer and Gebhart, 1994). Descending pathways modulate the spinal nociceptive reflex transmission, and the model may therefore be usable to gain more information of the pain modulation systems in these patients.

5. Conclusion

Visceral hyperalgesia/allodynia can be induced experimentally and assessed quantitatively by the newly introduced multi-modal psychophysical assessment approach. The area of the experimentally evoked referred pain patterns was massively increased after sensitisation. The increased size of the nociceptive reflex evoked from a distant somatic structure indicates that even short-lasting visceral hyperalgesia can generate generalised sensitisation. The evoked phenomena mimic mechanisms involved in many of the symptoms in clinical diseases of the visera, and the model should be used in future clinical and pharmacological studies.

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References


Parents of subjects aged 0–11 years (n = 512) were first invited to answer the questionnaires and then to keep the diary to report their child's pain characteristics and behavioral expression of the pain for three successive weeks. Subjects aged 12–18 years (n = 475) and their parents were each sent a pain booklet. The adolescents were first invited to answer the questionnaires and then to keep the diary to register pain intensities on their own. Their parents were also asked to fill out some questionnaires.

In case the child no longer experienced chronic pain in the previous three months, only demographic data and a possible reason for the remission of the pain were requested. Subjects who had previously reported more than one location of pain were asked to report only on the pain that troubled them most. Subjects received a calendar chart as an aide-mémoire.

Subjects with pain resulting from specific chronic diseases (e.g., rheumatoid arthritis, malignancies) were excluded. We defined chronic benign pain as continuous or recurrent pain with unknown organic etiology existing for three months or longer. In order to obtain a comprehensive picture on chronic pain we did not restrict ourselves to subgroups based on severity of pain or disability, as was the case in other studies on chronic pain (Verhaar et al., 1998).

In this paper, the baseline assessment (June 1997) will be denoted 'T0', halfway through the follow-up period (June 1998) will be denoted 'T1', and the end of the follow-up period (June 1999) will be denoted 'T2'.

2.3. Outcome measures and instruments

Table 1 gives an overview of the outcome measures and instruments used in this study. The structured pain list was partly based on the questionnaire used in our previous prevalence study (Perquin et al., 2000a) and comprised questions on location, frequency, intensity and duration of the pain. Additional questions concerned functional disability due to pain and co-morbidity of chronic diseases. To confirm that the pain did not have an organic etiology we asked whether a physician had made

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Outcome measures and instruments used in this study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Instrument</strong></td>
<td><strong>Reported by</strong></td>
</tr>
<tr>
<td>Family demographics</td>
<td>Parents</td>
</tr>
<tr>
<td>Pain list</td>
<td>Parent or adolescents</td>
</tr>
<tr>
<td>Health care use questionnaire</td>
<td>Parent or adolescents</td>
</tr>
<tr>
<td>Functional Status II (R) (Dutch version) (Stein and Jessop, 1991, Post et al., 1998)</td>
<td>Parent</td>
</tr>
<tr>
<td>The Dartmouth COOP Functional</td>
<td>Parent</td>
</tr>
<tr>
<td>Health Assessment charts / WONCA (Dutch version) (van Weel et al., 1995)</td>
<td>Adolescent</td>
</tr>
<tr>
<td>Impact on Family Scale (Dutch version) (Stein and Jessop, 1985; Hunfeld et al., 1999)</td>
<td>Parent</td>
</tr>
<tr>
<td>Quality of Life Headache – Youth (adapted for chronic pain) (Langenfeld et al., 1996)</td>
<td>Adolescent</td>
</tr>
<tr>
<td>Diary consisting of Visual Analog Scales (Hunfeld et al., 1997) and Pain Behavioral Change Measure (modified version of the Post-operative Pain measure for Parents) (Chambers et al., 1996)</td>
<td>Parent or adolescent</td>
</tr>
<tr>
<td></td>
<td>Parent</td>
</tr>
</tbody>
</table>
a medical diagnosis for the pain. The conditional part of the Functional Status II (R) (FSII) (Stein and Jessop, 1991), asking whether the child’s behavior could be attributed to the pain, was omitted because a pilot study revealed that in the written form this part caused comprehension problems when it was self-administered. The questionnaires used have shown acceptable reliability and validity.

The diary consisted of Visual Analog Scales (VAS) (Jensen and McFarland, 1993; Hunfeld et al., 1997) to obtain the intensity and frequency of pain. All subjects were asked to record pain intensity by VAS three times daily, during three successive weeks. In addition, parents of subjects aged 0–11 years completed the Pain Behavioral Change Measure (PBCM), a modified version of the Post-operative Pain Measure for Parents (Chambers et al., 1996), at the end of each day; the list was adapted for chronic pain and therefore shortened from 29 to 10 items.

2.4. Data reduction and analysis

To obtain intensity scores, the VAS markings were first converted into scores from 0 to 100 by reading off each mark against a millimeter ruler. Subsequently, VAS scores \( \leq 5 \) mm were recoded to zero, because a study on the recording of the measurement of the pain intensity in interviews with children showed that those scores turned out to be ‘no pain at all’ (Hunfeld et al., 1997). To score the child’s behavior due to pain the positively answered items of the PBCM were summed. To obtain an average pain intensity score, the VAS scores (and for participants aged 0–11 years also the PBCM scores) were divided by the number of VAS recordings or days in pain, respectively. Subjects with more than 25% missing values on VAS or PBCM in the diary were excluded from the analyses. The frequency of occurrence of pain was defined as the percentage of the number of recordings indicating the presence of pain divided by the total number of recordings (VAS and PBCM). For example, a pain frequency of 33% means that the pain was present in 21 (score \( > 5 \) mm) of the 63 VAS recordings, or in 7 (score \( > 0 \)) of the 21 PBCM recordings.

Regarding health care use, subjects were categorized into consultants and non-consultants. Consultants were those reporting use of some form of health care; non-consultants reported no use of the health service. In this classification medication use was left out of consideration, because it was not possible to differentiate whether medication was prescribed by the physician or was over-the-counter medication. The course of chronic benign pain was categorized into persistent and non-persistent pain. Subjects with persistent pain were those who responded at all three assessments and reported chronic benign pain at \( T_0 \) and at \( T_1 \) and/or \( T_2 \); subjects with non-persistent pain also responded thrice but reported chronic benign pain at \( T_0 \) only.

Data were analyzed by frequencies and cross-tabulations. Differences were tested for categorical variables by \( \chi^2 \) tests, for ordinal variables by Mann–Whitney \( U \) (M–W) tests or Kruskall–Wallis (K–W) tests, and for continuous variables by Student’s \( t \)-tests or oneway ANOVA. Linear (for ordinal and continuous variables) and logistic (for dichotomous variables) regression analyses with repeated measurements were carried out by SAS 8.0 to determine the course of pain of individual subjects. These analyses used the pain parameters, the pain-related consequences (functional status, quality of life domains, impact on family dimensions, school absence, health care use and medication use), and co-morbidity and chronic illness in the family as dependent factors and ‘time’ as within-subject factor. In the case the factor yielded a significant effect in a univariate regression analysis multivariate analyses were carried out with background factors such as age and gender as independent factors. Additionally, we tested the interaction of ‘time’ with pain location, age and gender, respectively. To identify predictors of persistent pain, univariate and multivariate logistic regression analyses were carried out. These analyses used persistence of chronic benign pain at follow-up as the dependent variable and the variables which showed differences between persistent and non-persistent pain assessed at baseline as the independent variables. A \( P \)-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Response

Fig. 1 shows the response rates and the occurrence of chronic benign pain in the three consecutive assessments of the cohort comprising 987 children and adolescents aged 0–18 years with chronic pain. A very small proportion of the subjects who had reported chronic pain at \( T_0 \), \( T_1 \) and \( T_2 \) was excluded because the pain had an organic etiology. At \( T_0 \), \( T_1 \) and \( T_2 \) a total of 254/506 (50%), 150/247 (61%) and 118/255 (46%) subjects, respectively, reported to have chronic benign pain.

A total of 445 subjects (45.1%) did not respond at any follow-up assessment, 255 subjects (25.8%) responded only once, 119 (12.1%) responded twice, and 168 subjects (17.0%) responded at all three assessments. Of the subjects who responded at all three assessments 39, 26, 26 and 77 subjects reported to have chronic benign pain at none of the assessments, and at 1, 2 and 3 assessments, respectively. Of these subjects responding thrice, 93 children had persistent pain. This is 9.4% (93/987) of the original sample of children with chronic pain at screening, but 55% (93/168) of the group responding at all three assessments.
3.2. Comparability of study groups

The responders at each assessment were compared with the initial cohort (n = 987) on demographic and pain characteristics obtained at the screening on chronic pain in order to investigate potential selection bias. In general, the responders were slightly younger than the non-responders. The results are shown in Table 2.

Furthermore, we compared subjects who responded at the follow-up assessments never, once, twice, and thrice with the initial cohort on the same variables as listed in Table 2. One-way ANOVA analysis revealed that, again, only age was found to be different (P < 0.001); the mean age was 11.4 years (SD 4.2), 10.3 (SD 4.2), 9.7 (SD 4.3) and 10.0 (SD 4.3) for subjects who responded never, once, twice and thrice, respectively.

To ensure equivalence for subjects with chronic benign pain between the three assessment times, their background factors were compared, as shown in Table 3. Except for an age difference, which was expected since subjects were followed for two years, no significant differences were found between the three samples. When comparing the age obtained at the screening no significant differences were found between the three samples.

3.3. Changes over time

Of the subjects who reported chronic benign pain at baseline (n = 254), 49% of them (n = 124) still complained of chronic benign pain at one-year follow-up and 30% (n = 77) at two-year follow-up.

Table 4 shows that there is little change in pain and pain parameters, except for pain frequency. For health status and impact of the pain on child and family, none of the instruments and subscales showed significant changes over the two-year period, except for functional status. The FSII showed a consistent deterioration over time, with mean values of 80.5, 77.5 and 67.7 for T0, T1 and T2, respectively.

The individual course of pain and its consequences was determined by regression analyses with repeated measurements. The analyses, described in this paragraph, were restricted to the 144 subjects (14.6%) who had reported to have chronic benign pain on at least two assessments (44 boys and 100 girls). In 35 (24%) of the 144 subjects, the pain location had switched to another location, mostly to the head. Of these 35 subjects, 14% reported to have headache at T0, 39% at T1, and 56% at T2 (data not shown). Of the pain variables, only the estimated pain intensity changed slightly over the follow-up period, i.e. a yearly decrease of 3.3 mm on the VAS (95% CI 0.66–5.20). For the consequences of pain (impact of pain, health status, school absence, health care use and medication use) there was little change over time. The impact of pain on the child's behavior and the social functioning deteriorated with a 6.22 (95% CI 4.87–7.57) decrease of the score on the FS-II and a 0.09 (95% CI 0.03–0.15) decrease on the QLH-Y yearly, respectively. These results were not modified after adjustment for the pain location. The impact on the family (assessed with the IFS) remained stable, but when

Table 2
Comparison between the responders and non-responders at the three follow-up assessment times on demographic and pain characteristics obtained at the screening on chronic pain

<table>
<thead>
<tr>
<th></th>
<th>T0 Responders</th>
<th>T0 Non-responders</th>
<th>T1 Responders</th>
<th>T1 Non-responders</th>
<th>T2 Responders</th>
<th>T2 Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean in years (SD)</td>
<td>9.9 (4.2)</td>
<td>11.4 (4.2)</td>
<td>10.0 (4.3)</td>
<td>10.9 (4.2)</td>
<td>10.1 (4.3)</td>
<td>10.8 (4.2)</td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Boys</td>
<td>188 (37.5)</td>
<td>165 (34.0)</td>
<td>221 (46.4)</td>
<td>246 (35.5)</td>
<td>264 (48.0)</td>
<td>271 (48.0)</td>
</tr>
<tr>
<td>Girls</td>
<td>313 (62.5)</td>
<td>321 (66.0)</td>
<td>154 (33.6)</td>
<td>480 (64.5)</td>
<td>163 (64.4)</td>
<td>471 (64.2)</td>
</tr>
<tr>
<td>Frequency of pain last month</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than once a week</td>
<td>181 (36.9)</td>
<td>164 (34.3)</td>
<td>92 (18.5)</td>
<td>253 (34.7)</td>
<td>83 (18.3)</td>
<td>262 (36.3)</td>
</tr>
<tr>
<td>At least once a week</td>
<td>310 (63.1)</td>
<td>314 (65.7)</td>
<td>147 (31.5)</td>
<td>477 (65.3)</td>
<td>165 (66.5)</td>
<td>459 (63.7)</td>
</tr>
<tr>
<td>Intensity of pain last month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean in mm on VAS (SD)</td>
<td>56.7 (22.7)</td>
<td>58.9 (24.4)</td>
<td>56.0 (21.6)</td>
<td>58.3 (24.2)</td>
<td>54.4 (22.2)</td>
<td>58.9 (23.9)</td>
</tr>
<tr>
<td>Physician consultation due to pain (N, %)</td>
<td>520 (64.5)</td>
<td>292 (60.7)</td>
<td>159 (66.5)</td>
<td>453 (61.4)</td>
<td>151 (60.6)</td>
<td>461 (63.3)</td>
</tr>
<tr>
<td>Medication use ever for the pain (N, %)</td>
<td>208 (41.9)</td>
<td>199 (41.4)</td>
<td>116 (48.1)</td>
<td>291 (39.5)</td>
<td>110 (44.0)</td>
<td>297 (40.9)</td>
</tr>
</tbody>
</table>

* Student's t-test differences between responders and non-responders significant at P < 0.05.

"χ²" differences between responders and non-responders significant at P < 0.05.
testing the interaction for pain location we found that, compared to the other pain types, for subjects with abdominal pain the total impact (score \( \leq 2.6 \) yearly, 95% CI 1.23–3.97) and personal strain (score \( \leq 1.0 \) yearly, 95% CI 0.45–1.65) diminished, and that families of subjects with limb pain were less able to master the stress of pain (score \( \leq 0.7 \) yearly, 95% CI 0.11–1.29). Health care use (consultant versus non-consultant) diminished consider-

### Table 3
Background factors of three samples of children suffering from chronic benign pain by time of assessment

<table>
<thead>
<tr>
<th>Factor</th>
<th>( T_0 ) N = 254</th>
<th>( T_1 ) N = 150</th>
<th>( T_2 ) N = 118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of child</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean in years (SD)</td>
<td>11.1 (4.3)*</td>
<td>12.0 (4.3)*</td>
<td>13.9 (4.0)*</td>
</tr>
<tr>
<td>Gender (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>80 (31.6)</td>
<td>51 (34.5)</td>
<td>31 (26.3)</td>
</tr>
<tr>
<td>Girls</td>
<td>173 (68.4)</td>
<td>97 (65.5)</td>
<td>87 (73.7)</td>
</tr>
<tr>
<td>Nationality of child (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch</td>
<td>244 (97.2)</td>
<td>144 (97.3)</td>
<td>113 (97.3)</td>
</tr>
<tr>
<td>Non-Dutch</td>
<td>7 (2.8)</td>
<td>4 (2.7)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Birth-order of child in family (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-born</td>
<td>118 (47.6)</td>
<td>64 (43.5)</td>
<td>50 (47.6)</td>
</tr>
<tr>
<td>Later-born</td>
<td>130 (52.4)</td>
<td>83 (56.5)</td>
<td>55 (52.4)</td>
</tr>
<tr>
<td>Family size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of children (SD)</td>
<td>2.4 (1.0)</td>
<td>2.4 (1.0)</td>
<td>2.3 (1.1)</td>
</tr>
<tr>
<td>Marital status of parents (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or cohabitant</td>
<td>204 (85.4)</td>
<td>121 (87.7)</td>
<td>90 (85.7)</td>
</tr>
<tr>
<td>Divorced or separated</td>
<td>35 (14.6)</td>
<td>17 (12.3)</td>
<td>15 (14.3)</td>
</tr>
<tr>
<td>Education level of mother (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>90 (39.8)</td>
<td>62 (47.7)</td>
<td>41 (41.8)</td>
</tr>
<tr>
<td>Middle</td>
<td>83 (36.7)</td>
<td>40 (30.8)</td>
<td>36 (36.7)</td>
</tr>
<tr>
<td>High</td>
<td>53 (23.5)</td>
<td>28 (21.5)</td>
<td>21 (21.4)</td>
</tr>
<tr>
<td>Education level of father (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>49 (25.9)</td>
<td>33 (30.8)</td>
<td>25 (30.1)</td>
</tr>
<tr>
<td>Middle</td>
<td>79 (41.8)</td>
<td>35 (32.7)</td>
<td>38 (45.8)</td>
</tr>
<tr>
<td>High</td>
<td>61 (32.3)</td>
<td>39 (36.4)</td>
<td>20 (24.1)</td>
</tr>
<tr>
<td>Chronic pain in mother (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>106 (44.5)</td>
<td>59 (41.8)</td>
<td>54 (51.9)</td>
</tr>
<tr>
<td>Middle</td>
<td>77 (36.7)</td>
<td>41 (33.3)</td>
<td>30 (34.5)</td>
</tr>
<tr>
<td>High</td>
<td>11 (4.5)</td>
<td>11 (7.3)</td>
<td>8 (6.8)</td>
</tr>
<tr>
<td>Co-morbidity (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic illness in family (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\* Significant difference between the three assessments; \( P < 0.05 \).

\* Education level was classified based on the highest completed school level: low (primary school or lower vocational training), middle (secondary school) and high (higher vocational training and university).

\* The definition used for chronic pain in parents was identical to that used in children.

### Table 4
Changes in pain and pain-related consequences in children suffering from chronic benign pain over the two-year follow-up period

<table>
<thead>
<tr>
<th>Location of pain (N, %)</th>
<th>( T_0 ) N = 254</th>
<th>( T_1 ) N = 150</th>
<th>( T_2 ) N = 118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb</td>
<td>71 (29.2)</td>
<td>31 (21.7)</td>
<td>26 (23.0)</td>
</tr>
<tr>
<td>Head</td>
<td>65 (26.7)</td>
<td>52 (37.1)</td>
<td>43 (38.1)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>61 (25.1)</td>
<td>30 (21.0)</td>
<td>25 (22.1)</td>
</tr>
<tr>
<td>Back</td>
<td>20 (8.2)</td>
<td>14 (9.8)</td>
<td>14 (12.4)</td>
</tr>
<tr>
<td>Other</td>
<td>26 (10.7)</td>
<td>15 (10.5)</td>
<td>5 (4.4)</td>
</tr>
<tr>
<td>Course of pain (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>41 (16.1)</td>
<td>20 (13.3)</td>
<td>27 (22.9)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>213 (83.9)</td>
<td>130 (86.7)</td>
<td>91 (77.1)</td>
</tr>
<tr>
<td>Duration of pain (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean in years (SD)</td>
<td>3.1 (2.7)</td>
<td>3.7 (2.7)</td>
<td>4.3 (2.6)</td>
</tr>
<tr>
<td>Frequency of pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>previous month (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than once a week</td>
<td>73 (29.7)</td>
<td>56 (38.1)</td>
<td>30 (26.8)</td>
</tr>
<tr>
<td>At least once a week</td>
<td>173 (70.3)</td>
<td>91 (61.9)</td>
<td>82 (73.2)</td>
</tr>
<tr>
<td>Frequency of pain in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diary period (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of % in pain on</td>
<td>49.8 (34.1)*</td>
<td>52.4 (34.9)*</td>
<td>61.8 (34.7)*</td>
</tr>
<tr>
<td>VAS (SD)</td>
<td>24.2 (22.0)</td>
<td>26.1 (23.4)</td>
<td>22.9 (24.7)</td>
</tr>
<tr>
<td>Mean of % in pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>on PBCM (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity of pain in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>previous month (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean in millimeters on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS (SD)</td>
<td>50.2 (20.3)*</td>
<td>44.5 (23.0)*</td>
<td>48.5 (21.5)*</td>
</tr>
<tr>
<td>Intensity of pain in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diary period (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean in millimeters on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS (SD)</td>
<td>30.7 (15.1)</td>
<td>30.4 (13.1)</td>
<td>32.1 (14.6)</td>
</tr>
<tr>
<td>Mean of PBCM score (SD)</td>
<td>3.1 (1.6)</td>
<td>3.1 (1.7)</td>
<td>2.7 (1.3)</td>
</tr>
<tr>
<td>Intensity of pain on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daily activities (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean in millimeters on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS (SD)</td>
<td>32.6 (28.0)</td>
<td>28.3 (25.3)</td>
<td>34.4 (24.7)</td>
</tr>
<tr>
<td>School absence due to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pain (N, %)</td>
<td>1.0 (3.1)</td>
<td>1.4 (3.8)</td>
<td>1.0 (2.1)</td>
</tr>
<tr>
<td>Health care use due to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pain (N, %)</td>
<td>109 (42.9)</td>
<td>59 (39.3)</td>
<td>42 (35.6)</td>
</tr>
<tr>
<td>Medication use for pain (N, %)</td>
<td>117 (46.6)</td>
<td>65 (43.9)</td>
<td>51 (44.7)</td>
</tr>
</tbody>
</table>

\* Significant difference between the three assessments; \( P < 0.05 \).

* Items of the Pain List.

\* Intensity of the pain and interference with daily activities were assessed using the Visual Analog Scale, a 100-mm long line with the verbal anchors 'no pain' versus 'the worst pain you can imagine' or 'no nuisance' versus 'unable to do daily activities', respectively, at both sides.

\* The score of the Pain Behavioral Change Measure (PBCM) ranges from 0 (no changes) to 10 (maximum number of changes).
ably during the follow-up period ($T_6$: OR 1.93, 95% CI 1.42–2.66; $T_5$: OR 1.48, 95% CI 1.04–2.12; $T_7$: OR 1.00). The course of pain over two years did not differ between boys and girls, or between different ages (age analyzed as a continuous variable).

3.4. Predictors for persistent chronic benign pain

At baseline there were a few differences for pain, its consequences and background factors between subjects with persistent pain ($n = 93$) and non-persistent pain ($n = 16$). Compared to subjects with non-persistent pain, those with persistent pain had at baseline more frequent pain in the diary period (mean 52.8% (SD 34.0) versus 32.6% (SD 30.5); $P = 0.039$), a longer pain history (mean 3.3 years (SD 2.5) versus 2.0 years (SD 1.9); $P = 0.028$), more often headache and less often limb pain (31.1% and 24.4% versus 6.3% and 56.3%; $\chi^2 = 9.76$, df = 4, $P = 0.045$), were more bothered by emotional problems (COOP WONCA mean score 2.6 (SD 1.0) versus 1.5 (SD 0.8); $P = 0.006$), and their mothers rated their own health in general lower (COOP WONCA mean score 2.5 (SD 1.0) versus 1.9 (SD 1.2); $P = 0.022$). By univariate logistic regression analyses, emotional problems of subjects (OR 4.23, 95% CI 1.35–12.50), their mother’s self-reported health in general (OR 1.92, 95% CI 1.08–3.33), and pain frequency ($>50\%$ pain in diary versus $<50\%$; OR 3.74, 95% CI 1.01–14.16) were identified as predictors of persistent chronic benign pain. Multivariate logistic regression analysis with these factors determined emotional problems to be the only predictor which classified the pain status correctly at follow-up in 86% of the subjects. Emotional problems were defined as the self-reported level of emotional well-being (feeling anxious, depressed, irritable or downhearted and blue) over the past two weeks on a 5-point ordinal scale.

4. Discussion

The present study shows that chronic benign pain is common in children and adolescents in the general population and that about one-third of those who had chronic benign pain at baseline still had this pain at two-year follow-up. In the group that responded at all occasions, 55% reported to have persistent chronic pain. This corresponds well with the 48% remission of musculoskeletal pain in schoolchildren at one-year follow-up reported by Mikkelsen et al., (1999). That same study showed remission rates of 38% and 42% for widespread pain and neck pain at one-year follow-up.

In the present study, girls were twice as much likely to have chronic benign pain, and at follow-up this gender difference was still present. Overall, at baseline these children had rather mild intense, but frequent pain, and were not severely disabled by the pain. Although these pains were benign and present for several years (about 3 years), a considerable proportion of the children had used some form of health care service or used medication for the pain in the prior 3 months. In general, the pain characteristics and the pain-related consequences remained relatively stable over the two-year follow-up, as was assessed in the subsample of subjects who reported chronic benign pain on at least two assessments. Yet, the chronic benign pain sufferers deteriorated in their behavior and social functioning, but reduced their use of health care services. This partly corresponds with a Canadian longitudinal survey on persistent pain in adults which showed that pain and its consequences remained stable over two years, except for the emotional and social consequences, and for health care use (Crock et al., 1989). However, contrary to our results, they found an improvement in the emotional and social consequences. We found that, through follow-up, a considerable proportion of the subjects changed pain location, which was mostly the head. However, there was no relation between the location of pain and the course of the behavior and social functioning that could have explained this deterioration.

Children with persistent pain over two years differed in some ways from those who did not report chronic benign pain at follow-up, but only emotional problems, their mother’s self-reported health in general, and the pain frequency were identified as prognostic factors. Since the prognostic factor ‘emotional problems’ was operationalized by only one question on the COOP WONCA charts and restricted to adolescents, it is therefore less reliable. However, a previous study found that, at follow-up, chronic pain patients attending a specialty clinic were still more distressed than those in the family practice, suggesting that emotional factors are probably among the most important factors in the chronic morbidity of these patients (Crock et al., 1989). Contrary to the findings of Crock et al., we found a longer pain duration at baseline for children with persistent pain than for those who had no chronic benign pain at follow-up. However, logistic regression analysis revealed that this is not a good predictor of the two-year prognosis.

Several limitations of our study should be discussed. First, selection bias introduced by non-participation is a potential limitation to be considered. However, the small and predominantly insignificant differences in demographics, pain characteristics, physician consultation and medication use as assessed in the previous prevalence study (Perquin et al., 2000a,b), between the responders at each assessment and the initial cohort, suggest that the selection bias is small. The non-significant differences in background factors (except for age, which was expected since we followed up subjects for two years) between responders at the three assessments, confirmed this opinion. Another drawback is use of parent ratings versus
self-report. Because pain is subjective, self-report should be the 'gold standard' for pain assessment (McGrath, 1990). We used parent ratings for subjects aged 0–11 years because this is the best proxy measure available in young children, particularly in longer lasting pain (Beyer et al., 1990; Manne et al., 1992). Bias due to the different way of obtaining data is unlikely, since we determined the individual course of pain and its consequences by adjusting for age and gender.

The implications of this study are that chronic benign pain in childhood and adolescence is common, and seems to persist in a considerable proportion (30–45%). Emotional problems, mother’s health, and pain frequency were identified as predictors of the two-year prognosis. Although children were not severely disabled by the pain and the pain generally did not deteriorate over time, the size of the group of children with chronic pain makes it sensible to investigate possibilities to prevent pain from becoming chronic. Future studies should focus on identifying risk factors for pain becoming chronic in children and adolescents.

Declaration of interests
The authors have no conflicting interests.

Acknowledgements
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Stein REK, Jessop DJ. Tables documenting the psychometric properties of a measure of the impact of chronic illness on a family. New York, Bronx: Albert Einstein College of Medicine of Yeshiva University; 1985.


Letter to the Editor


Finding the centre

Moog et al. (2002) studied a group of chronically distressed whiplash patients, known to score high on somatization scales on the SCL-90-R, and compared them to a control group consisting of age- and sex-matched healthy volunteers with no spinal, upper or lower limb pain in the 12 months prior to testing. They found that not only are the whiplash patients chronically distressed, they also have this convenient phenomenon known as “central sensitization”. We say that this is a convenient phenomenon because it cannot be proven or disproven. There is no “gold standard” for the identification of this phenomenon, and no known site for its origin. Moog et al. have made the assumption that if one finds that chronically distressed patients give a different pain interpretation and response to a physical stimulus, then there must be some central sensitization, particularly as this response seems to affect many body regions. We ask, however, “Where is the centre of this central sensitization”? There is a body of literature showing that if one selects healthy subjects, then makes them anxious and distressed, physical stimuli will be perceived differently and recorded as a more-noxious stimulus than when the same subjects are not distressed (Barsky et al., 1988; Barsky, 1992, 1986; Levine et al., 1982; Robinet et al., 1987). Clearly, the healthy subjects of these experiments have no disorder prior to the distress and yet will appear to have the very phenomenon Moog et al. reproduced.

Moog et al. note that the group of subjects reporting vibration-induced pain (VIP) used affective pain descriptors more frequently than those who did not report vibration-induced pain, but that higher psychological scores were not found compared with the other patients. Of course, the patient group tended to be a distressed group, so the overall psychological scores should tend to group them together. Even within the subject group of chronic whiplash, however, those who reported VIP had significantly higher affective but not sensory pain descriptor scores on the short form McGill Pain Questionnaire. Moog et al. found a relatively homogeneous psychological profile. This homogeneous psychological profile is thought to be the result of the chronic pain state and not a reflection of primary psychopathology. This is not relevant because it does nothing to negate the possibility that what the researchers observe may still be caused by the elevated psychological distress.

The authors further state that patients pursuing personal injury claims did not rate themselves as being significantly more disabled than those without ongoing litigation. They opine that the responses to vibratory stimuli were independent of litigation status. They have made the same error in thinking as Sapir and Gorup (2001) who used facet joint blocks on litigating and non-litigation patients to attempt to show that litigation was irrelevant to treatment outcome: they both failed to recall there are at least 12 other forms of secondary gain besides money, and some other ways of achieving monetary benefits without litigation (Ferrari and Kwan, 2001; Ferrari, 2002). The citation of facet joint studies is even less helpful for reasons explained elsewhere (Kwan and Frikel, 2002).

It is clear that the presence of psychological distress may be just as valid an explanation for the findings of Moog et al. The study design used by Moog et al. cannot test for the centre of central sensitization, as their control group was wholly inappropriate to address this important question.

We suggest, that the “gold standard” in this type of research has already been set and should be followed carefully (Carragee et al., 2000). Carragee et al. accomplished this in a study examining for responses to a noxious stimulus in chronic spinal pain. The results are quite revealing. To explain, Carragee et al. wanted to examine the responses to the noxious stimulus of discography (known to be painful to some extent even in healthy subjects). Discography tends to be painful in chronic low back pain patients, and the question is whether or not the physical cause of the back pain is the cause of the response to discography, or whether the psychological distress of back pain patients is the predictor of the discography response, independent of chronic pain. Carragee et al. chose 3 groups as control subjects: (1) healthy subjects with no low back pain and no psychological distress, (2) subjects with chronic neck pain, but no low back pain, and (3) subjects with chronic anxiety or other chronic psychological distress, but no pain. As expected, the chronic low back pain patients reported more severe and diffuse pain with the injection much more often than the healthy subjects. What was unexpected was that 43% of the subjects with chronic neck pain but no low back pain also reported more severe
and diffuse low back pain with the lumbar disc injection. This could mean that chronic neck pain patients with no low back pain share some common features with chronic low back pain patients. To eliminate the factor of chronic pain, one must review the response of the psychologically distressed subjects without pain: 83% had a response just like that of the chronic low back pain patients. Thus, the independent predictor of the painful response to lumbar discography is not the presence or absence of chronic pain, nor necessarily the presence or absence of tissue pathology. The independent predictor of the painful response is the presence or absence of psychological distress. The psychological distress causes what should be a mildly painful stimulus to be registered as more severe and more diffuse (i.e., symptom amplification). In this study it is the psychological construct entitled symptom amplification which is common to the chronic low back pain, chronic neck pain, and psychological-distressed subjects without chronic pain.

How does one interpret the results of Moog et al.? Certainly, without a proper control group included in the study it is difficult.

References


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Reply to Drs. Kwan and Friel

Drs. Kwan and Friel (2003) need to be reminded that “central sensitization” is an operational construct for which there is a neurobiological substrate. The relevant references are provided in our paper. We must of course ignore their challenge to “find the centre” of “central sensitization” on the grounds that to embark upon such an exercise would be doomed to failure, as has been the quest for a “pain centre” within the brain.

Without labouring the point, we deliberately chose to use standard non-noxious rather than noxious stimuli in our study for the very reasons so well outlined by Kwan and Friel (2003). Nonetheless, we are not aware of any scientific evidence that psychologically distressed but cognitively unimpaired subjects are thereby rendered more likely to perceive such non-noxious stimuli as painful.

As is made quite clear in our paper, we did not favour the model of primary psychogenesis as an explanation for the ongoing pain and disability in this cross-sectional group of patients fulfilling criteria for the “late whiplash syndrome”. We do not deny that cognitive processes have an important role in the experience of pain. However, if by “symptom amplification” Kwan and Friel (2003) are seriously suggesting that the putative amplifier of bodily pain lies within the patient’s disembodied mind, we reject their hypothesis on the grounds that it transcends science, being inherently untestable.

On the other hand, if their simplistic construct of “symptom amplification” is merely another way of suggesting that many of these patients have developed a central hypersensitivity state, which can be influenced by many psychological factors, we quite agree with Kwan and Friel (2003) that this complex neurobiological phenomenon could well be a factor common to many of our patients with otherwise unexplained persistent and disabling spinal pain.

Reference


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V. Apkarian, J. Grisart, W.A. Macrae, A. Savolainen
L. Arendt-Nielsen, N.H. Groenman, R. Malcom, M. Schneitz
N. Atai, M. Grönblad, A. Malmivuo, K. Seers
R. Baron, R. Granaa, A. Mannion, M. Segersdahl
H.-D. Basler, E. Guthrie, H. Mansikka, Z. Seltzer
U. Baumgärtner, M. Haapalä, P. Määttänsalo, L. Sharpe
G. Bennett, H.-J. Haeber, P. Marchettini, D. Simone
G. Bergström, M. Häkkinen, W. Martin, B.H. Sjölund
K. Berkley, M. Hamon, J. McBeth, L. Sorkin
F. Birklein, K. Hamanaka, L. McCracken, C. Spanwick
N. Bogduk, M. Hanna, R. Melzack, B. Stacey
L. Breau, S. Harkins, H. Merskey, A. Steptoe
S. Bruehl, M. Hasenbring, B. Meyerson, J. Strong
K. Casey, H. Havanka, V. Molony, A. Stubhaug
K. Craig, A. Herlitz, T.P. Nash, P. Svensson
M. Cummings, M.A. Horan, M. Nicholas, R. Tait
P. Chambers, S. Hunt, L. Niemistö, T. Tolle
A. Chen, M. Janal, J.R. Norrefalk, M. Tominaga
B. Chizh, R. Johnson, D. O'Donnell, J. Turner
O. Dale, M.H. Johnson, J. Palmer, A. Unruh
K. Davis, G. Jones, G. Peat, A. van den Hout
L. Decosterd, A.K.P. Jones, J. Persson, B. van Houweninghe
R. Dowman, M. Joukamaa, A. Petovaara, F. Viana de la Iglesia
C. Eccleston, R. Kakigi, M. Pitkänen, J. Vlaeyen
J. Eisenach, M. Kallera, L. Piipäräisks, S. Vogel
J. Ellrich, H. Karlsson, O. Pol, M. von Korff
V. Engle, E. Keogh, P. Puustjärvi, G. Waddell
J. Eriksson, P. Klepstad, K. Raphaël, G. Wassmer
A. Eschallier, L. Klinger, R. Pöyhöä, P.J. Watson
M. Färkkilä, V. Kontinen, K. Ren, D. Weiner
V. Fellman, G. Leijon, A. Rice, P.D. White
H. Flor, J. Levine, M. Robinson, Z. Wiesenfeld-Hallin
N. Foster, R. Likar, J. Rodofs, J.C. Willer
L. García-Lurraea, D. Lima, R. Rolke, A.C. de C. Williams
M. Geisser, J. Lindén, C. Roza, K. Zeitz

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## Contents of Volume 7

### Volume 7 Number 1 2003

#### Reviews
- Factors influencing the features of postherpetic neuralgia and outcome when treated with tricyclics
  - David Bowsher
  - 1

- Disuse and deconditioning in chronic low back pain: concepts and hypotheses on contributing mechanisms
  - Jeanine A. Verbau, Henk A. Seelen, Johan W. Vlachy, Geert J. van de Heijden, Peter H. Heuts, Kees Pons and J. Andre Knottnerus
  - 9

#### Original Articles
- Painful and non-painful neuropathy in HIV-infected patients: an analysis of somatosensory nerve function
  - Claes Martin, Gran Solders, Anders Sannerborg and Per Hansson
  - 23

- Implicit attitude towards pictures of back-stressing activities in pain-free subjects and patients with low back pain: an affective priming study
  - Liesbet Goubert, Geert Crombez, Dirk Hermans and Guy Vanderstraeten
  - 33

- The treatment of complex regional pain syndrome (CRPS) involving upper extremity with continuous sensory analgesia
  - Krunoslav Margić and Jelka Pirc
  - 43

- Comparison of the effect of video glasses and nitrous oxide analgesia on the perceived intensity of pain and unpleasantness evoked by dental scaling
  - Bo Bentsen, Ann Wenzel and Peter Svensson
  - 49

- Suppression of motor evoked potentials in a hand muscle following prolonged painful stimulation
  - Peter Svensson, Timothy S. Miles, Darrin McKay and Michael C. Ridding
  - 55

- The significance of Aδ and C fibres for the perception of synthetic heat
  - Heinrich Fruhstorfer, Eva-Liz Harju and Ulf F. Lindblom
  - 63

- Experimental muscle pain provokes long-lasting alterations of thermal sensitivity in the referred pain area
  - B. Tuveson, U. Lindblom and H. Fruhstorfer
  - 73

- Induction of non-painful and painful intestinal sensations by hypertonic saline: a new human experimental model
  - 81

doi:10.1016/S1060-3801(03)00122-8
Experimental pain by ischaemic contractions compared with pain by intramuscular infusions of adenosine and hypertonic saline
Thomas Graven-Nielsen, Ylva Jansson, Mrta Segerdahl, Jens D. Kristensen, Siegfried Mense, Lars Arendt-Nielsen and Alf Sollevi

Acknowledgements (Reviewers 2002)

Volume 7 Number 2 2003

Original Articles
Information processing biases among chronic pain patients and ankylosing spondylitis patients: the impact of diagnosis
Heather J. Wells, Tamar Pincus and Elaine McWilliams

Childhood adversities in patients with fibromyalgia and somatoform pain disorder
Katrin Immierowicz and Ulrich T. Ege

Epidural ketamine potentiates epidural morphine but not fentanyl in acute nociception in rats
Vincent L.H. Hoffmann, Alexis K. Baker, Marcel P. Vercauteren, Hugo F. Adriaensen and Theo F. Meert

Antinociceptive effect in mice of intraperitoneal N-methyl-D-aspartate receptor antagonists in the formalin test
Liberato Berrino, Patrizia Oliva, Francesco Massimo, Caterina Aurilio, Sabatino Maione, Antonio Grella and Francesco Rossi

Psychophysics of phasic and tonic heat pain stimuli by quantitative sensory testing in healthy subjects
Michal Granot, Elliot Sprecher and David Yarnitsky

Experimental muscle pain and tenderness following infusion of endogenous substances in humans
Hanne Mrk, Messoud Ashina, Lars Bendtsen, Jes Olesen and Rigmor Jensen

Low-dose diclofenac potassium in the treatment of episodic tension-type headache
Florian Kubitzek, Gabrielle Ziegler, Morris S. Gold, Jian-Min H. Liu and Elisabeth Ionescu

Validation of the arthritis self-efficacy short-form scale in German fibromyalgia patients
Annette Mueller, Mechthild Hartmann, Knut Mueller and Wolfgang Eich

Therapeutic approaches to fibromyalgia syndrome in the United Kingdom: a survey of occupational therapists and physical therapists
Julius Sim and Nicola Adams

Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain
Jan Magnus Bjordal, Mark I. Johnson and Anne Elisabeth Ljunggren
The effects of A-fiber pressure block on perception and neurophysiological correlates of brief non-painful and painful CO₂ laser stimuli in humans
Hicham Nahra and Lon Plaghki

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>189</td>
</tr>
</tbody>
</table>

**Erratum**

David Bowsher

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>201</td>
</tr>
</tbody>
</table>

**Volume 7 Number 3 2003**

**Original Articles**

Parents' perceptions of their 1–6-year-old children's pain
Pivi M. Kankkunen, Katri M. Vehtivainen-Julkunen, Anna-Maija K. Pietil and Pirjo M. Halonen

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>203</td>
</tr>
</tbody>
</table>

Colored pain drawings: preliminary observations in a neurosurgical practice
Roberto Masferrer, Virginia Prendergast and Peter Hagell

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>213</td>
</tr>
</tbody>
</table>

Patient reporting of adverse drug reactions: useful information for pain management?
Narumol Jarernsripornkul, Janet Kriska, R. Michael E. Richards and Phillip A.G. Capps

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>219</td>
</tr>
</tbody>
</table>

Long term depression of human nociceptive skin senses induced by thin fibre stimulation
Hans-Jorgen Nilsson, Elia Psouni and Jens Schouenborg

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>225</td>
</tr>
</tbody>
</table>

Pain as presenting symptom in Lyme neuroborreliosis
Leif Dotevall, Tore Eliasson, Lars Hagberg and Clas Mannheimer

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>235</td>
</tr>
</tbody>
</table>

Antinociceptive effects of RB101(S), a complete inhibitor of enkephalin-catabolizing enzymes, are enhanced by (+)-HA966, a functional NMDA receptor antagonist: a c-Fos study in the rat spinal cord
Jaroslava Buritova, Stephanie Le Guen, Marie-Claude Fourni-Zaluski, Bernard P. Roques and Jean-Marie Besson

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>241</td>
</tr>
</tbody>
</table>

Segmental and plurisegmental modulation of pressure pain thresholds during static muscle contractions in healthy individuals
Eva Kosek and Lena Lundberg

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>251</td>
</tr>
</tbody>
</table>

Interobserver reliability of diagnosis in patients with complex regional pain syndrome
Anton C. van de Vusse, Suzanne G.M. Stomp-van den Berg, Henrica C.W. de Vet and Wilhelm E.J. Weber

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>259</td>
</tr>
</tbody>
</table>

Somatosensory perception in patients suffering from long-term trapezius myalgia at the site overlying the most painful part of the muscle and in an area of pain referral
Ann-Sofie Leffler, Per Hansson and Eva Kosek

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>267</td>
</tr>
</tbody>
</table>
Experimental deep tissue pain in wrist extensors—a model of lateral epicondylalgia
Helen Slater, Lars Arendt-Nielsen, Anthony Wright and Thomas Graven-Nielsen 277

Clinical Note
Treatment of chronic pain with millimetre wave therapy (MWT) in patients with diffuse connective tissue diseases: a pilot case series study
Taras I. Usichenko and Horst F. Herget 289

Letter to the Editor
Fibromyalgia may mask onset of autoimmune diseases
Andrea Kerschbaumer, Christina Duffner, Martin Wenger, Andrea Klauser and Michael Schirmer 295

Volume 7 Number 4 2003

Editorials
Fernando Cervero 297

A tribute to Professor Ulf Lindblom, MD, PhD
Per Hansson 299

Guest Editorials
Ulf Lindblom, friend and mentor
Aleksandar Beric 301

Ulf Lindblom – a very distinguished neurologist
J.-M. Besson 303

Ulf Lindblom: a personal memoir
David Bowsher 305

Thank you, Professor Ulf Lindblom
Harald Breivik 307

Ulf Lindblom, the first steps
Jan-Otto Ottosson 309

Research Papers
Pain questionnaires in the analysis of long lasting (chronic) pain conditions
Anders Wiencek, Ylva Lidn and Staffan Arnr 311

Master scaling of perceived intensity of touch, cold and warmth
Birgitta Berglund and Eva-Liz Harju 323
Spinal cord injury pain
Aleksandar Beric 335

Central pain and the role of quantitative sensory testing (QST) in research and diagnosis
Jorgen Boivie 339

Secondary hyperalgesia and presynaptic inhibition: an update
Fernando Cervero, Jennifer M.A. Laird and Esther Garcia-Nieus 345

Difficulties in stratifying neuropathic pain by mechanisms
Per Hansson 353

The Lindblom roller
Paolo Marchettini, Claudio Marangoni, Marco Lacerenza and Fabio Formaglio 359

Ulf Lindblom and spinal cord stimulation
Bjørn A. Meyerson 365

Quantifying sensation: “Look Back in Allodynia”
Jos L. Ochoa 369

How Ulf Lindblom changed my life: studies of the mechanisms of pain and abnormal sensations following nerve injury and their treatment in cats, rats and humans
Zsuzsanna Wiesenfeld-Hallin 375

Volume 7 Number 5 2003

Editorial
Appropriate and responsible use of opioids in chronic non-cancer pain
Harald Breivik 379

Original Articles
Recommendations for using opioids in chronic non-cancer pain
Eija Kalso, Laurie Allan, Paul L. I. Dellenijin, Clara C. Faura, Wilfried K. Ilias, Troels S. Jensen, Serge Perrot, Leon H. Plaghki and Michael Zenz 381

Dispositional anxiety and the experience of pain: gender-specific effects
Allan Jones, Robert Zachariae and Lars Arendt-Nielsen 387

Evaluation of a short duration behaviour-based post-operative pain scoring system in rats
John V. Roughan and Paul A. Flecknell 397
<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic tolperisone for post-exercise muscle soreness causes reduced isometric force – a double-blind randomized crossover control study</td>
<td>Prem Bajaj, Lars Arendt-Nielsen, Pascal Madeleine and Peter Svensson</td>
<td>407</td>
</tr>
<tr>
<td>The influence of electroconvulsive therapy on pain threshold and pain tolerance in major depression patients before, during and after treatment</td>
<td>Shaul Schreiber, Dorit Shmueli, Leon Grunhaus, Orna T. Dolberg, Eli Feldinger, Florellia Magora and Shmuel C. Shapiro</td>
<td>419</td>
</tr>
<tr>
<td>Scopolamine into the anterior cingulate cortex diminishes nociception in a neuropathic pain model in the rat: an interruption of ‘nociception-related memory acquisition’?</td>
<td>J. Manuel Ortega-Legaspi, Alberto López-Avila, Ulises Coffeen, Rosendo del Angel and Francisco Pellicer</td>
<td>425</td>
</tr>
<tr>
<td>Personalized pain words and Stroop interference in chronic pain patients</td>
<td>Gerhard Andersson and Deborah Haldrup</td>
<td>431</td>
</tr>
<tr>
<td>Interaction between metamizol and tramadol in a model of acute visceral pain in rats</td>
<td>Raquel Poveda, Eulalia Planas, Olga Pol, Asunción Romero, Silvia Sánchez and Margarita M. Puig</td>
<td>439</td>
</tr>
<tr>
<td>Effect of muscle relaxants on experimental jaw-muscle pain and jaw-stretch reflexes: a double-blind and placebo-controlled trial</td>
<td>Peter Svensson, Kelun Wang and Lars Arendt-Nielsen</td>
<td>449</td>
</tr>
<tr>
<td>Incidence of complex regional pain syndrome type 1 after fractures of the distal radius</td>
<td>Pieter U. Dijkstra, Johan W. Groothoff, Henk Jan ten Duis and Jan H.B. Geertzen</td>
<td>457</td>
</tr>
<tr>
<td>Determinants of health-related quality of life in patients with persistent somatoform pain disorder</td>
<td>Frank Petrak, Joehen Hardt, Bernd Kappis, Ralf Nickel and Ulrich Tiber Egle</td>
<td>463</td>
</tr>
<tr>
<td>The role of uninjured nerve in spinal nerve ligated rats points to an improved animal model of neuropathic pain</td>
<td>Doo H. Lee, Smriti Iyengar and David Lodge</td>
<td>473</td>
</tr>
<tr>
<td><strong>Clinical Note</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal fentanyl: informed prescribing is essential</td>
<td>Joy R. Ross and Columba Quigley</td>
<td>481</td>
</tr>
<tr>
<td><strong>Volume 7 Number 6 2003</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Original Articles</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine for intractable sciatica: correlation between dose, plasma concentration and analgesia</td>
<td>Elon Eisenberg, Gassan Damanni, Erica Hoffer, Yelena Baum and Norberto Krivoy</td>
<td>485</td>
</tr>
</tbody>
</table>
Nerve terminals extend into the temporomandibular joint of adjuvant arthritic rats
Masanichis Shinoda, Takashi Honda, Noriyuki Ozaki, Hisashi Hattori, Hideki Mizutani, Minoru Ueda and Yasuo Sugita

Electrical neuromodulation improves myocardial perfusion and ameliorates refractory angina pectoris in patients with syndrome X: fact or future?

Efficacy of spinal cord stimulation for neuropathic pain: assessment by abstinence
Russell Monhemius and Brian A. Simpson

Psychological responses to episodic chest pain
Kam Badi Okpa, Stephen Morley, Anthony R. Hobson, Sanchoy Sarkar, Teri McAlpine, David Thompson and Qasim Aziz

Hypoalgesia to pressure pain in referred pain areas triggered by spatial summation of experimental muscle pain from unilateral or bilateral trapezius muscles
Hong-You Ge, Pascal Madeleine, Kelun Wang and Lars Arendt-Nielsen

Multi-modal induction and assessment of allodynia and hyperalgesia in the human oesophagus
Asbjorn Mohr Drewes, Klaus-Peter Schipper, Georg Dimcevski, Poul Petersen, Ole Kseler Andersen, Hans Greger sen and Lars Arendt-Nielsen

The natural course of chronic benign pain in childhood and adolescence: a two-year population-based follow-up study
Christel W. Perquin, Joke A.M. Hunfeld, Alice A.J.M. Hazebroek-Kampeschreur, Lisette W.A. van Suijlekom-Smit, Jan Passchier, Bart W. Koes and Johannes C. van der Wouden

Letters to the Editor
Oliver Kwan and Jon Friel

Reply to Drs. Kwan and Friel
Martina Moog, John Quintner, Toby Hall and Max Zusman

Acknowledgements (Reviewers 2003)

Contents of Volume 7

Index to Volume 7
Index to Volume 7

A-fiber: pressure block, painful and non-painful CO2 laser stimuli 189
Adams, N 173
adenosine, experimental vs intramuscular infusion (ischaemic contractions) 93
Adriaensen, HF 121
adverse drug reactions (ADRs), patient reporting 219
Allen, L 381
allodynia and hyperalgesia, multi-modal induction, human oesophagus 539 quantifying sensation 369
analgesics, vs transcutaneous electrical nerve stimulation (TENS), postoperative pain 181
Anderson, K 431
Anderson, G 431
angina, refractory syndrome X, electrical neuromodulation 507
animal models
acute noceception intraperitoneal NMDA receptor antagonists 131 ketamine potentiation 121 behaviour-based postoperative pain score 397 growth of nerve terminals 493 inhibition of (+)-HA966 (NMDA receptor antagonist) by RB101/S 241 interactions of tramadol and metamizol in visceral pain 439 neuropathic pain 473
ankylosing spondylitis, vs chronic pain patients, information processing bias 105 antidepressants, postherpetic neuralgia 1 anxiety, dispositional, gender effects 387 Arendh-Nielsen, L 81, 93, 277, 387, 407, 449, 531, 539 Arter, S 311 arthritis
animal models, growth of nerve terminals 493 self-efficacy short-form scale, fibromyalgia 163 Ashiaa, M 145 Aurilio, C 131 autoimmune diseases, fibromyalgia masking onset 295 Aziz, Q 521
Babenko, K 81
back pain
back-stressing activities, attitudes towards pictures 33 disuse and deconditioning 9
Bajaj, P 407 Baker, AK 121 Baum, Y 485 behaviour-based postoperative pain score, animal models 397 Bendtsen, L 145 Bentzen, B 49 Berglund, B 323 Bercic, A 301, 335 Bertino, L 131 Besson, J-M 241

Besson, J-M 303
Birket-Smith, L 81 Bjorjdal, JM 181 Botwie, J 339
carcinosis, Lyme disease 235 Bowsher, D 1, 201, 305 Breivik, H 307, 379 Burtova, J 241

Cappi, FA 219 central pain, quantitative sensory testing (QST) 339 Cervero, F 297, 245 chest pain, psychological responses 521 childhood, family's perceptions of child's pain 203 childhood and adolescence, chronic benign pain, 2-y follow-up study 551 childhood adversities, fibromyalgia and somatoform pain disorder 113 chronic low back pain see back pain chronic pain vs ankylosing spondylitis, information processing bias 105 benign, childhood and adolescence, 2-y follow-up study 551 pain questionnaires 311
Coffman, L 425 cold sensation, master scaling 323 colored drawings of pain 213 complex regional pain syndrome (CRPS)
tobacco smoking reliability of diagnosis 259 treatment 43 type-I, radial fractures 457 connective tissue disease, millimetre wave therapy (MWT) 295 Cronbech, G 33

Damuni, D 485
de Vey, HCW 229 Delonge, MJL 507 del Angel, R 425 Dellman, PJ 381 dental scaling, video glasses vs nitrous oxide analgesia 49 depression, electroconvulsive therapy, and pain tolerance 419 diagnosis impact, ankylosing spondylitis vs chronic pain patients 105 interobserver reliability. complex regional pain syndrome (CRPS) 259
diclofenac, low-dose, episodic tension-type headache 155 Dipatra, PU 457 Dimovski, G 539 disuse and deconditioning, chronic low back pain 9 Dolberg, OT 419 dosage and plasma concentrations, lamotrigine 485 Downie, L 235 Drewes, AM 81, 539 drugs, adverse drug reactions (ADRs), patient reporting 219 Dufner, C 295

doi:10.1016/S1090-3807(03)00123-X
Egle, UT 113, 463
Eich, W 163
Eisenberg, F 485
electrical neuro modulation, refractory angina in syndrome X 507
electroconvulsive therapy, depression, pain tolerance 419
Elisson, T 235
endogenous substances, experimental muscle pain in humans 145
encephalin-inactivating enzymes, inhibition by RB101(S), (+)-HA966 (NMDA receptor antagonist) 241
Epicondylalgia, deep tissue pain in wrist extensors 277

Faura, CC 381
fear, back-stressing activities, attitudes towards pictures 33
Feldinger, E 419
fentanyl
animal models of nociception 121
transdermal, prescribing issues 481
fibronyalgia
arthritis self-efficacy short-form scale 163
childhood adversities 111
masking onset of autoimmune diseases 295
fibronyalgia syndrome, OT and PT therapeutic approaches 173
Flecken, PA 397
Formaglio, F 359
Fournier-Zaluzki, M-C 241
fractures, complex regional pain syndrome type I 457
Friel, J 561
Fruhstorfer, H 63, 73
Funch-Jensen, P 81
Garcia-Nicoa, E 345
Ge, H-Y 531
Geertzen, JHB 457
Gold, M 155
Goubri, L 33
Granot, M 139
Graven-Nielsen, T 93, 277
Gregersen, H 339
Grilla, A 131
Groothoff, JW 457
Gronhansen, L 419
(+)-HA966 (NMDA receptor antagonist), inhibition by RB101(S), animal models 241
Hagberg, L 225
Hagberg, P 213
Halldor, D 431
Hama, T 563
Holmsen, PM 203
hand muscle, motor evoked potentials suppression 55
Horsman, P 23, 267, 299, 353
Hovda, J 461
Harju, E-L 63, 322
Harmsma, M 163
Hattori, H 493
Hautvast, RW 507
Hazebroek-Kampscheur, AAM 551
headache, episodic tension-type, low-dose diclofenac 155
health-related QoL scores, somatofacial pain disorder 465
heat, synthetica, A-delta and C fibres 63
heat pain stimuli, phasic and tonic, sensory testing 139
heat sensation, master scaling 323
Herget, RF 289
Hermans, D 33
Heus, PH 9
HIV infection, painful and non-painful neuropathy 23
Hobson, AR 521
Hoffer, E 485
Hoffmann, VLH 121
Honda, T 493
Hunfeld, JAM 551
hypalgesia
multi-modal induction, human oesophagus 539
secondary, and presynaptic inhibition 345
hypalgesia, triggered by spatial summation, referred pain areas 531
Iliad, WK 381
Imbierowiecz, K 113
information processing bias, chronic pain vs ankylosing spondylitis patients 105
intestinal sensations, painful and non-painful, induction by hypertonic saline 81
Ionescu, E 155
ischaemic contractions, experimental pain vs intramuscular infusion 93
Ivergard, S 473
Jansson, Y 93
Javarsniripomkul, N 219
jaw muscle pain, muscle relaxants 449
Jensen, R 145
Jensen, TS 381
Jessurun, GJ 507
Johnson, MJ 181
Jonas, A 387
Kalao, E 381
Kanikten, PM 203
Kappis, B 463
Kerschbaumer, A 295
ketamine, potentiation of morphine, animal models of nociception 121
Klauser, A 295
Knutzenas, JA 9
Koes, BH 551
Kosek, E 251, 267
Kristensen, JD 93
Krivoy, N 485
Kriska, J 219
Kubitzek, F 155
Kwan, O 561
Lacerenza, M 359
Laird, JMA 345
lamotrigine, dosage and plasma concentration in sciatica 485
laser (CO2, U) stimuli, A-fiber pressure block effects 189
lateral epicondylalgia, model, deep tissue pain in wrist extensors 277
Le Gouel, S 241
Lee, DH 473
Leffler, A-S 267
Liden, Y 311
Linclomb roller 359
Linclomb, UF 63, 73
Linclomb, Ulf guest editorials 301–310
and spinal cord stimulation 365
tribute 269, 375
Liu, J-M 155
Ljunggren, AE 181
Lodge, D 473
López-Avila, A 425
Lundberg, L 251
Lyme neuroborreliosis 235
saline, hypertonic
  experimental vs intramuscular infusion (ischaemic contractions) 93
  induction of painful and non-painful intestinal sensations 81
Sanchez, S 459
Sarkar, S 521
Schipper, K-P 539
Schirmer, M 295
Schouten, J 225
Schreiber, S 419
Sciatica, lamotrigine 485
scopolamine, interruption of nociception-
  related memory acquisition 425
Seelen, HA 9
Segregnhol, M 93
segmental and plurisegmental modulation of static contractions, experimental muscle pain 251
sensation
  master scaling 323
  quantifying, allodynia 369
sensory analgesia, treatment of complex regional pain syndrome (CRPS) 43
sensory testing
  heat pain stimuli 130
  quantitative (QST), central pain 339
Shapiro, SC 419
Shiroda, M 493
Shraneel, D 419
Sim, J 173
Simpson, BA 513
skin sensation, human nociception, long-term depression 225
Slater, H 227
Solders, G 23
Sollevi, A 93
somatofomed pain disorder
  childhood adversities 113
  health-related QoL scores 463
somatosensory perception, long-term trapezius myalgia 267
Sonnerborg, A 23
spatial summation, triggering hypoalgesia 531
spinal cord injury 353
spinal cord stimulation, neuropathic pain 513
Sprecher, E 139
Stamp-van den Berg, SGM 259
Stroop interference, personalized pain words 431
Sugano, Y 493
Svensson, P 49, 55, 407, 449
syndrome X, refractory angina, electrical neuromodulation 507
synthetic heat, A-delta and C fibres 63
ten Duis, HJ 457
thermal sensitivity
  alterations in experimental muscle pain 73
  see also synthetic heat
Thompson, D 521
Tio, RA 507
tolperisone, post-exercise muscle soreness 407
touch sensation, master scaling 323
tramadol, and metamizol, interactions, animal models 439
transcutaneous electrical nerve stimulation (TENS), vs postoperative analgesia 181
trapezius myalgia, long-term, somatosensory perception 267
tricyclic antidepressants
  postherpetic neuralgia 1
  erratum 201
Tuveson, B 73
Ueda, M 493
Usichenko, TI 289
van der Wouden, JC 551
van de Heijden, GF 9
van Suiflekom-Smit, LWA 551
van de Vissche, AC 259
Vanderstraeten, G 33
Vehvilainen-Julkunen, KM 203
Verbant, JA 9
Vercammen, MP 121
video glasses, vs nitrous oxide analgesia, dental scaling 49
visceral pain, interactions of tramadol and metamizol, animal models 439
Vlaeyen, JW 9
Wang, K 449, 531
Weber, WEJ 259
Wells, HJ 105
Wenger, M 295
Wenzel, A 49
whiplash, late syndrome, (letters) 561, 563
Wiesendfeld-Hallin, Z 375
Wincent, A 311
Wright, A 277
wrist extensors, deep tissue pain (lateral epicondylalgia) 277
Yarmitsky, D 139
Zachariae, R 387
Zenz, M 381
Ziegler, G 155
Zusman, M 563
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EFIC was formed by the Presidents of the European Chapters of the International Association for the Study of Pain (IASP) at a meeting held during the 7th World Congress on Pain in Paris in August 1993.

Aims

These are in general those of IASP, i.e. to promote research, education and the clinical management of pain. The specific aim is to create a forum for European collaboration on pain issues and to encourage communication at a European level between IASP Chapters, and also with other bodies interested or involved in the fields of pain research and therapy such as the European societies or federations of medical specialities (anaesthesiology, neurology, headache, palliative care, etc.), institutions of the European Community, European and national educators and legislators.

Constitution

The affairs of EFIC are conducted by its Council, which consists of the Presidents of the European IASP Chapters, and five elected officers who form the Executive Committee. The Council meets once a year while the Committee manages affairs between meetings. EFIC is being established as a charitable foundation in Belgium.

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