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Lamotrigine for intractable sciatica: correlation between dose, plasma concentration and analgesia

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Abstract

An open trial was conducted to study the potential efficacy of the antiepileptic agent lamotrigine in relieving the sciatic pain and the relationship between lamotrigine dosage, plasma concentration and the clinical response. Subsequent to a 1 week washout period from previous analgesics, lamotrigine dose was titrated on a weekly basis from 25 to 400 mg/day and was maintained at that dose for additional 4 weeks. Spontaneous pain, the Short Form McGill Pain Questionnaire (SFMPQ), the Straight Leg Raise (SLR) test, and range of motion of the lumbar spine (leaning forward, to the affected side) were used to assess lamotrigine efficacy. Lamotrigine plasma concentration was tested at the end of each week during the titration period and at the end of the study. Fourteen patients were enrolled in the study. All outcome measures improved compared to baseline during the titration period, but reached a statistically significant level of improvement only at the 400 mg dose. A linear correlation was found between mean lamotrigine dose, mean plasma concentration and mean weekly spontaneous pain, mean SLR and mean bending the affected side, but not with the SFMPQ score. Study results suggest lamotrigine is a potentially effective and safe compound for the treatment of painful lumbar radiculopathy, and that it is likely to act in a dose- and plasma concentration-dependent fashion.

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Keywords: Radiculopathy; NMDA; Hyperexcitability; Anticonvulsants; Neuropathic pain

1. Introduction

It is traditionally believed that the radiating pain of sciatica results from mechanical compression on one or more nerve roots by a herniated lumbar disk (Goebert et al., 1961), or from chemical irritation by substances, such as phospholipase A-2, emanating from the herniated nucleus pulposis (Goupille et al., 1998; Saal et al., 1990). The treatment of sciatica is therefore, usually aimed at the reduction of compression by surgery and physical therapy, and of inflammation by injection epidural steroids.

Abundant evidence has accumulated over the past several years indicating that abnormal neural firing is a principal cause of neuropathic pain (Devor, 1995). Spontaneous activity was found in sensory neurons (Liu et al., 2001) and in dorsal horn neurons of rats with experimental peripheral neuropathy (LaMair and Bennett, 1993). Furthermore, there is now evidence that excitatory amino acids, particularly glutamate, play a key role in dorsal horn spinal hyperexcitability by acting at the NMDA receptor (Dickenson and Sullivan, 1987; Dubner and Ruda, 1992).

Lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] is a novel antiepileptic agent with at least two antinociceptive properties: it stabilizes the neural membrane through blocking activation of voltage-sensitive sodium channels and it inhibits the pre-synaptic...
release of glutamate (Cheung et al., 1992; Leach et al., 1986).

Several open studies in humans have suggested that lamotrigine may reduce painful diabetic neuropathy (Eisenberg et al., 1998), trigeminal neuralgia (Lunardi et al., 1997), symptoms of complex regional pain syndrome type 1 (McCleane, 2000) and chronic refractory neuropathic pain of mixed etiologies (Devulder and DeLaat, 2000). Painful HIV-associated neuropathy and diabetic neuropathy have been relieved by lamotrigine but not by placebo in recent controlled trials (Eisenberg et al., 2001; Simpson et al., 2000). In spite of this emerging evidence, no attempts have yet been made to test this drug in patients with sciatica, and only minor efforts have been made to establish the concentration-response profile of lamotrigine in painful conditions (Lunardi et al., 1997).

Lamotrigine is absorbed rapidly and completely from the gastrointestinal tract, it is approximately 55% bound to plasma proteins and has a volume of distribution of about 1.1 L/kg (Yuen and Peck, 1987). The drug is extensively metabolized by conjugation with glucuronic acid. Lamotrigine elimination half-life is 25–30h (Perruca, 1993). The pharmacokinetic profile appears to be linear and kinetic parameters after multiple dosing are similar to those observed after a single dose. Because of the wide variability in lamotrigine kinetics caused by interaction with concomitant medications, monitoring serum lamotrigine concentrations could be theoretically useful in clinical practice (Perruca, 1993).

The present study was therefore, aimed to (1) test the analgesic efficacy of lamotrigine in patients with sciatica in an open trial fashion and (2) to study the relationship between dose, plasma concentration and clinical response.

2. Material and methods

2.1. Subjects

The study population consisted of patients with sciatica who were referred primarily by orthopedic surgeons to the Pain Relief Unit in Rambam Medical Center, Haifa, Israel, for pain control. Consecutive patients aged 18–75 were enrolled in the study upon meeting the following criteria: (1) Painful lumbar radiculopathy of 12–26 months duration with an intensity of at least 3 on a numerical scale of 0–10. Patients who were unlikely to recover spontaneously (pain duration of more than 12 months), or those who had had pain for many (>3) years and were unlikely to respond to any single intervention, were excluded. (2) Presence of a herniated disc, as per imaging studies (CT; MRI) correlating with the clinical picture in terms of level and side. Subjects with a history of cardiac disease, epilepsy, or impaired renal or liver function were excluded. A written informed consent was obtained from all patients. The study was approved by the hospital’s Ethics Committee.

2.2. Design

The study consisted of three phases: (1) a 1 week washout period from previous analgesics; (2) a 6 week titration period in which lamotrigine treatment was initiated at a dose of 25 mg daily, and was doubled on a weekly basis up to 400 mg/day. With the exception of the first week of treatment, the dose schedule for the remainder of the study was twice daily (morning and evening). The regimen of gradual dose increments was chosen to avoid the occurrence of adverse drug reactions (Goa et al., 1993); and (3) a period of 4 weeks in which patients were maintained on the dose of 400 mg/day. Following this period lamotrigine was discontinued. During the 11 weeks (the entire study period) patients were allowed to use rescue doses of simple analgesics.

2.3. Pain measurements

Patients were required to keep a record of their daily lamotrigine consumption, and of their pain level on a 0–10 Numerical Pain Scale (NPS) (Jensen and Karoly, 1992) twice daily. The weekly average of the NPS was regarded as the primary outcome measure. Nine office visits were held throughout the study period, in which spontaneous pain was measured with the use of a 10 cm blank Visual Analogue Scale (VAS) (Price et al., 1983) and by the Short Form of the McGill Pain Questionnaire (SFMPQ) (Melzack, 1975). The Straight Leg Raise (SLR) test was used to measure evoked sciatic pain with a manual goniometer. The angle at which the patient reported an increase in his or her pain as a result of the maneuver was recorded. Range of motion of the lumbar spine (leaning foreword, to the affected side) was also measured with a manual goniometer. Neurological examination was performed, blood sample for lamotrigine plasma concentration was drawn, and safety evaluations was conducted and included assessment of adverse effects, compliance with drug administration, and use of concomitant medications, at each visit.

2.4. Lamotrigine plasma levels

Patients were requested to come to the laboratory for blood sampling at 7.30 a.m. and administered not to take their morning medication. Lamotrigine was determined in human serum using a reversed phase HPLC technique with UV detection following liquid/liquid extraction of the pH 10.3 buffered sample with dichloroethane and incorporating methoxyccaramazapine as internal standard (Cardiff Bio analytical Services Cardiff, UK) The reference lamotrigine blood concentration range was
1–15 mg/L. The LOQ (limit of quantitation) level for this technique was 0.75 mg/L.

2.5. Statistical analysis

Statistical analysis was performed with SAS (SAS Institute, North Carolina, USA). Weekly visit measurements (VAS, SFMPQ, SLR and range of motion), were analyzed by repeated-measures ANOVA. Comparisons of the baseline visit (visit 2) to each subsequent visit were performed with Tukey–Kramer HSD test. All P values reported by these procedures were further protected by Bonferroni adjustments. Daily NPS were averaged across weeks and analyzed in a similar way. In this case the baseline week (week 0) was compared to all subsequent weeks. Pearson correlation studies were performed when indicated, P-value was considered significant at the 0.05 level. Data are presented as means ± SEM.

3. Results

3.1. Subjects

Treatment with lamotrigine was initiated in 14 patients (Table 1). Eight subjects completed the titration period, seven of them completed the entire treatment period. Six patients failed to complete the titration phase. One (number 9) left the study during the first week of treatment due to diarrhea. Two left the study after taking only 25 mg of lamotrigine, one (number 7) due to dizziness and one (number 10) for no specific reason. Two subjects left at the end of the 50 mg treatment dose, one (numbers 8) due to difficulties with traveling to the clinic and the other (number 13) for personal reasons. Subject number 14 withdrew from the study at the end of the 100 mg dose also for personal reasons. Of the remainder eight, one completed the titration phase but did not enter the last phase of the study due to lack of efficacy (patient number 6).

Data regarding lamotrigine efficacy refers to 13 subjects who received at least one week of drug treatment and in whom lamotrigine plasma concentration was available. There were 4 men and 9 females. Their median age was 47 (range 24–73 years). The median duration of their symptoms was 10.7 (range 2–37 months). The most common radiculopathy was at the L5 dermatome in 10 patients, 7 at the L4 dermatome, 5 at the S1 dermatome and four at the L3 dermatome. It is noteworthy that all patients had well-characterized sciatica and had no other types of pain. All patients had previously been treated for their painful radiculopathy either with analgesics, opioids, epidural steroid injections or surgery.

3.2. Pain measurements

The mean weekly NPS was before treatment, which was the primary outcome measure was 7.6 ± 1.5. The mean spontaneous pain intensity (VAS) at the office visit subsequent to the washout period (baseline) was 7.9 ± 1.5. The baseline SFMPQ score was 15.1 ± 7.1. The baseline SLR in the affected limb was 34 ± 12 degrees, and the baseline ranges of motion were: leaning forward 46 ± 19 degrees; leaning towards the affected side 30 ± 12 degrees and towards the contralateral side 30 ± 10 degrees.

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<th>Table 1</th>
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NSAID, non-steroidal anti-inflammatory drug; ESI, epidural steroid injection; PT, physiotherapy; AP, acupuncture; OP, opioids; Sur, surgery; SCS, spinal cord stimulation.

* Not included in the analysis.
Figs. 1A–C show the effect of lamotrigine on spontaneous pain. Mean spontaneous pain (NPS) dropped from baseline of 7.6 ± 1.5 to 5.5 ± 1.8 at the end of the titration period and to 4.5 ± 1.8 after 4 weeks of treatment with 400 mg of lamotrigine (Fig. 1A). Similarly, the VAS dropped from 7.9 ± 1.5 to 5.2 ± 2.3 and to 4.1 ± 2.5 (Fig. 1B), and the SFMPQ score from 15.1 ± 7.1 to 11.2 ± 9.6 and to 5.8 ± 4.4 (Fig. 1C). Improvement was also noted in the SLR and in the range of motions of the lumbar spine (Figs. 2A–C). The mean SLR has improved by 13 degrees, bending forward by 16.7 degrees and bending towards the affected side by 11.6 degrees. It should be noted that all measurers have reached a significant level of improvement compared to the baseline values, only at the 400 mg dose, both at the end of the titration period and at the end of the maintenance-dose period.

When judged according to the primary outcome measure (NPS), two patterns of response were observed in the eight subjects who completed the titration phase: a 'non-responding' subgroup of 2 patients (numbers 6 and 11) in whom no change in NPS was found (less than 1 point of improvement), and a 'responding' subgroup of 6 patients in whom NPS decreased substantially from baseline of 6.7 ± 0.7 to 4.7 ± 0.5 at the end of the titration period, and to 4.0 ± 0.5 after 4 weeks of treatment with 400 mg of lamotrigine. Regardless of not being a baseline measure, it is noteworthy that the consumption of rescue analgesics for the whole group dropped from a mean of 3.5 ± 2.7 pills during the baseline week to 2.2 ± 1.8 during the last week of the study.

3.3. Lamotrigine plasma levels

A total of sixty-two plasma lamotrigine levels determinations were performed according to the pre-established schedule. The median lamotrigine plasma levels were 1.0 mg/L (range 0.44–1.4), 0.93 mg/L (0.31–1.1), 2.2 mg/L (0.75–2.4), 4.4 mg/L (2.3–6.7), 4.1 mg/L (1.5–5.6) and 6.2 mg/L (2.1–8.3) for the daily dosages of 25, 50, 100, 200, 300 and 400 mg, respectively. A linear correlation was found between daily lamotrigine dose and mean plasma concentration ($r^2 = 0.951; p = 0.001$) (Fig. 3). It should be noted that the lamotrigine plasma concentrations of the 2 'non-responders' (numbers 6 and 11), at 400 mg dose were 5.23 and 6.30 mg/L, respectively.

Lamotrigine concentrations correlated with the mean weekly pain diary (NPS) ($r^2 = 0.945; p = 0.001$), mean pain intensity (VAS) ($r^2 = 0.94; p = 0.001$), mean SLR ($r^2 = 0.919; p = 0.003$) and mean bending to the affected side ($r^2 = 0.816; p = 0.014$), but neither with the SFMPQ score nor with forward bending (see Fig. 4).

3.4. Adverse events

A total of 4 adverse events were recorded. Three patients complained of dizziness, one (number 7) at the 25 mg dose, one (number 14) at 100 mg, and one
Fig. 2. The effect of lamotrigine on pain (Mean ± SEM), evoked by SLR (A), bending forward (B), and bending towards the affected side (C). *p < 0.05, 400m = after 4 weeks of 400 mg maintenance dose.

Fig. 3. Correlation between daily lamotrigine dose and mean plasma concentration.

(number 6) at 400 mg. One patient (number 9) developed diarrhea upon treatment initiation. All 4 patients left the study prematurely and their adverse events completely resolved within a few days following the discontinuation of treatment.

4. Discussion

In this open-trial on 14 patients with intractable sciatic pain, lamotrigine produced dose-related improve-

ment in spontaneous pain, as well as in the mechanical range of lumbar motion. This improvement seems to be dose- as well as plasma concentration-dependent. While it is clear that only randomized controlled trials can clearly demonstrate efficacy of a drug, the present results strongly suggest that lamotrigine is effective in painful radiculopathy.

The analgesic effect has reached statistical significance at lamotrigine daily dose of 400 mg/day. It is possible that a larger patient population would have allowed statistical significance at lower doses (e.g., 200–300 mg). Yet, similar dosage of lamotrigine was suggested as efficacious in several other trials of diabetic neuropathy (Eisenberg et al., 2001, 1998), complex regional pain syndrome type 1 (McCleane, 2000), painful HIV-associated neuropathy (Simpson et al., 2000) and chronic refractory neuropathic pain of mixed etiologies (Devulder and Delaat, 2000). The only exception to that is trigeminal neuralgia, which seems to respond to lower dosages of lamotrigine, at least in some patients (Lunardi et al., 1997). Even though the majority of patients with various types of neuropathic pain benefit from lamotrigine at daily dose of 300–400 mg, a group of ‘non-responding’ patients have been identified in several previous studies (Eisenberg et al., 2001, 1998). In the present study, two such ‘non-responding’ patients were also identified. It is possible that increased titration of the dose can still be effective in these patients, but it should be noted that a superior analgesic effect of higher lamotrigine doses has not been confirmed yet by controlled clinical trials.
The average degree of pain relief found in the present study directly correlated with the lamotrigine daily dose and with the drug plasma concentrations. This was observed in each of the six 'responding' patients as well as in the entire group. In their study, Lunardi et al. (1997) found similar relationship within single patients with trigeminal neuralgia, but not within the entire group. These authors reported that 'similar amounts of pain relief were achieved with a wide range of plasma levels', and for that reason they felt that 'it is not possible to suggest either an optimum dosage or plasma level that should be attained'. The results of our study seem to differ in this regard and may suggest that median plasma concentration of 6.2 mg/L is likely to be efficacious in the majority of patients with painful lumbar radiculopathy.

The pathophysiology of sciatica is not fully understood and the role each of the main suggested underlying mechanisms – nerve root compression and inflammation – plays in the pathogenesis of the sciatic pain has not been clarified yet (Goupille et al., 1998; Mixter and Barr, 1934; Thelander et al., 1992). However, it is generally accepted that abnormal neural firing is a principal cause of nerve injury-induced pain (Liu et al., 2001), and that glutamate plays a key role in dorsal horn spinal hyperexcitability by acting at the NMDA receptor (Dickenson and Sullivan, 1987; Dubner and Ruda, 1992). Thus, the rational for using anticonvulsants, and specifically lamotrigine, in the treatment of sciatica is clear solid. Interestingly, a recent survey in the US (Cluff et al., 2002) indicated that anticonvulsants consist of the third most commonly used class of medications in the treatment of radiculopathy (preceded only by NSAIDs and opioids), yet clinical trials showing the efficacy of anticonvulsants in this condition are lacking.

It is important to note that the time course of lamotrigine treatment also seems to bear importance, as the analgesic effect becomes more profound after prolonged treatment with a steady dose. This observation is interesting from several aspects: (1) From the clinical
standpoint, it may suggest that prolonged maintenance before dose titration should become the standard clinical practice. This way an analgesic effect can possibly be achieved with lower lamotrigine dose and fewer adverse events. (2) From the pathophysiology point of view, it can imply that the reversal of nociceptive neurons hyperexcitability is an extended process, which requires a long treatment period (far beyond the time necessary to reach steady plasma concentration). (3) This finding increases the reliability of the study by reducing the chance that the reported pain relief can be attributed to a placebo effect.

Lastly, this study can be criticized for being an open trial. It is true that only a randomized controlled trial can provide clear evidence for efficacy. We therefore, propose that these results should be interpreted as ‘suggestive’ only, and not regarded as a ‘proof’ for the efficacy of lamotrigine in the treatment of sciatica. A second point for criticism is the relatively high dropout ratio, which can hamper the interpretation of the results. However, a careful observation of the reasons for leaving the study prematurely shows that only two subjects left the study because of adverse events and one due to lack of efficacy. Furthermore, most patients left the study at its early stages, before either efficacy or in contrast, adverse effects, are usually reported with the use of lamotrigine in the treatment of neuropathic pain (Devulder and DeLaat, 2000; Eisenberg et al., 1998, 2001; McClean, 2000). We believe that these observations can reduce the concerns about the interpretation of the study results raised by the high dropout ratio.

In conclusion, the present open study provides for the first time data suggesting that lamotrigine is a potentially effective and safe compound for the treatment of painful lumbar radiculopathy. It is likely that lamotrigine acts in a dose- and plasma concentration-dependent fashion.

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References


Nerve terminals extend into the temporomandibular joint of adjuvant arthritic rats

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Abstract

The innervation of the temporomandibular joint (TMJ) has attracted particular interest because of the close association with complex mandibular movement. Although the pathological changes of disk innervation may have a crucial role in the development of TMJ pain, the innervation of the TMJ disk by experimentally induced arthritis has rarely been examined in detail. Arthritic rats were induced by injection with 0.1 ml solution of Complete Freund's adjuvant (CFA). We investigated three-dimensional distribution of nerve fibers in the TMJ disk using immunohistochemistry for protein gene product-9.5 (PGP-9.5) and calcitonin gene-related peptide (CGRP) in naive and arthritic rats. To clarify the possible role of nerve growth factor (NGF) and its receptor on changes in peripheral innervation of the TMJ, the expressions of trkA and p75 receptor in trigeminal ganglia were examined. Although PGP-9.5 and CGRP immunoreactive (ir) fibers were seen in the peripheral part of the TMJ disk, they were not seen in its central part. The total length and the length density of PGP-9.5 ir and CGRP ir nerve fibers increased in arthritic rats. The innervation area of fibers proliferating in the rostro-medial part merged with that of fibers in the rostro-lateral part in the arthritic rats. In addition, the ratio of trkA- and p75-positive small- and medium-sized cells increased in trigeminal ganglia. It is assumed that increasing innervation of the TMJ disk may be important for the pathophysiology of TMJ pain. NGF and its receptors are likely involved in pathological changes of the TMJ disk.

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Keywords: TMJ disk; PGP-9.5; CGRP; Trigeminal ganglion; Complete Freund's adjuvant arthritis

1. Introduction

The temporomandibular joint (TMJ) consists of the temporal articular tubercle, the mandibular fossa in the upper part, and the mandibular condyle in the lower part. The TMJ disk is an oval plate of fibrous tissue, which completely divides the TMJ into its upper and lower parts. Many muscles in this joint produce complicated joint movements including depression, elevation, protrusion, retraction and lateral movement. These peculiar anatomical features of the TMJ indicate that the TMJ disk accepts various kinds of pathological stress in mobility. It is important to understand the physiological and pathological aspects of the TMJ, especially the innervation of the TMJ disk in patients suffering from temporomandibular joint disorders (TMD).

Previous studies reported various results regarding the innervation of the TMJ disk and the synovial membrane of the TMJ. Nerve fibers reportedly extended into the synovial villus and contacted the synovial cells of the TMJ disk in monkeys (Keller and Moffett, 1968). No nerve fiber was found in the synovial lining layer of the mouse TMJ disk (Dreessen et al., 1990), even at the electron-microscopic level. Virtually all morphological observations of the innervation of the TMJ disk have
been obtained from silver impregnation techniques. However, silver impregnation does not stain nerve fibers specifically (Fundin et al., 1995). Current immunohistochemical studies have served to identify the peptidergic innervation in the TMJ disk and its surrounding soft tissues. Substance P (SP)-like immunoreactive (ir) fibers exist in the joint capsule, disk attachment, and periosteum in monkey TMJ (Johansson et al., 1986). The central part of the TMJ disk contains no nerve fibers from postnatal days 0 through 24 (Shimizu et al., 1996). Although these studies have described the distribution of nerve fibers, the pathological changes of innervation over the whole body of the TMJ disk are still unclear.

Recent arthroscopic and histopathological investigations on painful TMJ in humans have demonstrated the occurrence of inflammatory reactions in synovial membrane (Murakami et al., 1991). Experimental models of arthritis have been available for clarifying the initial stage of the inflammatory process. Several studies have documented morphological changes in the synovial membrane (Nozawa-Inoue et al., 1998) or other periarticular tissues (Kapila et al., 1995; Kapila and Xie, 1998) of the TMJ following experimentally induced arthritis in animals. Other investigations have shown increasing concentrations of tachykinins or prostaglandins in the synovial fluid of the inflamed TMJ (Alstergren and Kopp, 1997; Appelgren et al., 1998; Carleson et al., 1997; Swift et al., 1998). Although these studies have described pathological changes in the TMJ and surrounding tissue, changes in innervation of the TMJ disk in experimental arthritis have not been extensively studied.

Nerve growth factor (NGF) is the prototypic molecule of the neurotrophin family of polypeptide trophic factors. NGF has been established as a required trophic factor for the differentiation and survival of sympathetic and some sensory neurons in the peripheral system (Barde, 1989). In addition to its effect on neuronal survival, NGF locally regulates the amount of axonal branching (Campaonet, 1987). For example, injury to tooth pulp often results in extensive sprouting of sensory nerve fibers at the site of wound repair in response to the local increase in NGF concentration (Byers et al., 1990; Byers et al., 1992). Increased expression of NGF has also been implicated in the nociceptive response (Dyck et al., 1997; Wheeler et al., 1998). When NGF was induced in the peripheral tissue, the NGF receptor (trkA and p75 receptor) on the membranes of responsive neurons would change in the peripheral nervous system. A recent study has indicated that trkA expression increased in the trigeminal ganglia innervated in injured teeth by retrograde transport of NGF (Wheeler and Bothwell, 1992).

In the present study, we investigated nerve distribution to clarify the changes under pathological conditions, and the overall features of innervation were examined in the TMJ disk of both naive and complete Freund's adjuvant (CFA) arthritic rats. In addition, to clarify the possible role of NGF and its receptor on changes of peripheral innervation in the TMJ, the expressions of trkA and p75 receptor in trigeminal ganglia were examined in the CFA arthritic rats. Characterization of this molecular system that mediates both repair and pain perception is important to develop novel clinical tools for promoting repair and relief of TMJ pain.

2. Methods

2.1. Animals

Twenty-five male Lewis rats weighing around 230 g were used in this study. Rats were exposed to a light-dark cycle (L:D 12:12-h) and kept in a temperature-controlled room (23°C). This study was conducted in accordance with the guidelines of the International Association for the Study of Pain (Zimmermann, 1983).

2.2. Complete Freund's adjuvant arthritis

Under anesthesia with inhalation of diethyl ether, twenty rats were intraeutaneously injected with 0.1 ml solution of CFA at both the parietal scalp and base of tail (Nozawa-Inoue et al., 1998). The adjuvant solution contained 6 mg of heat-killed Mycobacterium butyricum (Difco Laboratories, Detroit, MI, USA) in 1 ml of paraffin oil (Wako, Tokyo, Japan). After the injection, rats were given laboratory chow and tap water ad libitum in conventional laboratory conditions. Five nontreated naive rats weighing around 230 g were used as the control. Sequential changes in body weight, food, and water consumption were measured daily in five CFA-treated rats and five naive rats. Five rats each were sacrificed at 2, 3, 4 and 5 weeks post-CFA injection for immunohistochemistry of trigeminal ganglia. The immunohistochemistry was carried out for the TMJ disks and pain of five rats sacrificed at 5 weeks post-CFA injection.

2.3. Tissue preparation

Rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg, Nembutal, Abbot Laboratories, Chicago, IL, USA), and transcardially perfused with heparinized saline followed by a cold fixative containing 4% paraformaldehyde in 0.1 M phosphate buffer (PB, pH 7.4). Bilateral TMJ and trigeminal ganglia were immediately dissected out after perfusion, and immersed in the same fixative for 4 h at 4°C. The TMJ disk with its surrounding synovial tissues was carefully removed from the maxillary and mandibular bones. Post-fixed disks were rinsed with 0.1 M
phosphate-buffered saline (PBS) and dehydrated through an ascending series of ethanol (70%, 80%, 90%, 95%, 100%). Disks were then delipidized with xylene until they became transparent, and were rehydrated with a descending series of ethanol to PBS (pH 7.4).

To visualize the pathological changes after CFA treatment, tissues of TMJ in the naive and 5-week rats after CFA treatment were stained by Hematoxylin-Eosin.

Post-fixed trigeminal ganglia were kept in PBS containing 20% sucrose for cryoprotection. The specimens were then embedded in Tissue Mount (Chiba Medical, Japan) and stored until cryosectioning at −30°C.

The trigeminal ganglia were cut in the horizontal plane along the long axis of the ganglion on a cryostat at a thickness of 15 μm. Every twentieth section – approximately five sections per trigeminal ganglion – was chosen for each rat. In the trigeminal ganglia at 5-weeks post-CFA injection, the frozen trigeminal ganglia were serially cut. Sections were mounted on glass slides coated with chrome alum gelatin and dried at room temperature overnight.

2.4. Immunohistochemistry

2.4.1. TMJ disk

Anti-PGP-9.5 rabbit IgG against synthetic rat PGP-9.5 (Ultra Clone, UK) and anti-CGRP rabbit IgG against synthetic rat CGRP (Serotec, Japan) were used as a primary antibody. Each antibody was diluted at a concentration of 1:1000 in 0.1 M PBS containing 4% normal goat serum and 0.3% Triton X-100 (Sigma, St. Louis, MO, USA). Whole tissues of the TMJ disk were incubated in a solution of either anti-PGP-9.5 or anti-CGRP antisera for a week at 4°C.

After rinsing with 0.1 M PBS, all samples were reacted with biotinylated goat anti-rabbit IgG (Vector Laboratories, Burlingame, CA, USA) at a dilution of 1:200 in 0.1 M PBS for 2 h at 4°C. After rinsing with 0.1 M PBS, they were immersed in a solution of avidin and biotin-peroxidase complex (Vector Laboratories) at a dilution of 1:100 in 0.1 M PBS for 30 min at 4°C.

Disks were then immersed in PBS containing 0.1% 3,3'-diaminobenzidine dihydrochloride (DAB) (Sigma). Antigen-binding sites were made visible by adding 0.004% hydrogen peroxide. After staining, disks were treated with 0.05% osmium for 30 min at room temperature. As a control, the TMJ disk of another CFA arthritis rat was processed using rabbit serum without each primary antisera using the same process described above.

Immunoreactive fibers in the TMJ disk were manually traced, and reconstructed three-dimensionally by a light microscope-equipped, computer-aided imaging system (Neurolucida, MicroBrightfield, VT, USA). This system allows three-dimensional mapping of nerve fibers within thick TMJ disk while focusing and tracing fibers by using stage position encoders. The total length of ir fibers were automatically calculated by this system. The length density of nerve fibers was calculated by the formula: (total length of nerve fibers (mm)/area of TMJ disk (mm²)).

2.4.2. Trigeminal ganglia

For the immunohistochemistry of trigeminal ganglia, anti-trkA rabbit IgG against synthetic rat trkA (Chemicon International, Temecula, CA, USA), anti-p75 rabbit IgG against synthetic human p75 (Promega, Madison, WI, USA) were used after dilution at a concentration of 1:1000 in 0.1 M PBS containing 4% normal goat serum and 0.3% Triton X-100 (Sigma). Sections were reacted with either anti-trkA or anti-p75 antibodies for 3 days at 4°C. After rinsing with 0.1 M PBS, all samples were reacted with biotinylated goat anti-rabbit IgG (Vector Laboratories) at a dilution of 1:200 in 0.1 M PBS for 2 h at 4°C. After rinsing with 0.1 M PBS, the sections were immersed in a solution of avidin and biotin-peroxidase complex (Vector Laboratories) at a dilution of 1:100 in 0.1 M PBS for 90 min at 4°C. Then, the sections were immersed in PBS containing 0.1% 3,3'-diaminobenzidine dihydrochloride (DAB) (Sigma). Antigen-binding sites were made visible by adding 0.004% hydrogen peroxide. Diameters of the labeled cells were measured by a computer-aided imaging system (Neurolucida).

In the trigeminal ganglia at 5-weeks post-CFA injection, adjacent sections were stained with antibodies to trkA, CGRP or p75. Pairs of adjacent sections were assessed to determine double labeling of ganglion cells. The anti-trkA (Chemicon International), anti-p75 (Promega Corp) and anti-CGRP rabbit IgG (Serotec) were used for primary antibody after dilution at a concentration of 1:1000 in 0.1 M PBS containing 4% normal goat serum and 0.3% Triton X-100 (Sigma). Antigen-binding sites were made visible by the above method.

2.5. Statistical analysis

The results were expressed as means ± standard error (SEM). Results were analyzed by Student's unpaired t test, one-way ANOVA, or two-way ANOVA for repeated measures where appropriate, followed by Tukey’s test for multiple comparisons, if warranted. A P value of < 0.05 was considered significant.

3. Results

3.1. Body weight, food and water consumption

Polyarthritis was induced by CFA injection. About one week later, the elbow joints and ankles swelled, and became immobile. The rats in which CFA arthritis
showed no more body weight gain at about 250 g after CFA administration. In contrast to the arthritis group, naïve rats showed a continuous increase in body weight during the experimental period (Fig. 1A). Food intake of the arthritis group was significantly decreased after CFA treatment compared to the naïve rats (Fig. 1B). Also, water intake of the arthritis group was significantly lower than the naïve rats at 6, 12 and 18 days (Fig. 1C).

3.2. Observations of synovial membrane

Fig. 2 showed the synovial membrane of post-inflammatory features in arthritic rats.

In arthritic rats, a few lymphatic (arrowheads) or granular cells (arrows) were scattered throughout the subintimal synovial tissue. There was no infiltration by inflammatory cells, and no proliferation of the synovium. Increased fibroblasts (white arrowheads) and dense collagenous fibers (white arrows) were observed in the synovial membrane in the arthritic rats.

3.3. Macroscopic observations of TMJ disk innervations

Three kinds of nerve bundles were found to enter the TMJ disk. The deep temporal nerve entered the joint capsule at the rostro-lateral margin of the disk. The masseteric nerve entered at the rostro-medial margin of the disk, while a nerve bundle of the auriculotemporal nerve and its small branches entered the joint capsule at the caudal margin (Fig. 3). In specimens with whole-mount preparation, immunopositive nerve fibers were observed in the similar relation to the distribution of three nerves. The distributional overlapping and nerve origins in TMJ disk are identified by tracing nerve fibers in the carefully oriented disk.

3.4. Immunohistochemical observation

Although PGP-9.5 immunoreactive (ir) fibers were found in the rostro-lateral, rostro-medial, and caudal parts of the TMJ disk in naïve rats, they were not seen in the central part of the disk (Figs. 4A, B and 5A). The PGP-9.5 ir fibers took a meandering route in the rostral and caudal part of the disk, but in the medial and lateral part they showed different features; several nerve fibers forming nerve fascicles ran together and then branched off thin nerve fibers to the peripheral portion of the disk. In the medial and lateral part, on the other hand, the nerve fascicles were thin, consisted of a few fibers and branched out into a thin fiber plexus. Observations of the specimens processed immunohistochemically by whole-mount preparation methods revealed that fibers had no special terminals and showed free nerve endings.

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Fig. 1. Rat behavior following injections of complete Freund's adjuvant (CFA). Graphs showing changes in body weight (A), food intake (B), water intake (C). n = 5 for each group. Black point, CFA arthritic rats; White point, Naive rats. For statistical analysis, Student's t test and standard error were used. * P < 0.05.
In both naive and arthritic rats, nerve fibers were observed in the rostro-medial, rostro-lateral and caudal parts of the disk. In the naive rats there was no overlapping of the distribution area, whereas in the arthritic rats the proliferating fibers overlapped their distribution area (arrowheads in Fig. 5). The arthritic rats showed fiber extension toward the central part of the TMJ disk in comparison with the naive rats, in which the nerve fibers never extended to the central part of the disk (arrows in Fig. 5). The total length of PGP-9.5 ir nerve fibers increased from 80.9 to 98.1 mm in arthritic rats. Similarly, the length density increased from 9.8 to 11.8 mm/mm² (Fig. 6A).

Similar to PGP-9.5 ir fibers, the CGRP ir fibers were seen in the peripheral part of the TMJ disk (Figs. 4C, D and 7A). No fibers were observed in the central part of the TMJ disk. Nerve fibers meandered along the rim in the rostral and caudal parts of the TMJ disk. The distribution pattern of CGRP ir fibers was also similar to that of PGP-9.5 ir fibers. The nerve fascicles consisted of two or three nerve fibers and branched off into terminal fibers (Fig. 4C, D). Microscopic observation revealed CGRP ir nerve fibers to be thinner than PGP-9.5 ir fibers.

The length density of the CGRP ir fibers was smaller than that of the PGP-9.5 ir fibers (Fig. 6). Compared to those of the naive rats, the total length of CGRP ir fibers increased from 35.7 to 44.7 mm, and the length density increased from 4.3 to 5.4 mm/mm², as seen among the PGP-9.5 ir fibers in arthritic rats (Fig. 6B). The fiber distribution area in the rostro-medial part merged with that of the rostro-lateral part of the disk (Fig. 7).

3.5. Trigeminal ganglion

After the immunohistochemistry for trkA and p75 NGF receptors, immunopositive cells were stained dark or light brown in color and could be easily distinguished from the non-positive cells (arrowheads in Fig. 8). We arbitrarily classified the cell sizes according to the frequency distribution of the ganglion cells and data in the literature (Lee et al., 1985). The imaging system can measure cell size by tracing cells. TrkA- and p75-positive cells were found in varying percentages in the small to large cells in the trigeminal ganglia (Fig. 9).
After 2 weeks of CFA treatment, the trkA-positive cells strikingly increased to 9.2% in the small cell group (< 20 μm); they showed a consistently higher level than naive rats throughout the experimental period (Fig. 9). In the medium cell group (20–30 μm), trkA-positive cells significantly increased from 3 (8.8%) through 5 (9.9%) weeks after CFA injection. In the large cell group (> 30 μm), the ratio of trkA-positive cells slightly but significantly increased at week 4 (2.3%).

Similar to the findings of trkA-positive cells, p75-positive cells in the small cell group increased to 8.9% at week 2 after CFA injection, and kept increasing after week 5. The p75-positive cells increased at week 4 (8.4%) after CFA injection in the medium cell group. There was no change in ratio of p75-positive cells in the large cell group after CFA injection (Fig. 9).

In trigeminal ganglia at week 5 after CFA injection, there were CGRP-positive cells with trkA or p75 (Fig. 10).
4. Discussion

4.1. Assessment of CFA arthritic rats

Body weight and food intake decreased and water intake slightly decreased in the CFA-injected groups compared with the naive rats. Food intake was especially difficult for rats probably due to the pain of TMJ arthritis, whereas their water intake was less affected because only slight TMJ movement was required for drinking. The data suggested that the decrease in body weight, food and water intake correlated with the development of TMJ arthritis.

In our morphological study, we also confirmed that the arthritic rats had several changes in TMJ. In a clinical case, marked fibrosis and degenerative cartilage were observed (Kobayashi et al., 2001). In the monoarthritic TMJ induced by CFA injection into the superior joint space of the rats, a very active chronic inflammation developed.
CGRP-immunoreactive fibers

In the synovial membrane in the ankle joint of CFA polyarthritic rat, mononuclear cells infiltrated significantly (Wu et al., 2000). A previous report confirmed that the synovial membrane in polyarthritic rat showed enhanced vascularization in the sublining layer in the rostro-caudal portion of the synovial membrane at 3 weeks after CFA injection but no progressive inflammatory findings such as synovial hypertrophy or inflammatory cell infiltration in TMJ (Nozawa-Inoue et al., 1998). Our results were rather similar, except that a few lymphatic cells or granular cells were scattered throughout the subintimal synovial tissue.

4.2. Innervations of TMJ and TMJ disk

The TMJ was innervated caudally by the auriculotemporal nerve, rostro-medially by the masseteric nerve, and rostro-laterally by the deep temporal nerve (Kobayashi et al., 1994). In the present study, we have macroscopically confirmed that the disk was also innervated by the same nerves.

Some investigators have examined the innervations of the TMJ by silver impregnation techniques (Dreessen et al., 1990; Johansson et al., 1986; Wink et al., 1992). Nerve distribution in the disk has been variously reported, presumably depending on the technique used.

Current immunohistochemical studies have served to identify the peptidergic innervations in the TMJ disk and its surrounding soft tissues. We have focused on nerve fibers containing neuropeptides such as PGP-9.5 and CGRP in the joints using immunohistochemical methods. PGP-9.5 is a major protein component of the neuronal cytoplasm (Doran et al., 1983; Thompson et al., 1983), and is the most sensitive marker of nerve fibers (Dalsgaard et al., 1989; Gulbenkian et al., 1987; Maeda et al., 1994). CGRP is predominantly present in small and medium-size primary sensory neurons, and is a good marker of peripheral sensory nerve fibers (McCarthy and Lawson, 1990).

All of the innervations of the TMJ using antiserum to PGP-9.5 and CGRP in 18-day-old rat have been identified (Shimizu et al., 1996). Moreover, the distribution of CGRP ir fibers in the rat TMJ was investigated focusing in particular on the disk and synovial membrane by the whole-mount preparation method from the dorsal and ventral view (Kido et al., 1993). These reports provided a wealth of information on the nerve fibers in the TMJ, but the three-dimensional distribution and detailed innervation of the disk remain unclear. Nerve fibers were innervated toward the central part of the TMJ disk with complex meandering in the rostral and caudal parts, but with less meandering in the medial and...
lateral parts. The reason for the different nerve extension was suspected to be the variety of animal conditions in which the TMJ disk is forcefully expanded and contracted in the rostro-caudal direction by the movement of the TMJ. A dense innervation was observed in the rostral and caudal edges of the disk. The TMJ mainly moves in the rostro-caudal direction (Byrd and Chai, 1988). These innervation patterns may be important to receive sensory inputs to modulate the TMJ movement.

PGP-9.5 ir fibers were distributed more densely than CGRP ir fibers in the TMJ disk. This results suggested that PGP-9.5 positive- but CGRP negative-nerve fibers were innervating the TMJ disk. Previous studies indicated the existence of other peptidergic nerve fibers such as substance P (Kido et al., 1993), neuropeptide Y (Shimizu et al., 1996), tyrosine hydroxylase (Kido et al., 2001), and vasoactive intestinal polypeptide (Kido et al., 2001) in the TMJ disk. These fibers were suspected to be involved in metabolic function as well as nociception.

4.3. Increased innervation in TMJ disk

We studied innervation of TMJ disk 5 weeks after CFA. It was reported that substance P and CGRP extraction in the arthritic TMJ were increased 28 days after CFA injection (Carleson et al., 1997). Numerous
CGRP or PGP-9.5 immunoreactive fibers were observed on day 21 in tarsal joints (Imai et al., 1997). Compared with the naive rats, the total length and length density of PGP-9.5 and CGRP ir fibers increased in the arthritic rats. Although each fiber plexus of the rostro-medial, rostro-lateral and caudal parts are located separately on the disk in naive rats, the proliferated fiber plexus in the rostro-medial part merged with the rostro-lateral part of the disk in the arthritic rats. Fiber plexus of caudal part did not seem to be affected by arthritis. Further experiments were needed to clarify regional difference of increased innervation.

Compared to naive rats, nerve fibers were distributed in the central part of the TMJ disk of arthritic rats, and
the sprouted fibers coursed toward the central part of the disk. This fact suggested the possibility that some trophic factors promoted the nerve extension.

We explored the possibility that neurotrophic factors may have been involved in this plastic change of the nerve fibers. The inflammatory cytokines such as interleukin-1 (Kopp, 1998; Nordahl et al., 2001), interleukin-6 (Kubota et al., 1998), interleukin-8 (Nanki et al., 2001), and tumor necrosis factor-α (Fu et al., 1995) increased in peripheral tissue following CFA injection. Interleukin-1 and tumor necrosis factor-α also contributed to the secretion of NGF in peripheral nervous systems (Bennett et al., 1998; Carman-Krzan et al., 1991; Hattori et al., 1993; Koltzenburg et al., 1999; Lindholm et al., 1987; Oddia et al., 1998; Steiner et al., 1991). NGF promoted the sprouting of peripheral nerves (Albers et al., 1994; Kinkelin et al., 2000). CGRP fibers were shown to sprout in the peripheral tissue in inflammation (Weihe et al., 1988; Reinert et al., 1998). It was assumed that the sprouting occurred as a result of the infiltration of cytokines and neurotrophins in the peripheral tissue after inflammation such as TMJ arthritis.

The fibers sprouted toward the central part of the TMJ disk, and distributed on the surface of the disk in the arthritic rats. The trophic factor may intensively promote the sprouting of fibers on the surface of the disk. This factor supplied from synovial membrane may be kept in the synovial fluid contacting the disk. Inflammatory cells in the synovial membrane secreted NGF (Wu et al., 2000) and infiltrated the joint cavity with synovial fluid of arthritic rats. Previous studies reported that NGF increased in synovial fluid in arthritis (Aloe et al., 1992; Dicon et al., 1996; Falcini et al., 1996).

Neurotrophin-sensitized sensory neurons induced hyperalgesia (Shu and Mendell, 1999), and NGF-induced hypersensitivity by the sprouting of peripheral nerves in peripheral tissue (Bennett et al., 1998; Donnerer et al., 1992a; Donnerer and Stein, 1992b; Leslie et al., 1995; Wooff et al., 1997). With TMJ arthritis in the CIA arthritic rats, sensitization and hyperalgesia of sensory neurons reflectively induced behavioral changes such as lower food and water intake.

4.4. Up-regulation of trkA and p75 in trigeminal ganglia of CIA arthritic rats

The proportion of neurons with p75 and trkA was rather low in the present study compared to data reported in the literature (Kashiba et al., 1995; McMahon et al., 1994). From observing the specimens to determine strictly immunopositive cells, when no clear decision could be made, we opted for negative. Any difference may be explained by the variety of spinal levels or rat species.

We showed that expression of trkA and p75 increased in small and medium trigeminal ganglia neurons from weeks 2 to 5 after CFA injection. However, there is no evidence that the increase in expression of trkA and p75 among trigeminal ganglia neurons was directly related to arthritis of the TMJ per se. But it is proper that up-regulation of trkA and p75 in trigeminal ganglia related to arthritis of the TMJ since all of the sensory nerves innervating TMJ disk was originated from trigeminal ganglia. These facts suggest that small and medium neurons may be sensitive to NGF and that the sprouting fibers are mostly thin. We confirmed that the trkA- or p75-positive cells in the trigeminal ganglion are also CGRP-positive, which suggests the possibility that the sprouting CGRP fibers in the TMJ disk originated from trkA- or p75-positive cells in the trigeminal ganglia.

Earlier studies showed that trkA could be up-regulated after exposure to NGF (Goodness et al., 1997; Holtzman et al., 1992). NGF increased in the synovial membrane and synovial fluid after CFA injection, and was retrogradely transported to dorsal root ganglia (DRGs) (Goedert et al., 1981). Our result supported that the NGF receptor, trkA and p75 expression increased in trigeminal ganglia reacting to the transported NGF. However, some investigators reported a decrease in p75 in L3-L5 DRGs after CFA injection (Pezet et al., 2001). This difference may be caused by the variety of joints, spinal levels or rat species. We indicated that CFA arthritis increased NGF receptors in the trigeminal ganglia and had the potential ability to extend nerve terminals in the TMJ disk.

Expression of trkA and p75 at the TMJ disk is still unclear. The presence of these receptors on the sprouting fibers should be investigated in future.

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References


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


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Abstract

At present, there is no reliable antianginal drug therapy for patients with cardiac syndrome X. Therefore, the effect of electrical neuromodulation on refractory angina pectoris and myocardial perfusion in cardiac syndrome X was assessed. Eight patients (aged 55 ± 7 years) with heterogeneous myocardial perfusion and no esophageal abnormalities were included. The subjects were nonresponders to antianginal drug therapy. Angina pectoris attacks and myocardial perfusion dynamics were evaluated by positron emission tomography at baseline and following 4 weeks of (transcutaneous electrical nerve stimulation) TENS. Following TENS there was a reduction of angina pectoris episodes (baseline 20 ± 3, TENS 3 ± 1; p = 0.012), and short acting nitroglycerin intake per week (baseline 10 ± 3, TENS 2 ± 1; p = 0.008). The rate pressure product (mmHg min⁻¹) during the cold pressor test (CPT) was reduced during TENS (baseline 12800 ± 1200, TENS 11500 ± 900; p = 0.02). Following TENS, the perfusion reserve ratio between rest and dipyridamole flow increased (baseline 1.59 ± 0.15, TENS 1.90 ± 0.11 ml min⁻¹ × 100 g⁻¹; p = 0.05). The coronary vascular resistance had a trend towards a reduction (baseline 0.96 ± 0.04, TENS 0.85 ± 0.06 mmHg min⁻¹ × 100 g/ml; p = 0.06) during CPT. This observation may suggest that neurostimulation improves angina pectoris with a concomitant improvement of myocardial perfusion in cardiac syndrome X.

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Keywords: Neurostimulation; Syndrome X; Angina pectoris; Myocardial flow

1. Introduction

The cardiological “Syndrome X,” is used to denote the uncertain etiology of chest pain in patients with angina pectoris and a normal coronary angiogram (Kemp et al., 1986; Kaski, 1994). The demonstration of myocardial ischemia is a prerequisite for the diagnosis. However, commonly available diagnostic methods might fail to demonstrate ischemia, which may be related to the used tool or underlying mechanism of action (Kaski, 1994; Sheps et al., 1998). Cardiac syndrome X encompasses several causative factors such as restricted coronary vasodilator capacity, increased sympathetic tone, decreased pain threshold, abnormal endothelial function, esophageal abnormalities, behavioral abnormalities, and microvascular spasm (Cannon et al., 1992; Mohri et al., 1998).

The disabling chest pain in cardiac syndrome X patients is frequently unresponsive to conventional antianginal drug therapy. In a previous study it was shown that electrical neuromodulation is effective in patients with angina pectoris and normal coronary angiograms (Eliaison et al., 1993). Others found that the efficacy of electrical neurostimulation in these patients was not related to changes in epicardial coronary vasomotion (Norris et al., 1998; Sanderson et al., 1996).

In a positron emission tomography study (PET) it was shown that many subjects with cardiac syndrome X have a heterogeneous myocardial perfusion probably related to a patchy distribution inappropriate sympathetically mediated constriction of prearteriolar
vessels related to autonomic dysfunction (Meeeder et al., 1997). In addition, it was suggested that the mechanism of action of neurostimulation involves the autonomic control of the heart (Chauhan et al., 1994). Therefore, we postulated that in subjects with cardiac syndrome X, electrical neurostimulation may harbour a potential therapeutic response on the abnormal myocardial perfusion at rest and during cold pressor testing (CPT).

2. Methods

2.1. Study patients

Patients with syndrome X, typical angina pectoris, angiographically normal coronary arteries and heterogeneous myocardial perfusion were included. At baseline, after withholding vasoactive medication, clinical characteristics, continuous 24-h esophageal pH and manometric monitoring, and parametric positron emission tomography segmental myocardial perfusion measurements at rest, during CPT and after dipyridamole stress test (DST) were assessed. All patients are interviewed by a psychologist, which participates in the multidisciplinary neuromodulation group. Subjects with a depression were excluded. Other exclusion criteria were the use of antidepressants, antiepileptics or tranquilizer drugs. The study was approved by the Institutional Review Board. The subjects were included after written informed consent was obtained. Telephonic interviews were implemented to guide compliance.

2.2. Angina pectoris score and nitroglycerin intake

The frequency of anginal attacks was registered as number of episodes per week. The intensity of angina pectoris sensation was scored according to a visual analogue scale from 0 (no pain) to 10 (intolerable pain). The number of nitroglycerin tablets used per week was registered.

2.3. Esophageal test

In patients with abnormal manometric findings, the response of esophageal balloon dilatation was measured. Subjects with a positive balloon dilatation result were excluded. In patients with chest pain not related to gastroesophageal reflux, a Bernstein acid perfusion stress test was performed. Positive Bernstein test patients were excluded. Negative acid stress tests were included, if 4 weeks of antireflux-therapy had no effect on angina pectoris episodes.

2.4. Positron emission tomography study

An ECAT Siemens 951/31 camera (Siemens CTI, Knoxville, TN, USA) was used. This camera produces 31 simultaneous image planes with an axial length of 10.8 cm. Measured resolution of the system is 6 mm full width at half maximum. Each patient was accurately positioned in the camera image field with the aid of a rectilinear positioning scan. A transmission scan was obtained for tissue attenuation. Subsequently, dynamic imaging was started as a control study, simultaneously with the intravenous injection of 10mCi $^{13}$NH$_3$. Hereafter, the perfusion study was repeated with dipyridamole provocation and with cold pressor testing (Meeeder et al., 1997). Parametric polar maps of the resting and dipyridamole perfusion study were calculated as described previously (Blanksma et al., 1995). The following variables were calculated: resting perfusion, coefficient of variation, as a measure of perfusion heterogeneity, (Visser et al., 1998) perfusion during the CPT and DST. In addition, the perfusion response to both tests and the coronary vascular resistance was calculated. Coronary vascular resistance is a functional state of the coronary arteries in which a pressure gradient is present to ensure coronary flow. The perfusion reserve ratio is the ratio of the myocardial perfusion at rest and during a hyperemic condition. The cold pressor test is an autonomic reflex which is mediated mainly by sympathetic fibers and elicited by submerging the hand in cold water. The dipyridamole stress test is used to provoke ischemia. Dipyridamole induces vasodilatation, of which the final effect is more pronounced in the healthy than diseased arteries. This will result in a relative steal from diseased to normal regions and subsequently enhance flow differences for appropriate detection.

2.5. Procedures

After baseline PET measurements and evaluation of the pattern of angina pectoris, nonresponders to antianginal drug therapy were treated by 4 weeks of TENS. Hereafter, the clinical condition of the patient was reassessed by evaluation of the number of anginal episodes and PET measurements. During the PET study the TENS apparatus was off. Therapy with vasoactive agents, including calcium channel blockers, β-adrenergic blockers (reduced in two steps), and long acting nitrates were discontinued before the study.

2.6. TENS treatment

The patients were treated with conventional transcutaneous electrical nerve stimulation (TENS, Life Care, Hi Tec Para Medical Products; P.O. Box 2368, Givat Shmuel, Israel) 3 times per day during 1 h, by providing a continuous flow of symmetrical rectangular TENS biphasic pulses. The frequency of stimulation was 80 Hz, pulse-width 200 µs and the patient output 30–40 V. Carbon electrodes with adhesive gel were placed on the precordial area with referred anginal pain to elicit par-
esthesias within that area. Twenty-four hours before the study the stimulus parameters were individually tested.

2.7. Statistical analysis

A Wilcoxon matched-pairs signed-ranks test was used. All data are represented as mean with standard error of the mean. The \( p \) values are two-tailed. A \( p \) value \( \leq 0.05 \) was considered statistically significant.

3. Results

Ten patients were included in the study. Two subjects were omitted, one because of a protocol violation and one due to a technically inadequate second positron emission tomography scan by movement artefact. The clinical characteristics are shown in Table 1. The mean age of the patients was 55 ± 7 years. There were three males. All subjects had a normal left ventricular function with a left ventricular ejection fraction above 55%, and there were no past or current smokers. The episodes of angina pectoris per week were reduced (baseline 20 ± 3, TENS 3 ± 1; \( p = 0.012 \)), and the visual analogue scale showed a reduction of the intensity of pain sensation (from 7.5 [7–8] to 1.9 [1–3]). The use of short acting nitrates per week was less during TENS (baseline 10 ± 3, TENS 2 ± 1; \( p = 0.008 \)). The mean arterial pressure at rest did not change with TENS (baseline 89 ± 5 mm Hg, TENS 85 ± 3 mm Hg; \( p = 0.18 \)) (Table 2), however, there was a lower mean arterial pressure with TENS during the CPT (baseline 108 ± 6, TENS 101 ± 5; \( p = 0.03 \)). The mean arterial pressure was unaffected during the DST (87 ± 6 at baseline and 84 ± 4 during DST; \( p = 0.49 \)). The rate pressure product (mm Hg min\(^{-1}\)) was not altered with TENS at rest (baseline 9100 ± 1100, TENS 8300 ± 800; \( p = 0.39 \)) and during TENS with DST (baseline 11900±, TENS 1400 to 11100 ± 900; \( p = 0.33 \)). However, the rate pressure product decreased when TENS was applied during CPT (baseline 12800 ± 1200, TENS 11500 ± 900; \( p = 0.02 \)) (panel 1, Fig. 1A). Perfusion heterogeneity, expressed as coefficients of variation of segmental perfusion, was reduced during TENS at rest (baseline 17.6%, TENS 13.8%; \( p = 0.018 \)) and not during CPT (baseline 15.7 ± 2.8, TENS 14.5 ± 1.4; \( p = 0.88 \)) and DST (baseline 17.7 ± 1.9, TENS 18.9 ± 3.0; \( p = 0.73 \)) (panel 1, Fig. 1B). Following TENS the DST perfusion reserve increased (baseline 1.59 ± 0.15, TENS 1.90 ± 0.11; \( p = 0.05 \)) (panel 1, Figs. 1A and B). The coronary

Table 1
Clinical characteristics of the study group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Risk factor</th>
<th>Medication</th>
<th>Gastric pH</th>
<th>Med. Hist.</th>
<th>Yrs of AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f</td>
<td>57</td>
<td></td>
<td>Ca-a, Lan</td>
<td>Norm</td>
<td>Cholecystectomy, hypothyroidism</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>59</td>
<td>Ht, DM</td>
<td>Ca-a, Lan</td>
<td>Norm</td>
<td>Cystitis, nephro lithiasis</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>55</td>
<td></td>
<td>Ca-a, β-bloc</td>
<td>Norm</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>51</td>
<td></td>
<td>Ca-a</td>
<td>Norm</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>58</td>
<td>Ht, Chol</td>
<td>Ca-a, β-bloc</td>
<td>Norm</td>
<td>Hysterectomy</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>40</td>
<td></td>
<td>Ca-a</td>
<td>Norm</td>
<td>Hyperthyroidism</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>m</td>
<td>65</td>
<td></td>
<td>Ca-a, Lan</td>
<td>Norm</td>
<td>COPD</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>f</td>
<td>57</td>
<td></td>
<td>Lan</td>
<td>Path. refl.</td>
<td>Hysterectomy</td>
<td>4</td>
</tr>
</tbody>
</table>

f, female; m, male; Ht, hypertension; DM, diabetes mellitus; chol, hypercholesterolemia >6.50 mmol/L; pat. refl., pathological reflux; COPD, chronic obstructive pulmonary disease; Ca-a, calcium antagonist; β-bloc, beta blocker; Lan, long acting nitrate; yrs of AP, years of angina pectoris.

Table 2
Effect of TENS on mean arterial pressure, perfusion heterogeneity and myocardial perfusion

<table>
<thead>
<tr>
<th>Patient</th>
<th>MAP before TENS</th>
<th>MAP during TENS</th>
<th>CV before TENS</th>
<th>CV during TENS</th>
<th>Perfusion before TENS</th>
<th>Perfusion during TENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>81</td>
<td>13.6</td>
<td>11.3</td>
<td>100</td>
<td>103</td>
</tr>
<tr>
<td>2</td>
<td>101</td>
<td>95</td>
<td>21.1</td>
<td>16.5</td>
<td>111</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>87</td>
<td>86</td>
<td>11</td>
<td>11</td>
<td>94</td>
<td>103</td>
</tr>
<tr>
<td>4</td>
<td>92</td>
<td>95</td>
<td>18.8</td>
<td>15.9</td>
<td>127</td>
<td>105</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>77</td>
<td>13.6</td>
<td>13.5</td>
<td>119</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>72</td>
<td>12.1</td>
<td>12</td>
<td>72</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>103</td>
<td>86</td>
<td>17.5</td>
<td>12.5</td>
<td>182</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>90</td>
<td>33</td>
<td>17.8</td>
<td>126</td>
<td>124</td>
</tr>
<tr>
<td>Mean</td>
<td>89</td>
<td>85</td>
<td>17.6</td>
<td>13.8</td>
<td>116</td>
<td>100</td>
</tr>
<tr>
<td>SEM</td>
<td>5</td>
<td>3</td>
<td>2.5</td>
<td>0.9</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

Values are given in mean and standard error of the mean. MAP, mean arterial pressure in mm Hg; CV, coefficient of variation (%). Perfusion = mean myocardial blood flow in ml/min x 100g.
vascular resistance did not change during TENS either at rest (0.79 ± 0.04–0.86 ± 0.04; \( p = 0.26 \)) or during DST (0.50 ± 0.03–0.45 ± 0.02; \( p = 0.09 \)). During CPT the coronary vascular resistance had a trend towards a reduction (baseline 0.96 ± 0.04; TENS 0.85 ± 0.06; \( p = 0.06 \)).

Fig. 1. Panel 1: (A) The influence of TENS (T) on the perfusion ratio in relation to the rate pressure product (mmHg min\(^{-1}\)) (RPP) at rest (B = baseline), during CPT and DST. The squares represent DST and the circles CPT measurements. (B) The effect of TENS on coronary vasomotion is shown by the relation between the perfusion ratio and coefficient of variation (CV) at baseline, during CPT and DST. Panel 2: Parametric polar maps of myocardial perfusion in a patient with syndrome X treated with TENS. Each polar map represents the perfusion of the whole myocardium, the apex is located in the center, the anterior region (A) at the upper side, the lateral region (L) at the right side, the septal region (S) at the left side and the inferior region (I) at the lower side. Perfusion values are indicated by color values as can be seen in the color scale at the right of each polar map. The upper panels represent the situation before treatment, at the left the control situation and at the right the situation during cold pressor testing. The lower panels represent the situation during TENS treatment. It is shown that before treatment the perfusion is high and heterogeneous, and does not increase during cold pressor testing. During TENS resting perfusion is lower and more homogeneous, which indicates a lower oxygen consumption. During cold pressor testing there is a normal increase of myocardial perfus.

The compliance of all patients was confirmed by weekly telephonic interviews. All subjects were willing to continue TENS treatment. The most important limitation is an ortho-ergic skin reaction, which was not present in our study group. As TENS is not a predictor for the outcome of spinal cord stimulation, this modality
is not used for screening objectives at the University Hospital Groningen.

4. Discussion

This is the first clinical report which demonstrates a significant reduction of angina pectoris in conjunction with improved myocardial perfusion dynamics in a subgroup of patients with cardiac syndrome X. In this study the effect of electrical neurostimulation was evaluated in subjects with syndrome X and heterogeneous myocardial perfusion at rest and during CPT. A prior investigation showed that patients with syndrome X have a significantly higher resting perfusion than normal controls. Furthermore, the syndrome X patient group had a heterogeneous myocardial perfusion distribution at rest and during CPT. No differences were observed in the mean values of the CPT and DST perfusion reserves. Finally, 50% of syndrome X patients showed less increase of myocardial perfusion during CPT (Meeder et al., 1997). Based on these results, the main objective of the present investigation was to study the effect of TENS on the myocardial perfusion at rest and during CPT in patients with cardiac syndrome X.

Homogenisation of myocardial perfusion during TENS (panel 2, Fig. 1) in association with an improvement of anginal complaints in the study group may indicate a mechanistic effect at the microcirculatory level. The observed myocardial blood flow alterations with a concomitant reduction of angina pectoris in patients with syndrome X are compatible with earlier findings in another group of patients with chronic refractory angina pectoris caused by severe multivessel coronary artery disease unsuitable for revascularisation procedures (Hautvast et al., 1996; Mannheimer et al., 1998). Hautvast et al. suggested that the change in myocardial blood flow can be denoted as a steal phenomenon at the microcirculatory level. The observed dynamic perfusion changes during TENS support the assumption that the underlying cause in many patients with syndrome X is a patchily distributed inappropriate sympathetically mediated constriction of prearteriolar vessels related to autonomic dysfunction, with a concomitant local accumulation of adenosine sufficiently enough to stimulate cardiac efferent nerves (Rosano et al., 1994; Meeder et al., 1995; Di Carli et al., 1997). Whether this phenomenon is a central or peripheral disturbance of autonomic function is unknown. Previous investigations to unravel the role of the autonomic nervous system through analysis of heart rate variability during neurostimulation may suggest that this diagnostic tool is unable to elucidate a potential autonomic involvement (De Jongste et al., 1994; Andersen, 1998; Hautvast et al., 1998).

Contradictory results on the effect of neurostimulation on coronary flow velocity were unable to propose any firm conclusions on coronary hemodynamics (Chauhan et al., 1994; Sanderson et al., 1996; Norrrell et al., 1998). In a recent study, simultaneous coronary flow measurements in both branches of the left coronary artery showed that electrical neuromodulation causes a "reverse steal" phenomenon in the epicardial coronary circulation. This response leads to an increase of volumetric flow in the nonstenotic conduit artery and a reduction in the stenotic vessel of the left coronary artery (Jessurun et al., 1998). These findings give more insight into the precise mechanism of action of neurostimulation on the coronary circulation and suggest either a direct operating mechanism on epicardial coronary vasoconstriction or a secondary response to microcirculatory alterations. The final effect results in flow shifts rather than an increase in total flow through the epicardial and myocardial vasculature.

The slight not significant decrease of the coronary vascular resistance and increase of perfusion reserve during DST and TENS in the present report may support the clinical impression that neuromodulation reduces the microvascular resistance and subsequently induces a redistribution of myocardial blood flow (Blanksma et al., 1995). In addition, the reduction of the rate pressure product during sympathetic stimulation and a lower resting perfusion following TENS is compatible with the findings of Sanderson et al. (1996) and suggests a potential clinical effect on myocardial oxygen consumption.

However, the overall clinical effect of electrical neuromodulation results from an interaction of several peripheral and central mechanisms. Whether or not these are related to either an increase of supply or a reduction of myocardial oxygen demand has yet to be unraveled (Jessurun et al., 1998; Kim et al., 2002; Murray et al., 2002).

4.1. Study limitations

Although, the impact of the data is reduced by the small number of patients evaluated, the relatively short period of follow-up provided and the uncontrolled study set-up, these preliminary results encourage further clinical trials to ascertain the role of neurostimulation in the treatment of patients with cardiac syndrome X.

Despite the wide natural variation in PET perfusion, a small but significant improvement was found with a concomitant reduction of angina pectoris. Since earlier studies (Hautvast et al., 1996) with neurostimulation showed a beneficial effect on myocardial perfusion dynamics, our findings support the clinical impression of an operational link between electrical current and myocardial flow.

A cross-over design and variation of the TENS period may contribute in differentiating between a "honey-moon effect" or true TENS effect. The study group was
not imposed on a restriction of methylxanthinines such as coffee, tea, chocolate and caffeine containing soft drinks in the normal daily diet during TENS treatment. They refrained from these products 24h before the positron emission tomography study. This might have influenced optimal TENS performance and the present data (Marchand et al., 1995), such as the apparently unaffected coefficients of variation after TENS in patients 3, 5 and 6. It is impossible to conduct placebo-controlled trials with electrical neuromodulation, because there is no alternative for the paresthesias induced by the neurostimulator. Sham TENS does not provide regional paresthesias. The patient and doctor can not be blinded as the patients feels the paresthesias and doctor observes the electrocardiographic artefacts during stimulation.

In conclusion, the wide spectrum in the clinical presentation of cardiac syndrome X implicates that an accurate pathophysiological diagnosis in the individual subject should be established. Subsequently, this study demonstrates that amongst several treatment strategies, the management of subjects with cardiac syndrome X and heterogeneous myocardial perfusion, warrants the implementation of electrical neuromodulation.

References


were holistic and non-quantitative. In those assessments, benefit from SCS was judged as “significant” (SB, significant benefit), “moderate” (MB, moderate benefit) or NE (no effect) according to the reports of the patient and of partners and relatives, and to changes in medication, activity, etc. Some patients changed category over time, e.g., SB → MB, MB → NE. Patients are followed up long-term in our unit in a regular nurse-run stimulator clinic and by B.A.S. with face to face consultations. Waiting lists often preclude expeditious corrective surgery for internal malfunctions.

3. Results

A summary of the outcomes relative to the original protocol is given in Fig. 1. A reply to the original invitation to take part in the study could not be obtained from 12 patients. Twenty-nine (46%) of the remaining 63 agreed to take part. Of the 34 who declined, 10 were explicit that they did not wish to be without the benefit of their stimulators (previously assessed as 9 SB, 1 MB). Fifteen gave no reason for declining (previous assessment 8 SB, 2 MB, 1 NE, 1 SB → MB, 2 SB → NE, 1 MB → NE). Eight declined for a variety of reasons including: stimulation effective but very positional, rising impingement (but these two did not want corrective surgery), intercurrent illness and various other problems such as some loss of efficacy requiring surgery but which had not yet been corrected; one patient no longer required SCS (previous assessment 7 SB, 2 MB).

Of the 29 who consented, questionnaires were not received from 10 (7 SB, 3 MB). Four of these reported that they had posted them. A further three patients dropped out during the study through ill health (2 SB, 1 MB). Ten returned completed questionnaires but had failed to follow the protocol correctly (8 SB, 2 MB). Only six of the 63 (9.5%, or 20.6% of those consenting) completed the trial correctly (6 SB). The median time since implantation of these six was 42 (14–110) months and their median age was 54 years 10 months (50 years 6 months – 67 years 2 months). Overall, those consenting were previously rated 23 SB and 6 MB. Five of the original cohort were previously rated NE and these patients either did not reply (one) or declined to take part without giving a reason (four).

In addition to the written instructions, nine of those who agreed to take part had only postal-plus-telephone contact with one of the investigators (R.M.) and 20 were visited at home by him. Fourteen of the 16 who returned completed questionnaires had been visited at home compared with only six of the 13 who did not.

Five of the 10 participants who broke the protocol did so because they could not tolerate leaving their stimulators off, switching them back on during the “off” periods (4 SB, 1 MB). Four of these took significantly more analgesic medication when the stimulator was off. The man previously rated MB (moderate benefit) used his stimulator during 16 of the 28 “off” days and another could leave his off for only one day. Another used his during 18 of the 28 days “off” days and showed improvement in sleep ($p < .001$), activity ($p < .005$) and drug intake ($p < .008$) compared with the days when he did leave it off (SB). One lady used hers only when her pain intensity was high (SB). Another patient completed only the evening questionnaires (MB) and there was no significant difference in his pain scores between “on” and “off” periods. One patient in this group, a senior academic, sometimes left his off during the “on” periods (SB) and his scores showed no significant differences on any measure. Similarly, another used his stimulator on only two days (SB) and one woman did not use hers at all during the study despite agreeing to take part (SB).

Her results showed wide daily variation in VAS pain scores from 6/100 to 87/100 (mornings) and from 3/100 to 96/100 (evenings). Thus four patients previously assessed by the implantor as obtaining pain relief apparently did not, but one of these did experience a considerable improvement in bladder function. On the other hand, two patients rated as only MB would not, or could not, leave their stimulators off. The other 13 of the 15 who could not manage without SCS had previously been rated SB.

The results from the six who correctly followed the protocol (all SB) are summarised in Table 1. Although all had lower pain scores with the stimulator on (Fig. 2), none showed an improvement in activity levels and only one reduced his drug intake. Four demonstrated some improvement in sleep during periods of stimulator use. A diurnal variation emerged in some cases, two having more pain in the evenings with and without SCS (Fig. 3). The
average absolute reductions in VAS scores with SCS on were smaller in the mornings than in the evenings for five of the six patients. For the six patients the average additional pain when the stimulator was off compared with the stimulator on ranged from +9% to +71% in the mornings and from +18% to +58% in the evenings. (This represents a range of ‘average pain relief’ of 8–42% and 16–37% respectively; in Table 1 the results are expressed in this latter, more traditional, manner).

Of nine patients whose results could be analysed in these respects, including the six described above, three reduced their drug intake, one increased his activity levels and five had improved sleep during the periods of stimulator usage. Overall, 15 out of 51 would not, or could not, be without SCS and 9 of the 6 fully analysed cases benefited significantly, giving a minimum ‘success rate’ of 40% but a true success rate cannot be derived from the data available; a meaningful denominator cannot be derived.

Table 1
Results from the six patients who completed the study correctly

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pain levels higher any or pm</th>
<th>Average change in VAS pain score (mm/100)</th>
<th>Other outcomes with stimulator ON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stimulator ON mornings</td>
<td>Stimulator ON evenings</td>
</tr>
<tr>
<td>1</td>
<td>No</td>
<td>−12.8 (21%) p &lt; .001</td>
<td>−12.2 (19%) p &lt; .001</td>
</tr>
<tr>
<td>2</td>
<td>pain p &lt; .001</td>
<td>−15.3 (42%) p &lt; .001</td>
<td>−23.1 (13%) p &lt; .001</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>−9.1 (13%) p &lt; .02</td>
<td>−10.3 (16%) p &lt; .004</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>−9.5 (13%) p &lt; .05</td>
<td>−11.6 (16%) p &lt; .002</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>−3.7 (8%) NS</td>
<td>−7.3 (16%) p &lt; .04</td>
</tr>
<tr>
<td>6</td>
<td>pain p &lt; .001</td>
<td>−2.4 (28%) p &lt; .02</td>
<td>−12.0 (37%) p &lt; .001</td>
</tr>
</tbody>
</table>

Pooled results from two 14-day periods of abstinence from SCS compared with 22 days of normal SCS usage.

* Pain level very low in mornings – small absolute differences gives large percentage change.

Fig. 2. Twice-daily pain scores for one patient (#1, Table 1; amputation and phantom pain, finger and thumb) showing relatively modest but consistent effect of SCS.

Fig. 3. Twice-daily pain scores of patient #2 (Table 1; brachial plexus damage) showing lower pain scores during SCS and a marked diurnal variation in pain levels.

The diagnoses and usual stimulator usage patterns of the six who completed the trial correctly, of the 10 who declined to take part because they could not leave it off and of the five who broke the protocol for the same reason are given in Tables 2-4. All our patients are instructed not to use their stimulator for 24 h per day, to reduce the risk of developing tolerance.

4. Discussion

The authors are not aware of any previously published study which uses “abstinence methodology” to assess the outcome of SCS in neuropathic pain.

The patients in this study suffered from a variety of neuropathic pain syndromes and had been referred because of inadequate pain control by standard medical
Table 2
Diagnosis and SCS usage patterns of the six patients who completed the trial correctly

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Stimulator usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Phantom index finger and thumb and stump CRPS</td>
<td>All day; off at night</td>
</tr>
<tr>
<td>2 Brachial plexus damage</td>
<td>All day; off at night</td>
</tr>
<tr>
<td>3 CRPS I lower limb</td>
<td>Most of the day plus some nights</td>
</tr>
<tr>
<td>4 CRPS I lower limb</td>
<td>Several hours twice per day; off at night</td>
</tr>
<tr>
<td>5 FBSS</td>
<td>3 days per week for several hours</td>
</tr>
<tr>
<td>6 Post surgical pelvic pain</td>
<td>All day; off at night</td>
</tr>
</tbody>
</table>

CRPS I, complex regional pain syndrome type I (RSD); FBSS, failed back surgery syndrome.

Table 3
Diagnosis and usage patterns of the 10 patients who declined to take part because they did not wish to be without their stimulators

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Stimulator usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS I upper limb</td>
<td>All day except when driving</td>
</tr>
<tr>
<td>CRPS I lower limb</td>
<td>All day; off at night</td>
</tr>
<tr>
<td>CRPS I hand</td>
<td>All night; off all day</td>
</tr>
<tr>
<td>CRPS I lower limb</td>
<td>Several hours every day</td>
</tr>
<tr>
<td>Brachial plexus damage</td>
<td>All day; some nights</td>
</tr>
<tr>
<td>Phantom hindquarter</td>
<td>All day; off at night</td>
</tr>
<tr>
<td>FBSS</td>
<td>2-3 h, variable number of times in day</td>
</tr>
<tr>
<td>FBSS</td>
<td>Most nights and every day with several hours off</td>
</tr>
</tbody>
</table>

Table 4
Diagnosis and stimulator usage patterns of the five patients who broke the protocol by using their stimulators during the “off” periods

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Stimulator usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS I lower limb</td>
<td>All day; off at night</td>
</tr>
<tr>
<td>CRPS I lower limb</td>
<td>Most of the day; off at night</td>
</tr>
<tr>
<td>Brachial plexus damage</td>
<td>Approx 45 min, 3-5 times per day</td>
</tr>
<tr>
<td>Brachial plexus damage</td>
<td>Most of the day; off at night</td>
</tr>
<tr>
<td>Lower limb neuropathic 2° to spinal anaesthetic</td>
<td>All day; off at night</td>
</tr>
</tbody>
</table>

and interventional therapies. All were selected for SCS by one of the authors (B.A.S.) who was also the implanting surgeon. All implants included identical plate electrode systems. Patients were thoroughly counselled as part of the selection procedure but trial stimulation was not employed. Trial stimulation is not employed routinely in our unit on the grounds that it is not a reliable predictor of long term success and that the main criterion for “passing” a trial (50% reduction in VAS score) is flawed, which itself touches on the subject of the present study (Simpson, 1994, 1999). Furthermore, plate electrodes probably perform better than the percutaneous systems used for trial stimulation (North et al., 1999; Villavicencio et al., 2000).

A surprisingly small proportion of the original cohort who were approached (six out of 75) completed the trial correctly. As eight had various problems which precluded participation (and were either waiting for surgery or did not want surgery) and one no longer required SCS, these and the 12 from whom a reply to the first enquiry could not be obtained could be subtracted to give a true original cohort of 54. A further three could not be assessed because of intercurrent illness occurring during the study. Ten patients declined to take part because they did not wish to be without their stimulators for even two weeks. Although this is an acceptable endpoint, it deprives the study of data. The previous clinical assessment was that nine of these were enjoying significant benefit and one moderate benefit from SCS, suggesting a close correlation. Five of 10 patients who returned completed questionnaires but had broken the protocol did so because they could not tolerate being without SCS during the “off” periods and this is also an acceptable endpoint. Of these five, four were clinically rated “significant benefit” and one “moderate benefit”, again indicating concordance. The other five broke the protocol through simple misunderstanding or for reasons unknown. Personal home visits by one of the investigators greatly increased the yield compared with the use of telephone communication. However, a home visit did not prevent failure to follow the protocol in some cases.

Of the six who completed the study correctly, all had previously been rated “significant benefit”. However, although all recorded higher pain scores during the “stimulator off” periods, and it is this additional pain that is of interest in an abstinence study, when expressed in the traditional format of pain reduction with the stimulator on the average absolute difference in VAS scores was surprisingly modest in five of the six (Table 1). The former expression (additional pain with stimulator off) would obviously give a higher percentage change. The results from these six cases highlight the difficulty in setting standards and criteria for assessing the efficacy of SCS in chronic pain. An average percentage reduction in VAS pain score as low as 16% was highly significant statistically and occurred in three patients who were fulsome in their praise of the stimulator. In a prospective, multicentre study Burchiel and colleagues similarly found that a relatively low percentage reduction in average pain VAS score (14%) was highly significant statistically (Burchiel et al., 1996). A 50% reduction in the
VAS pain score is the usual standard for “success” but this has no inherent meaning and was rather arbitrarily adopted from drug trials in acute pain without validation of its application to chronic pain. Not only is there evidence that a lower score (30%) corresponds with a clinically meaningful degree of pain relief (Farrar et al., 2000, 2001) but also such notations are insufficient in isolation to gauge the effectiveness of treatment for chronic, complex conditions.

After the study, three from this group of six wrote letters. Patient #2 (Table 1) said he already knew that SCS was very effective, patient #3 said that he had found the periods without the stimulator very difficult but he had persevered and patient #4 said that prior to the study he had not realized just how good the stimulator was. The average percentage reduction in VAS scores of these three patients during SCS was 25% (mornings) and 22% (evenings). Clearly, changes on the VAS alone provide too limited a measure of outcome in this context and the interpretation of these changes is not fully established. Statistical and clinical significance are not necessarily the same. The duration of different levels of pain during the day is an important measure (Van Buyten et al., 2001) which was not captured by the present study. Two patients (#2 and #6) showed clear diurnal variation both in pain levels and in the effect of SCS (Fig. 3), further complicating the assessment of outcome of such treatments. Similarly, several patients showed day-to-day variation in pain intensity.

An attempt was made to enhance the assessment by rating functional changes and changes in medication. Although sleep improved in four, none recorded a significant change in activity levels and only one reduced his analgesic intake with SCS. The intervals used in this study (two weeks off and one week on) may have been too short to reveal changes in drug intake and activity levels in some of these long-term patients and the crude scoring system was probably inappropriate. Many of these patients are on long-term medication, e.g., gabapentin, that is not likely to be changed in the short term. The co-existence of other pains, including nociceptive, may also be relevant in some cases. One patient was proud of the fact that he had taken no medication for his neuropathic upper limb pain since the stimulator was inserted eight and a half years earlier. The incorporation of a more comprehensive verbal assessment both by the patients and by a partner, relative or friend would probably have added greater value to the evaluation.

Further (circumstantial) evidence for a correlation between the study outcome and previous clinical assessment comes from the five patients deemed clinically to be obtaining no benefit from SCS: one did not reply and four declined to take part without giving a reason. No patients rated NE were found to be obtaining pain relief. Overall, in patients other than the six whose results could be analysed in detail, the previous clinical assessment of outcome (significant benefit, moderate benefit or no effect) was validated by the results of this study. From the questionnaires returned, three patients previously rated “significant benefit” and one “moderate benefit” appeared to obtain no pain relief but one had been rated SB because an improvement in bladder function which was induced by SCS had been extremely valuable to him, enabling him to work normally. Clearly some patients give a misleading impression to an involved clinician and it has become increasingly accepted that assessment by a disinterested third party is superior (North et al., 1993; Kupers et al., 1994; Van Buyten et al., 2001). However, in addition to the present study, there is some evidence that assessment by an involved clinician does have validity (Koeze et al., 1987) but such assessments must be interpreted with caution and there are clear examples of inaccuracy.

From our experience with this preliminary study we would propose that the following might increase patient compliance and improve the power of this methodological approach:

- Conduct all recruitment interviews face to face rather than by telephone.
- Reduce the length of the periods when the stimulator is off to one week or even three days. Two weeks is clearly excessive.
- Increase the verbal rating element of the assessment – of the pain and of functional and quality of life factors.
- Employ a more relevant and sophisticated evaluation of changes in sleep, activity and medication. A simplistic rating is particularly inappropriate for activity and medication changes in this group of patients, especially in the short term.
- Include a third party (partner, carer, etc.) assessment where possible.

In conclusion, the present study does not permit an overall “success rate” to be calculated but uses a novel methodological approach to demonstrate a positive effect of SCS on neuropathic pain. It highlights the complexity of such assessments of outcome and generally validates the clinical rating of an involved assessor but with some clear exceptions which deserve further study. While operational shortcomings in the present study yielded a relatively low return, it is proposed that the principle of the methodology employed may provide a useful tool which strengthens the assessment of outcome of SCS in patients with neuropathic pain.

Acknowledgements

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References


Psychological responses to episodic chest pain

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Abstract

Patients with chronic musculo-skeletal pain have been profiled as 'dysfunctional', 'interpersonally distressed' or 'adaptive copers'. The relevance of these for episodic visceral pain is unknown. Our aim was to replicate conceptually the taxonomy in patients with episodic visceral pain. Patients with chest pain and gastro-esophageal reflux disease (GERD; n = 25), coronary artery (CAD; n = 20), or with chest pain but without either reflux or coronary artery disease (non-cardiac chest pain – NCCP, n = 23) were assessed using several standard affective and cognitive measures relevant to pain. Differences between the diagnostic groups were explored. K-means cluster analysis broadly replicated the groups found in previous research but the 'interpersonally distressed' group had few members. An additional cluster analysis suggested a more parsimonious solution for the sample was a two-cluster one, which approximated to the 'adaptive coper' and 'dysfunctional' profiles. Membership of both the three- and two-cluster profiles was not associated with membership of specific diagnostic category.

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1. Introduction

Approximately a third of new patients undergoing clinical investigation for chest pain have normal coronary arteries (Chambers and Bass, 1990). Despite a low mortality and adequate reassurance the outcome with regard to reduction in these patients of concern, distress, and disability is poor (Potts and Bass, 1993). Substantial evidence suggests that psychological disturbance is more prevalent in patients who experience chest pain without gastro-intestinal or cardiac pathology than those for whom a clear organic pathology has been established (Clouse and Carney, 1995; Salkovs, 1992; Stansfield et al., 1993; Fleet et al., 1994; Cornier et al., 1998). Nevertheless, no single psychiatric diagnosis is typical of the unexplained chest pain sufferer. In seven studies reviewed for evidence of co-morbidity of unexplained chest pain and psychiatric disorder (Clouse and Carney, 1995), the incidence for psychiatric diagnosis ranged from 47% (Kisley et al., 1992) to 80%. Anxiety and affective disorders predominated, with the incidence of major depressive illness ranging from 14% (Ayuso Mateos et al., 1989) to 39% and for panic disorder from 11% (Kisley et al., 1992) to 50% (Alexander et al., 1994).

Some empirical evidence suggests that patients with cardiac chest pain and unexplained chest pain differ on cognitive, rather than affective, dimensions. Comparison of psychological profiles of these two patient groups (Tennent et al., 1994) has demonstrated few differences with regard to anxiety, depression or neuroticism. Yet, there were clear differences in the way patients in these two groups expressed anger and in their methods of coping. One way to increase understanding of the
psychological characteristics of unexplained chest pain sufferers is to make use of multi-axial methods of psychological assessment to 'profile' them. Turk and Rudy used the Multidimensional Pain Inventory (MPI) to conduct a multi-axial assessment on samples of individuals with a variety of chronic somatic pain conditions (Turk and Rudy, 1987). In their study, three clusters with distinct psychological profiles were identified. 'Dysfunctional' patients typically report high pain severity, widespread interference across most aspect of their lives, low levels of activity and high levels of affective distress. 'Interpersonally distressed' patients were very similar to the dysfunctional patients but they also reported that they perceived that other people were not supportive of their troubles. In contrast to these groups, the 'adaptive copers' reported high levels of social support, high levels of activity and correspondingly low levels of pain, affective distress and perceived interference. Subsequent research has established the reliability and validity of this taxonomy and has demonstrated its robustness for patients with a variety of chronic musculoskeletal pain conditions such as back pain and temporomandibular pain (Turk and Rudy, 1990; Walters and Brannen, 1991; Jamison et al., 1994); most importantly, these profiles were independent of diagnoses. It is less certain whether this taxonomy has any utility with regard to more episodic forms of pain such as chronic visceral pain states like angina and non-cardiac chest pain. A previous study (Beck et al., 1992) applied the MPI taxonomy to 43 patients with non-organic chest pain and found that the taxonomy fitted only 35% of the sample. In their study, Beck et al. used the proprietary clustering and decision algorithm software developed by Rudy in their initial studies on musculo-skeletal pain samples. While this ensures a literal replication variations in the characteristics of the sample may curtail the generalizability of the findings. Indeed Beck et al. (1992) observed that their sample produced different means on the MPI sub-scales and variation in the inter-correlations between scales. An alternative approach is to attempt a conceptual replication using a similar strategy but different analytic tools (Lykken, 1968).

The aim of the present study was to test whether the MPI responses of patients with a variety of episodic visceral pain would cluster in a manner that was similar to the clusters previously observed in chronic musculoskeletal pain. The study is a conceptual rather than an exact replication of the Turk and Rudy taxonomy because it did not use the clustering algorithm and decision rules devised used by Turk and Rudy (Turk and Rudy, 1987, 1988, 1990). We used conventional K-means clustering algorithm on MPI scores to form clusters. The profile of these clusters was compared with previously published profiles for musculoskeletal pain. In addition, validation was sought by testing for between-cluster differences on additional (external variables) measures of distress, coping and pain perceptions and beliefs. If the clusters observed in the current study are conceptually similar to the MPI clusters we expected that there would be differences between groups in measures of distress and coping. More specifically a profile of affective distress should be associated with elevated scores on a measure of anxiety and depression, and it might also be expected that this group would report an increase in the use of externally attributed control strategies and more catastrophic appraisal of their pain. We assessed these variables using validated measures of distress (General Health Questionnaire — Goldberg and Hillier, 1979) and pain specific coping (Coping Strategies Questionnaire — Rosenstiel and Keefe, 1983). We also assessed participants' beliefs about their pain with the Pain Beliefs and Perceptions Inventory (PBPI — Williams and Thorn, 1989). This instrument assesses patients' perceptions of the temporal pattern of their pain and beliefs about the cause. There were no specific hypotheses concerning groups and PBPI scores but it was expected that in general the patients would differ from previous chronic musculo-skeletal samples in their assessment of these characteristics of pain experience.

We expected that there would be few differences between diagnostic groups with respect to psychosocial measures but that cluster analysis of the MPI data would replicate Turk and Rudy's classification. We further hypothesized that the classification would not relate to diagnostic groups, that is, patients within each diagnostic category would be distributed across the psychosocial classification.

2. Methods

2.1. Participants

Individuals who had experienced episodic chest pain for at least 6 weeks were identified from consecutive cases referred to the gastro-intestinal physiology and cardiology departments of two inner city teaching hospitals. Their ages ranged from 25 to 75 years. Those who had previously been given a formal diagnosis (including diabetes, myocardial infarction, chronic obstructive airways disease, congestive heart failure), or chronic pain due to other non-chest related disorders such as backache and headache were excluded from the study. In addition, those who were taking psychoactive medication, e.g., antidepressants, sleeping tablets and neuroleptics at the time of their attendance at the secondary service, were also excluded. Informed consent was sought, and the local ethics committee approved the study.

In all, 75 patients were recruited, seven were excluded during final analysis because both cardiac and esophageal diagnoses could account for their symptoms. Details of the 68 participants and the number of patients...
in each diagnostic category and their demographics are given in Table I. Social class was assessed using the UK standard occupational classification (Office of Population Census and Surveys, 1990). Patients received the following assessments.

2.2. Cardiological assessment

All patients in the coronary artery disease (CAD) group were diagnosed on the basis of an abnormal coronary angiogram. The absence of coronary artery disease in the unexplained chest pain group was determined either by a normal coronary angiogram or a negative exercise electrocardiogram and were not considered to have angina or any other cardiac cause of chest pain by an experienced Cardiologist.

2.3. Gastro-intestinal assessment

All patients in whom a cardiac cause for the chest pain was excluded had an upper GI endoscopy, esophageal manometry and 24h pH monitoring. These patients were then sub-divided into two groups. The first group was gastro-esophageal reflux disease group (GERD) as defined by either the presence of oesophagitis and/or their 24h ambulatory esophageal pH was less than 4 for greater than 5% of the time with a Demeester score of greater than 15 (Kahrilas and Quigley, 1996).

The second group was non-cardiac chest pain (NCCP) as defined by the absence of oesophagitis on endoscopy and a 24 ambulatory esophageal pH below 4 for less than 5% of the total time with a Demeester score of less than 15. None of the patients in either group had a primary esophageal motility disorder.

2.4. Psychological measures

General Health Questionnaire (GHQ-28), (Goldberg and Hillier, 1979; Goldberg, 1980) This has 28 items and consists of four scales: somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. It is widely used in surveys and has excellent reliability and standardisation data.

McGill Pain Questionnaire (MPQ). (Melzack and Katz, 1992) The MPQ assesses the sensory, affective and evaluative components of pain experience. It has good reliability and is widely used in clinical and research settings.

Multidimensional Pain Inventory (MPI). (Kerns et al., 1985) This instrument consists of 52 items and is divided into three parts. Part one measures five dimensions of pain experience: the perceived interference by pain on the individuals' functioning, support and concern from others, degree of life control, pain severity and negative mood. Part two consists of three sub-scales that measure the frequency and type of response made by significant others to the individuals' communication of pain. Part three is a 'general activity' scale and was not used in the present study because its items were deemed by the investigators to be of limited relevance to individuals with episodic forms of pain. The validity and reliability of the MPI has been demonstrated on diverse samples of chronic pain patients (Rudy et al., 1989; Turk and Rudy, 1988, 1990).

Coping Strategies Questionnaire (CSQ). (Rosenstein and Keele, 1983) This instrument requires respondents to rate how frequently they use various coping strategies to deal with their pain. The first forty-eight items are in the form of self-statements such as "I try to think of something pleasant". For the last two items, the respondent has to provide an overall rating of both the amount of control they have over their pain, and their ability to decrease it. Of the various subscales 'catastrophizing' has been shown to be a robust predictor of psychological adjustment to pain (Sullivan et al., 2001).

Pain Beliefs and Perception Inventory (PBPI). (Williams and Thorn, 1989) The 16 items on this questionnaire can be described in terms of three different factors: 'self-blame', 'perception of pain as mysterious' and 'time'.

<table>
<thead>
<tr>
<th>Table 1: Demographic characteristics of participants</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>Gender ratio</td>
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<tr>
<td>Age</td>
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<tr>
<td>Socio-economic</td>
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<td></td>
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<tr>
<td>% In litigation pending</td>
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<tr>
<td>% Claiming benefits</td>
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</table>

Note: There was no information on socio-economic class for three participants in the CAD group and one in NCCP group.
Research has shown this last factor to be a composite of two sub-scales: 'pain constancy' and 'pain permanence' (Morley and Wilkinson, 1995; Strong et al., 1992).

2.5. Procedure

All 48 participants in the GERD and NCCP groups, and 12 in the CAD group were interviewed in the outpatients department at one of the sites of recruitment by an investigator who was unaware of the diagnosis. The remaining eight participants in the CAD group were interviewed during admission for angiography, and the investigator remained blind to the outcome of the procedure.

2.6. Data analysis

Between-group pair-wise comparisons were carried out on the data for all five measures to test for homogeneity of variance and normality. Although, there were minor violations of these assumptions for the MPQ, MPI, CSQ and PBPI on some sub-scales, overall, these were not sufficient to preclude the use of multivariate analysis. In the case of the GHQ however, the results of pair-wise comparisons and graphical analysis indicated the Kruskal–Wallis test to be more appropriate. Differences between groups were explored with multivariate analysis of variance (MANOVA) and univariate tests were examined using the Bonferroni correction with a familywise $\alpha = 0.05$. Where assumptions for multivariate analysis were not met non-parametric univariate analysis was conducted and a Bonferroni corrected $\alpha$ was set.

2.6.1. Cluster analysis

Cluster analyses were carried out on the MPI data using the ‘nearest centroid sorting pass’ algorithm (K-means clustering). The statistical package SPSS 7.5 was used. Initially, $K$ was constrained to a value of three, i.e., the number of profiles obtained by Turk and Rudy (Turk and Rudy, 1987, 1988, 1990). Further exploration of the data was undertaken using an internal criterion of fit. The index used was the pseudo-$F$ statistic (Calinski and Harabasz, 1974). This is given by $[\text{trace } B / (k - 1)] / [\text{trace } W / (k - n)]$; where $k$ is the number of clusters and $n$ is the number of variables used to generate the cluster. Trace $B$ and trace $W$ are the sum of the diagonal elements in the 'between subjects' and 'residual error' sum of squares and cross-products matrices, respectively.

3. Results

3.1. Between-group differences

The diagnostic groups differed with respect to their mean age ($F = 8.4$, $df = 2, 64$, $p < 0.001$): CAD patients were on average 10 years older than the GERD and NCCP patients. There were no differences between the groups with regard to gender or social class. Most patients were drawn from social classes C1 and C2 representing skilled workers.

Separate MANOVAs were conducted on the set of sub-scale scores for the MPQ, MPI, CSQ and PBPI. The multivariate $F$ (Wilks' $F$) provided a test of multivariate between-group differences and subsequent univariate tests identified differences between groups on particular sub-scales.

Multivariate analysis revealed that there were no significant between-group differences on the MPQ (Wilks' $F = 1.82$, $df = 8, 124$, $p = 0.08$). Analysis of the total score was not computed. There was no difference between groups on the multivariate test of the MPI sub-scales (Wilks' $F = 3.10$, $df = 16, 114$, $p = 0.613$) or on any of the univariate tests.

The MANOVA for the CSQ revealed a significant between-group difference (Wilks' $F = 2.17$, $df = 16, 114$, $p = 0.01$). Univariate tests showed that the differences were confined to the 'catastrophizing' and 'feeling in control' sub-scales. With regard to 'catastrophizing' GERD patients had a greater tendency to catastrophize (mean = 12.88) in comparison to CAD patients (mean = 5.88), but neither of these groups was statistically different from the NCCP group (mean = 9.81). With respect to 'feeling in control' CAD patients felt they had more control (mean = 4.05) than GERD patients (mean = 2.58), but neither of these groups was different from the NCCP group (mean = 2.96). A MANOVA conducted on the PBPI data was also significant (Wilks $F = 3.78$, $df = 8, 122$, $p < 0.01$) with the NCCP group considering their pain to be more mysterious (mean = 3.13) than the CAD group (mean = 1.95): the mean (−2.8) score for the GERD patients was not different from the other groups. With regard to the GHQ, the only significant difference was that between the GERD and CAD groups for severe depression ($\chi^2 = 9.63$, $df = 2$, $p = 0.008$). Although this suggests that the GERD group experienced higher levels of affective distress that the CAD group, this conclusion was not supported by the between-group comparison on the affective distress sub-scale of the MPI.

3.2. Cluster analysis

Profiles based on the initial, three-cluster, solution are plotted in Fig. 1 using the mean $T$-scores. Cluster 1 comprised 33 patients whose mean $T$-scores, with one exception were below the sample mean, i.e., 50. The single exception was the 'life control' score, which was above 50 and higher than either of the other two clusters. Cluster 2 (26 patients) had a profile that was essentially the mirror image of Cluster 1, with elevated $T$-scores with the exception of 'Life control'. Cluster 3
was comprised of just 8 patients: on average they had lower $T$-scores for all scales except 'Affective distress' but most marked feature of this cluster was a low score for 'Support'. We cross-tabulated cluster membership with diagnostic group and tested for association (Table 2): there was none, $\chi^2 = 6.74$, df 4, $p = 0.15$.

The mean scores of the three clusters were compared on the GHQ, CSQ and PBPI measures. Initial analysis revealed that the preferred MANOVA analysis could not be conducted because the data violated the necessary assumptions. We therefore conducted univariate non-parametric ANOVA (Kruskal–Wallis) analyses to test for between-cluster differences. Post-hoc comparisons between each pair of clusters were conducted using the Mann–Whitney test. For each set of variables $a$ was corrected using the Bonferroni method. Table 3 shows the means and standard deviations for each cluster and a summary of the statistical tests. There were statistical significant between-cluster differences ($\alpha = 0.0125$) for all four of the GHQ sub-scales. Pair-wise comparisons between the clusters revealed that clusters 1 and 2 were significantly different from each other (cluster 2 were more distressed) but there were no differences between the other cluster pairs. A similar pattern of significant differences was observed for two sub-scales of the CSQ ($\alpha = 0.006$), praying and hoping and catastrophizing, and for the constancy and mysteriousness scales of the PBPI ($\alpha = 0.0125$). Cluster 2 reported using more praying and hoping strategies, more catastrophic cognitions, and regarded their pain as less constant (more intermittent) but also as having a less mysterious origin than did cluster 1. There was also an overall between-cluster difference in the self-blame PBPI sub-scale but the were no pair-wise differences. There were significant differences between clusters 2 and 3 on catastrophizing (CSQ) and constancy (PBPI): these were in the same direction as differences between clusters 2 and 1.

The three profiles generated from the current data set show reasonable approximation to those expected on the basis of other studies but the patients in the present study suffered more episodic forms of pain than those used in previous studies and it could not be assumed, a priori, that a three-cluster solution was optimal. To check that the clusters represented a meaningful partitioning of the data we re-clustered the data using an internal criterion of fit. Cluster solutions were obtained for $k = 2–7$, the upper limit being $n – 1$; where $n$ is the number of variables used to generate the clusters. It was found that the variance ratio fell monotonically with each successive increment of $k$. It has been demonstrated that a two-cluster solution is optimal under these conditions (Calinski and Harabasz, 1974). The mean $T$-score profiles for the two-cluster solution are shown in Fig. 2. The 8 patients in cluster 3 from the first solution were redistributed to the other two clusters; 6 moving to the new cluster 1 and 2 moving to the new cluster 2. Clusters 1 and 2 remained stable across the two analyses. Cross-tabulation (Table 2) indicated that cluster membership was independent of diagnostic category ($\chi^2 = 4.3$, df 2, $p = 0.116$).

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Gastro-esophageal reflux disease</th>
<th>Coronary artery disease</th>
<th>Non-cardiac chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-Cluster solution</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster 1</td>
<td>8</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>12</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>2-Cluster solution</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster 1</td>
<td>14</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>10</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>
Table 3
Summary statistics (M and SD) of the 3 and 2 group cluster solutions for the external variables: GHQ, CSQ and PBPI

<table>
<thead>
<tr>
<th>Variable</th>
<th>3-Cluster solution</th>
<th>2-Cluster solution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cluster 1 (n = 33)</td>
<td>Cluster 2 (n = 26)</td>
</tr>
<tr>
<td>GHQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic symptoms</td>
<td>5.6 (2.3)</td>
<td>10.5 (3.5)</td>
</tr>
<tr>
<td>Anxiety and insomnia</td>
<td>4.0 (2.4)</td>
<td>10.1 (5.3)</td>
</tr>
<tr>
<td>Social dysfunction</td>
<td>7.7 (2.3)</td>
<td>10.6 (4.1)</td>
</tr>
<tr>
<td>Severe depression</td>
<td>0.5 (1.1)</td>
<td>4.0 (4.8)</td>
</tr>
<tr>
<td>CSQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distracting attention</td>
<td>7.7 (7.9)</td>
<td>11.3 (6.9)</td>
</tr>
<tr>
<td>Restless pain sens&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.2 (6.7)</td>
<td>2.9 (3.8)</td>
</tr>
<tr>
<td>Coping self-statements</td>
<td>20.1 (7.5)</td>
<td>20.3 (8.3)</td>
</tr>
<tr>
<td>Ignoring pain sens&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12.2 (8.2)</td>
<td>10.8 (8.4)</td>
</tr>
<tr>
<td>Praying and hoping</td>
<td>14.2 (9.4)</td>
<td>21.2 (8.1)</td>
</tr>
<tr>
<td>Catastrophizing</td>
<td>6.1 (5.4)</td>
<td>15.0 (9.4)</td>
</tr>
<tr>
<td>Increase activity</td>
<td>12.7 (7.8)</td>
<td>12.5 (7.3)</td>
</tr>
<tr>
<td>Increase pain behavior</td>
<td>13.4 (6.3)</td>
<td>15.4 (5.4)</td>
</tr>
<tr>
<td>PBPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constancy</td>
<td>3.6 (2.2)</td>
<td>0.3 (3.8)</td>
</tr>
<tr>
<td>Mysteriousness</td>
<td>-0.2 (3.7)</td>
<td>-3.8 (4.4)</td>
</tr>
<tr>
<td>Permanence</td>
<td>-1.3 (2.1)</td>
<td>-0.9 (2.4)</td>
</tr>
<tr>
<td>Self-blame</td>
<td>3.2 (2.5)</td>
<td>4.0 (2.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Bonferroni adjusted p < 0.05.<br><sup>o</sup>K-W, Kruskal-Wallis test.<br><sup>o</sup>M-W, Mann-Whitney test.<br><sup>d</sup>Reinterpreting pain sensations.<br><sup>d</sup>Ignoring pain sensations.
Comparisons between the two clusters on the GHQ, CSQ and PBPI were again made with the Mann–Whitney test with a Bonferroni corrected α. Table 3 displays the cluster summary statistics and the results of the Mann–Whitney tests. The two clusters showed the same pattern of differences as in the previous three-cluster analysis. Thus cluster 2 were more distressed, used more praying and hoping strategies, showed greater catastrophizing, experienced less constant pain that they regarded as less mysterious. In addition cluster 2 reported greater self-blame on the PBPI.

4. Discussion

The purpose of this study was to explore variations in cognitive and affective responses in patients with visceral pain. The study had two inter-connected aims. The first was to assess differences between diagnostic groups with respect to affective, cognitive and belief measures. Previous data suggested that any differences between the groups would be limited. The second aim was to replicate a classification of psychological features developed in chronic musculo-skeletal pain; it was hypothesized that this classification would be independent of medical diagnosis. The replication was conceptual rather than literal and the study sought to establish validity through the use of additional external measures.

With respect to the first aim we examined a group of patients who experienced episodic chest pain. For some of these patients pain was clearly related to cardiac or gastro-intestinal disease but for another group (NCCP) the cause of pain was not frankly obvious following diagnostic testing. Previous studies have reported elevated sores on psychological tests of mood but this evidence is not consistent. Previous studies sought to establish whether an increased incidence of psychiatric disorder occurred in NCCP suffers compared to those suffering from other pain syndromes (Clouse and Carney, 1995; Salkovis, 1992; Stansfield et al., 1993; Fleet et al., 1994). This approach is based on the assumption that psychological disturbance will align with pathophysiological signs and symptoms. We did not include a non-diseased control group and we cannot make claims as to whether the affective and cognitive responses in our sample are raised. Our main concern was to explore differences between patients. Although there were one or two differences between diagnostic groups with respect to scores on psychological tests these differences were few when set against the number of comparisons that were made. 4 significant pair-wise comparisons in a possible 96. We also note that none of these differences were predicted a priori and as a consequence we conclude that medical diagnosis carries no predictive information for differences in psychological responses to pain. One possible exception to this was the difference between groups in 'mysteriousness', i.e., the degree to which a person believes they have a satisfactory explanation for their pain. In our sample patients with CAD had a better understanding of their pain than the other two groups, but this only reached significance with respect to the NCCP group, i.e., the group with essentially a diagnosis by exclusion. This study also suggests that those with NCCP do not significantly differ in affective distress or their methods of coping from those suffering other forms of episodic pain. On the contrary, with regard to the limited number of measures where significant differences were noted, it is the patients with chest pain associated with GERD rather than those with NCCP, that tend to employ less adaptive ways of coping and exhibit greater levels of affective distress. However this finding may be specific to GERD suffers presenting with episodic chest pain in contrast to those presenting with less severe forms of disease.

With respect to the second aim, the initial three-cluster solution appears to correspond to that observed in other studies using Turk and Rudy's method (Turk and Rudy, 1990; Walters and Brannon, 1991; Jamison et al., 1994). Cluster 2 corresponds well with the affective distress cluster and cluster 1 fits the profile of the adaptive cope group. This interpretation is supported by the observed differences between the clusters on two external measures – the GHQ and the CSQ. The elevation on all the GHQ sub-scales suggests that affective distress in this group is general and not limited to a specific emotional domain, and it is also expressed through somatic symptoms and social distress. Although no predictions were made concerning the PBPI sub-scales these scales did reveal differences. Cluster 2
(affective distress) regarded their pain as less constant (more intermittent) but also as less mysterious. Cluster 3 does show some resemblance to the previously identified interpersonally distressed samples. The most prominent features are the low levels of support and relatively, i.e., within cluster, high levels of affective distress and negative responses. This cluster showed few differences from either of the other groups on external measures. This result should be treated with caution given the small number of participant allocated to this group, i.e., reduced statistical power to detect differences; and also the fact that it could be argued that none of the external measures assessed theoretically important aspects of this group, e.g., partner satisfaction. The two-cluster solution for the sample used in this study would appear to be more parsimonious for two reasons. First, it is a better fit of the internal statistical criteria suggested by Calinski and Harabasz (1974), and second, the differences on the external variable remain consistent. However, this interpretation could be dependent on the unique characteristics of this sample. Although we did not collect detailed information on the duration of pain in this sample it is likely that many of these patients have experienced pain and discomfort for considerably shorter duration that the samples typically recruited in other profiling studies. In these studies participants are frequently reported as having experienced pain for several years (mean durations in excess of 5 years). The present study recruited participants undergoing investigation for their symptoms at a relatively early stage of disease. One consequence of this is that interpersonal reactions to pain may still be relatively supportive and that less supportive interactions have not yet developed. This speculation, however, requires further elaboration and testing.

Finally, in contrast to the lack of relationship between diagnostic group and psychological response the current data did broadly replicate earlier work on musculo-skeletal pain by showing that psychological measures appeared to be clustered in a meaningful way. The three-cluster solution derived from the MPI data showed parallels with previous findings in larger sample of patients with predominantly musculo-skeletal pain. Our secondary, exploratory analysis reduced the clusters to two, but these still approximated to the 'dysfunctional' and 'adaptive cope' profiles reported in previous studies. Moreover for both solutions medical diagnosis appeared to be independent of cluster membership.

There are limitations with regard to this study the major one being the relatively small sample size which limits the power of the between-group comparisons. It is possible that there are subtle differences between the diagnostic groups with regard to the cognitive and affective responses and these would be detected with a larger sample. Our expectation, that there would be no differences between the diagnostic groups is also problematic to test under the assumptions of the inferential statistical model where it amounts to 'proving the null hypothesis'. Further tests of the hypothesis could be made with larger samples and clear theoretically derived expectations of differences between groups on specific variables. Our study might be further limited by the fact that all patients were recruited from a tertiary centre – a University Hospital. However the sample does appear to be representative of the population that the hospital serves as it comprised predominantly skilled and unskilled manual workers.

In conclusion we note that there is considerable variation in the psychological responses in people with chest pain with different diagnoses. At present there is no theoretical reason to expect major differences between diagnostic groups and we suggest that a more scientifically productive question is to consider the psychosocial antecedents to variation in responses to the experience of pain. This study has provided preliminary evidence that patients with episodic chest pain show similar profiles to patients with chronic musculo-skeletal pain. It may be more productive to ask why some individuals develop an adaptive coping style rather than to pursue what may be small differences between groups with different diagnoses.

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