DO THE EFFECTS OF REPETITIVE TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) ON EXPERIMENTAL PAIN CUMULATE OVER TIME?

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March, 1994

A thesis submitted to

the Faculty of Graduate Studies and Research

in partial fulfillment of the requirements for the degree of

Master of Science in Rehabilitation Science.

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ABSTRACT

This study investigated the immediate and possible cumulative effects respectively of a single 60 min session and of 10 repeated daily applications on subjective pain sensation and flexion reflex (FR). Twenty young healthy subjects were randomly assigned to a TENS or a placebo group, with ten each. TENS or placebo stimulation was applied to the lumbosacral region for 60 minutes on 10 treatment days over a two-week period. *Before*, *during* and *after* TENS and placebo stimulation on Day1, Day5 and Day10, the FR was elicited by electrically stimulating the sole of subject's right foot and recorded electromyographically from biceps femoris (BF), tibialis anterior (TA) muscles. Subjective pain sensation was measured using the visual analog scale (VAS). Compared to placebo stimulation, a single session of 60 min TENS significantly decreased the VAS scores ($p < 0.05$) and TA FR areas ($p < 0.05$) obtained during the 60 min *post*-stimulation period. However, the *between*-group difference in the decrease of the BF FR area did not reach statistical significance. After 10 repeated daily applications of TENS, the pre-stimulation VAS scores and FR areas of both muscles were significantly more inhibited ($p<0.01$) than placebo stimulation. Furthermore, the suppression of VAS scores *during* and *after* TENS was linearly correlated with that of FR areas of both muscles in each of the 3 testing days. These findings indicated that repeated daily TENS applications produced cumulative inhibitory influence on both subjective pain sensation and FR over a two-week period. Such a gradual development probably implicated that plastic changes could have been induced in the neural pathway. The similar time course of the inhibitory effects of TENS on the two pain indices, which could cumulate over time, suggest possible similar processing at both cortical (subjective pain) and spinal (FR) levels.

ABREGE

Cette étude a investigué les effets immédiats et cumulatifs possibles, respectivement d'une seule application de 60 min. et de 10 applications répétées journalières de SETC (stimulation électrique trans-cutanée) sur la sensation subjective de douleur et sur le réflèxe de flexion (RF). Vingt sujets jeunes et en bonne santé ont été assignés au hazard à un groupe SETC ou placébo. Dix applications de 60 min. par jour de SETC ou de stimulation placébo ont été données au niveau de la région lombo-sacrée, sur une période de deux semaines. *Avant, pendant* et *après* la stimulation SETC ou placébo lors des $Jour_1$, $Jour_5$ et $Jour_{10}$, le RF a été élicité en stimulant électriquement la plante du pied droit des sujets, et enregistré électromyographiquement au niveau des muscles biceps fémoral (BF) et jambier antérieur (JA). La sensation subjective de douleur a été mesurée à l'aide de l'échelle visuelle analogue (EVA). En comparaison avec la stimulation placébo, une seule session de 60 min. de SETC a diminué significativement les scores EVA ($p<0.05$) et l'aire sous la courbe des RF du JA ($p<0.05$) obtenus lors de la période de post-stimulation. Cependant, la différence *entre* les deux groupes de sujets pour la diminution de l'aire des RF du BF n'a pas atteint le seuil statistique. Suite à l'application répétée de 10 sessions de SETC, les scores EVA et les aires de RF des deux muscles obtenus en pré-stimulation étaient significativement plus inhibés ($p<0.01$) que lors de la stimulation placébo. De plus, la suppression des scores EVA était corrélée linéairement à celle des aires de RF des deux muscles *pendant* et *après* la SETC à chacun des 3 jours de test. Ces résultats indiquent que l'application répétée journalière de SETC a produit une influence inhibitrice cumulative, tant sur la sensation subjective de douleur que sur le RF, pendant une période de deux semaines. Un tel développement graduel implique probablement que des changements plastiques ont pu avoir été induits dans les voies neurales. Le patron temporel semblable de l'inhibition par la SETC des deux index de douleur, qui peut cumuler avec le temps, suggère que des transformations semblables ont pu survenir au niveau cortical (douleur subjective) et spinal (RF).

DEDICATION

To my friends:

Mr. David John Weir

Mrs. Pamela Elizabeth Weir

Mr. Kung Ching Chan

Without your help, none of this would have been possible.

Thank you from the bottom of my heart.

ACKNOWLEDGEMENTS

First of all, I would like to thank Dr. Christina W.Y. Hui-Chan, my supervisor, for her patience, encouragement and support throughout my graduate studies. Among many precious personal qualities, her dedication to work, logistic guiding principals and demand for excellence will always inspire me in my future life. To you, Dr. Hui-Chan, I have much more gratitude than I am able to express in words, but I will simply say: "*Thank you!*".

I wish to express my gratitude to all volunteers who participated in this painful study. Sincere thanks to Drs. James Henry, Catherine Bushnell and Hugues Barbeau for their valuable advice at my research proposal presentation. I am also very grateful to Prof. Rhonda Amsel for her advice on the statistical analyses of the data. I would like to thank in particular Mr. Ahmed Alfat who developed the computer programs for on-line experimental control, data collection and analysis.

My special thanks are extended to my fellow student, Nicole Paquet, for her kind guidance and emotional support. Many thanks to Nicole Paquet, Yu Kyung, Kim and Xiaobo Ma for their help in the preparation of this thesis. Finally, Wei Li (my wife) and Catherine (my daughter) deserve my warmest gratitude for their love, patience and support.

This study was supported by a grant from the *Fonds de la Recherche en Santé du Québec.*

PREFACE

This thesis includes, as parts, copies of two papers in preparation for submission to *Pain*. This option is in accordance with the Guidelines Concerning Thesis Preparation (June 1994) Part B section 2, which is cited below in full as required by the Faculty of Graduate Studies and Research, McGill University. It has also obtained the approval of the Chairperson, School of Physical and Occupational Therapy.

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LIST OF REFERENCES

Chapter 2: Hui-Chan, C.W.Y. and Liu, J., TENS exerts a prolonged and parallel inhibition of electrically induced pain sensation and flexion reflex in man. In preparation for submission to *Pain*.

Chapter 3: Liu, J. and Hui-Chan, C.W.Y., Antinociceptive effects of TENS on experimental pain and flexion reflex will cumulate over time. In preparation for submission to *Pain*.

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CHAPTER 1

General Introduction

LITERATURE REVIEW

History of TENS

Transcutaneous electrical nerve stimulation (TENS) is used extensively in the clinic for the relief of chronic and acute pain. Long before electrical methods existed to generate electricity, man had learned how to use the 'naturally occurring' electricity therapeutically to relieve pain. It is believed that the ancient Egyptians used electric fish over painful wounds (c.f. Madigan and Raj, 1992). However, the structure of their organs limits the amount of electricity produced.

There were also methods to relieve pain in ancient China. One can find the earliest known description of using acupuncture as a cure for different types of pain conditions in Huan Ti Nei Ching, dating back from the time of the legendary Huan Ti or the 'Yellow Emperor' (2600 BC) (c.f. Majno, 1975). A French physician, Sarlandiere, became interested in pain relief by acupuncture during the early nineteenth century. At that time in Europe, it had long been possible to generate static electricity and to store it in condensers called Leyden bottles. Sarlandiere developed the classical Chinese technique further by using acupuncture needles as electrodes to discharge Leyden bottles. He reported good pain relief in a number of conditions treated with this technique (c.f. Sjolund and Erikson, 1985). Some other man-made electrical devices, such as the galvanic current, were poorly received by the medical community,

because of their poor quality and a reliance on patient testimonials for its efficacy (c.f. Lampe, 1978).

The construction of various electricity machines for pain-relief was not developed until the end of the nineteenth century. Several such machines were patented in the U.S. and used in various medical and surgical conditions such as amputation, chronic back pain and joint pain, tooth extraction, surgery and delivery of babies. Unfortunately, the electrical stimulation techniques were nearly forgotten for about one century after anaesthetic agents were introduced (c.f. Kane and Taub, 1975).

The so-called 'gate control theory', introduced by Melzack and Wall in 1965, reawakened interest in pain treatment by electrical stimulation. The hypothesis that stimulation of large myelinated fibers suppresses the pain transmission via small diameter fibres led to the evolution of preferential stimulation of predominantly large diameter fibers in the dorsal column with inplanted electrode (Shealy, 1967) and then stimulation of the peripheral nerve transcutaneously as a way of relieving pain. Subsequently, transcutaneous electrical nerve stimulation in its modern form has been used extensively in the clinic for relieving chronic and acute pain.

Technical Aspects of TENS Devices

Before we discuss the mechanisms underlying TENS analgesia, let us look at some technical aspects of TENS units commonly used in the clinic.

TENS machine used in the clinic is usually a pulse generator consisting of electronic circuits and an energy source. The accessories comprise two or more electrodes and a corresponding number of electrical cables for connecting the electrodes to the stimulator. The efficacy of TENS treatment depends on many factors which likely include stimulus parameters, such as the size of electrodes, electrode placement, waveform, pulse duration, current intensity and frequency.

The size of electrodes is important with regard to current density. In the clinic, electrodes of different sizes are available for different surface areas of the body parts being treated. With the same current output, increasing the size of electrodes will decrease the current density. In contrast, the smaller the electrodes, the greater the current density will be (c.f. Mannheimer and Lampe, 1984), but the risk of skin being burned will also increase. To obtain the required current intensity in the tissue and to prevent the skin from being damaged by the current, it was recommended by Sjolund and Eriksson (1985) that the surface electrodes should be of a certain size, usually 10 - 15 cm^2.

Proper selection and placement of electrodes ensure more efficient stimulation of the nerve fibres. The electrode placement is usually selected based on evaluation of the dermatome where pain exists, so that trigger points located within the dermatome can be coupled with the corresponding level of spinal cord innervation (Lampe, 1981). According to some investigators, trigger point, dermatomes and acupuncture points are common electrode sites for

TENS application to relieve chronic pain (Mannheimer and Lampe, 1984; Melzack, 1975). However, Le Bars et al. (1979) noticed that noxious stimuli applied to various parts of the rat body powerfully inhibited the nociceptive (C fiber) response of a majority of convergent dorsal horn neurones. Consistent with this finding from animal experiment, TENS stimulation applied to a remote contralateral body part was found to be effective in inhibiting the lower limb flexion reflex in man (Tsang and Chan, 1984). Note that the latter could be regarded as an objective and quantitative assessment of experimental pain under certain conditions (Chan and Dallaire, 1989).

Over the years, various combinations of wave forms, pulse duration, frequencies and current intensities have been tried. Yet, it is still unclear what kind of waveform is the most effective one for pain relief. Accordingly, most TENS devices have biphasic square wave form, variable pulse duration, amplitude and frequency features (c.f. Baumgartner, 1981).

According to the gate control theory (Melzack and Wall, 1965), stimulation of large diameter group A afferent fibers should relieve pain. The larger the diameter of the nerve fibers, the less their resistance to electrical current; hence the lower the current intensity will be needed for their activation. In other words, low intensity TENS with short pulse duration should selectively activate large diameter myelinated fibers (Howson, 1978). According to Sjolund and Eriksson (1985), the most suitable pulse to activate myelinated fibers via surface electrodes is a monophasic rectangular

pulse with a duration of 0.05 - 0.5 msec. To ensure sufficient current intensity for stimulating the nerve fibers, currents of 10 - 60 mA should be applied between the surface electrodes. Of course, the variation in the required current intensity depends, among other factors, upon the distance from the skin surface to the nerve to be activated. That factor aside, the optimal stimulus parameters for activating large diameter nerve fibers should preferentially be low intensity and high frequency.

Indeed, frequency of TENS has been found to be another important parameter which influences the efficacy of its analgesia. In animal studies, Sjolund (1985) showed that, among a frequency range from 10 to 160 Hz, 80 Hz TENS produced the most profound inhibitory effect on the size of C-fiber-evoked flexion reflex, which was considered as a measure of transmission from nociceptive afferent fibers in the spinal cord. Consistent with the above finding, Johnson et al. (1989) reported that TENS significantly elevated human ice pain threshold when compared with control, and that frequencies between 20 and 80 Hz produced greatest analgesia, while frequencies below and above this level (10 Hz and 100 Hz), although with similar stimulation intensity, produced lesser analgesia. A later study by the same research group demonstrated that continuous 80 Hz TENS produced the greatest elevation in ice pain threshold in normal healthy subjects when compared with several other pattens of stimulation (Johnson et al., 1991). Thus, low intensity, high frequency TENS at 80 Hz was used in the present studies, which will be described in detail in Chapter 2 and 3.

However, not all proposed mechanisms underlying TENS analgesia discussed below wholly support the above concept.

Mechanisms Underlying TENS Analgesia

Although the mechanisms underlying TENS analgesia are still unclear, several hypotheses have been proposed so far. These include (1) peripheral mechanisms; (2) gate control theory; (3) endogenous pain control system; and (4) diffuse noxious inhibitory controls (DNIC).

Peripheral Mechanisms. A peripheral mechanism has been proposed as one of the mechanisms underlying TENS analgesia. This theory suggested that peripheral nerve stimulation could cause peripheral fatigue or peripheral electrogenic blockade of pain-mediating fibers (Cambell and Taub, 1973). Ignelzi and Nyquist (1976) reported that peripheral neurostimulation in cats altered the conduction velocity and the amplitude of Aα, Aβ and Aδ waves, with the more slowly-conducting Aδ component showing the greatest changes. They concluded that this direct alteration of peripheral nerve activity *distal* to the first synapse in the spinal cord might contribute to the pain relief observed. Consistent with these animal findings, Pertovaara (1980) demonstrated that high intensity TENS at high frequency caused human pain threshold elevation for thermal stimuli only when thermal stimuli were applied at a site *distal* (but not *proximal*) to the TENS electrodes. These findings suggest that pain carrying fibres of the peripheral nervous system are subject to fatigue.

Gate Control Theory. In the early 1960's, neurophysiological studies provided evidence that stimulation of low-threshold myelinated primary afferent fibers decreases the response of dorsal horn neurons to small unmyelinated nociceptive fibers, whereas blockade of conduction in the large myelinated fibers enhances the nociceptive response of the dorsal horn neurons. The firing of certain spinal cord neurons may therefore not be reflected simply by the level of activity in nociceptive afferent input, but by the balance of activity between the unmyelinated nociceptive fibers and the myelinated afferents not directly concerned with pain. This idea was introduced and elaborated upon by Melzack and Wall in 1965 as the gate control theory.

Endogenous Pain Control System. The endogenous pain control system was firstly proposed by Basbaum and Fields (1978, 1984). Basically, it means that opioid peptides, such as enkephalin or dynorphin, mediate inhibition of nociceptors in the central nervous system. Now, there is a general agreement that high intensity, low frequency acupuncture-like TENS (acu-TENS) involves an opiate-mediated pain control system, although the precise mechanisms are not quite well understood. Sjolund and Eriksson (1979) observed that chronic pain patients receiving acu-TENS reported suppression of analgesic effects after injection of naloxone, an opiate antagonist; whereas those receiving low intensity, high frequency (called *conventional*) TENS reported no change in analgesic effects after naloxone injection. Cheng and Pomeranz (1979) also reported that naloxone hydrochloride could reverse the low frequency electro-

acupuncture analgesic effects on the noxious radiant heat response in mice. Further evidence exists that acu-TENS, like acupuncture, produces an analgesic effect that has a slow onset and offset, which is consistent with the release of opioid substances such as endorphins, enkephalins or dynorphins into the circulatory system (Hughes et al., 1984; He, 1987).

Results of studies concerning whether conventional TENS also involves an endogenous opioid pain control system are conflicting. According to the gate control theory mentioned above, it is expected that low intensity TENS should generate a pain relief having a rapid onset and offset. The latter has been attributed to a non-opiate segmental inhibitory mechanism (Willer et al., 1982). Several researchers demonstrated that the analgesic effects of conventional TENS was immediate (Sweet and Law, 1983) or within 10 to 15 min (Eriksson and Sjolund, 1976), showing a relative rapid offset after stimulation (Andersson and Holmgren, 1976; Hughes et al., 1984), and the effects could not be blocked by the administration of naloxone (Freeman et al., 1983; Sjolund and Eriksson, 1979; Willer et al., 1982). However, there is abundant evidence showing that TENS analgesia has a gradual onset and offset. Chan and Tsang (1987) observed that the time to peak maximum inhibitory effect on the flexion reflex recorded in both the hip flexor (HF) and biceps femoris (BF) took 20 and 30 min respectively after the administration of conventional TENS. Moreover, the flexion reflex often did not return to control values even at 40-50 min after the stimulation. Comparing conventional TENS (100 Hz) with acu-TENS

(2 Hz), Hansson and Ekblom (1983) found no significant difference in the induction time (15-30 min after stimulation) for the first detectable or maximal reduction of acute oro-facial pain between the two types of TENS. An increase in endorphin in the cerebrospinal fluid was found in pain-free patients who received conventional TENS (Salar et al., 1981). Facchinetti et al. (1984) also reported a concomitant increase in nociceptive flexion reflex threshold and plasma opioids following conventional TENS stimulation. In addition, Atweh and Kuhar (1977) demonstrated that primary afferent terminals were laden with opiate receptor sites. Furthermore, the analgesic effect generated by low intensity TENS on the tail immersion test was found to be antagonized by naloxone in rats (Woolf et al, 1977).

The reason behind these conflicting findings is becoming clear. Han et al. (1991) demonstrated that whereas acupuncture-like TENS (2 Hz) significantly increased met-enkephalin-arg-phe from the preproenkephalin, conventional TENS (100 Hz) produced a significant increase of dynorphin A from preprodynoephin. These authors proposed that proenkephalin-derived peptides acted on the *mu* receptors; whereas preprodynorphin-derived peptides worked on the *kappa* receptors which were relatively resistant to naloxone blockage (Fei et al., 1987; Goldstein et al., 1979; Han et al., 1984). Therefore, insufficient dosage of naloxone used and/or failure to employ specific *kappa* antagonists in the previous studies (Freeman et al., 1983; Sjolund and Eriksson, 1979) could explain why they

failed to show that conventional TENS analgesia was naloxone reversible.

Diffuse Noxious Inhibitory Controls (DNIC). Diffuse Noxious Inhibitory Controls (DNIC) was first proposed by Le Bars and his colleagues in 1979. It was so termed because the majority of convergent dorsal horn neurones being investigated, which received input from both large diameter and C afferent fibres, were found to be powerfully inhibited by noxious stimuli applied to various parts of the rat body. In contrast, non-noxious stimuli were ineffective in this respect. Among many different forms of noxious stimuli studied, transcutaneous electrical stimulation of the rat tail was found to be one of the most effective noxious stimuli in eliciting DNIC. DNIC strongly depressed the C fibre response by 60-100% following supra-inhibition threshold transcutaneous electrical stimulation (Le Bars et al., 1979). Further studies indicated that DNIC involved endogenous opiates. Le Bars et al. (1981) noticed a partial reduction in the DNIC inhibitory effects with a decrease of about 50% for both Aα and C fibre response 10 min after naloxone administration. Additional evidence reported from the same research laboratory demonstrated that acupuncture, applied at either an acupoint or a non-acupoint, and noxious thermal stimulation induced similar strong inhibitory effects on the C-fibre-evoked responses of trigeminal convergent neurons, and these inhibitions were followed by long-lasting after-effects and could be significantly reduced by systemic naloxone (Bing et al., 1990). Moreover, noxious mechanical stimulus was found to increase the

release of met-enkephalin-like material from heterosegmental levels of the spinal cord, but not from the neural segments related to the stimulated area of the rat body (Le Bars et al., 1987). Thus, it is speculated that the involvement of endogenous opiates in DNIC could play an important role in pain relief by TENS treatment.

Pain Measurements

One more issue concerning TENS analgesia is how to evaluate the effects of TENS on pain sensation. A wide variety of approaches to measuring pain has been advocated. Among them, the *visual analogue scale* as well as the *flexion reflex* will be employed in this study, and will be discussed in detail below.

Visual Analogue Scale (VAS): The VAS is probably the most commonly used approach in both clinical practice and experimental settings. The VAS was first described by Huskisson (1974). Normally, it consists of a 10-cm straight line anchored at one end by a label such as "no pain", and at the other end by a label such as "pain as bad as it could be". The line may be drawn either vertically or horizontally. Scoring is accomplished by having the patient mark the line to indicate pain intensity, and the line is then measured to the mark on either a 1-10 or 1-100 scale (Huskisson, 1974, 1982). Scott and Huskisson (1976) obtained a correlation of 0.75 between a four-point descriptive scale and a VAS drawn vertically. Dowine (1978) also reported correlation coefficients ranging from 0.71 to 0.78 between a four-point scale and the VAS drawn vertically or horizontally used in two samples of rheumatoid patients.

Correlation coefficients were found to range from 0.60 to 0.63 between the VAS and McGill Pain Questionnaire (Elton et al., 1979) Other researchers have also supported the reliability and validity of the VAS as a sensitive measure of pain intensity and of a change in pain sensation (c.f. McDowell and Newell, 1987, Ohnhauts and Adler, 1975). However, the VAS, like other subjective measures, is constrained by its potential susceptibility to contamination by a multitude of factors external to the immediate pain sensation. The flexion reflex described below has been found to be an objective and quantitative method of measuring experimental pain, and linearly correlated with stimulus intensity ($r = 0.91$) and with VAS scores ($r = 0.84$) in our previous study (Chan and Dallaire, 1989).

Flexion Reflex (FR): The FR, evoked by either a noxious or non-noxious stimulus, is considered to be a polysynaptic spinal reflex. Lloyd (1943) observed that the FR in cats has two components, namely RII and RIII. They were so termed because the early component was mediated by group II fibers and the late component by the slower conducting group III fibers. Similarly, two distinct electromyographic (EMG) components of the lower-limb flexors have been demonstrated in human subjects upon electrical stimulation of the sural nerve. The first component is accordingly termed RAII, and has a latency between 40 to 60 msec. The second higher threshold component is named RAIII and has a longer latency of 70 to 150 msec (Hugon, 1973). These findings were confirmed in a previous study from our laboratory upon stimulation of the plantar nerve in the sole of the foot (Chan and Tsang, 1985).

It is widely accepted that the RAII response is a tactile reflex which is evoked by non-noxious stimuli; whereas the RAIII response has a protective, nociceptive function and is elicited by higher intensity noxious stimuli (Collins et al., 1960; Hugon, 1973; Sherrington, 1910; Willer, 1977). Many pain researchers are interested in the RAIII response, because it is mediated by group III fibres which also mediate fast pain sensation (Lloyd, 1943; Perl, 1969). Thus, it has the same threshold as that of pain sensation (Hugon, 1973; Willer, 1977). Indeed, good correlation between subjective pain sensation and flexion reflex in terms of threshold, amplitudes and/or area values has been demonstrated by various investigators (Bromn and Treede, 1980; Chan and Dallaire, 1989; Chan and Tsang, 1985, 1987; Luu et al., 1988; Willer, 1985; Willer et al., 1984). For example, Chan and Dallaire (1989) showed that both VAS ratings and BF FR area bore a direct linear relationship with stimulus intensity ($r = 0.91$; $r = 0.95$, respectively) and with each other ($r = 0.84$). Furthermore, the FR amplitude was found to be modulated in parallel with that of pain sensation by the same mental task or morphine administration (Willer et al., 1979, 1980). In addition, Willer (1985) reported a clear increase in the RAIII response threshold after morphine administration (0.2 mg/kg). As a result, the FR has increasingly been used as an objective pain measurement in experimental pain research. The methodology for providing quantitative measurements of the human FR has been further refined by Chan and Tsang (1985). It will be described in detail later (Capter 2), since this technique will be employed in the present study together with the VAS.

PROBLEM FORMULATION and OBJECTIVES of STUDIES

As discussed above, the analgesic effects produced by low intensity, high frequency TENS were reported by some investigators to be *instant* (Erikson and Sjolund, 1976; Sweet and Law, 1983). However, one of our previous studies (Chan and Tsang, 1987) showed that TENS produced a *progressive* rather than immediate depressing action on the flexion reflex (FR) which was considered to be a quantitative pain measure, and the FR depression *outlasted* the stimulation for more than 50 min. A possible explanation for these contradictory results could be that TENS produces *different* rather than *similar* depressing influences on the FR processed at the *spinal cord* and subjective pain sensation processed at the *cortical* level. Therefore, the *first* objective of our study was to examine whether the antinociceptive influence of TENS on subjective pain sensation followed a *similar* or *different* time course from that of the FR induced by the same maximally tolerable electrical stimulation.

Our *second* question was: would the inhibitory effects of repeated TENS applications on both subjective pain sensation and FR cumulate over time? It is known that perception of pain in humans involves the transmission of neural signals via many synapses connecting various neurons. These synapses are subject to plastic changes (Nakata et al., 1979; Raisman and field, 1973; Starr and Wolpaw, 1993). Indeed, evidence is accumulating to indicate that even the hard-wired, monosynaptic spinal stretch reflexes can be

modified over time as a result of mental conditioning. Wolpaw et al. (1983) found that the amplitude of the spinal stretch reflex could be operantly conditioned to increase or decrease with respect to the up- or down-training mode in monkeys. Later studies by this research group (Wolpaw and O'keefe, 1984; Wolpaw et al., 1985) showed that the conditioned SSR change had two phases. A rapid initial jump, termed phase I, occurred within the first 6 hours and contributed to about 8% of the total changes. Phase II change occurred much more slowly and contributed to over 90% of the total change over weeks, with an average change of 2% per day. Studies on humans demonstrated similar changes as those on monkeys in both the time course and the magnitude of the spinal stretch reflex (Evatt et al., 1989; Segal et al., 1989).

Consistent with the above findings, Levin and Chan (1989) found that 45 min of TENS stimulation produced a significant prolongation of H and stretch reflex latencies in the spastic calf muscles, for up to 60 min post-stimulation. They also demonstrated that repeated application of TENS for two and three weeks respectively increased the vibratory inhibition of the soleus H reflex ($p = 0.02$), and decreased the magnitude of stretch reflexes ($p = 0.05$) in hemiparetic patients (Levin and Hui-Chan, 1992). In other words, possible plastic changes in the stretch reflex pathway have been shown to occur after long-term afferent conditioning in patients.

Acute change (inhibition) in the flexion reflex has also been reported to occur after a single session of afferent conditioning in

human studies (Chan and Tsang, 1987; Facchinetti et al., 1984). More specifically, in the majority of 11 normal human subjects, 30 min of low intensity, high frequency TENS produced a progressive inhibition of the flexion reflex in biceps femoris (BF) and tibialis anterior (TA) muscles. This inhibition lasted for up to 50 min after TENS. In contrast, placebo TENS application resulted in no significant change of the flexion reflex in all the muscles examined (Chan and Tsang, 1987).

In animal experiments, Chung et al. (1983) demonstrated that the flexion reflex was maximally inhibited to 40.1% and 42.7% of the control reflex after 15 min or 30 min peripheral nerve stimulation in 27 decerebrate and spinal cats, respectively. The post-stimulation effects lasted from less than 10 min to over one hour.

Since the findings mentioned above suggest that afferent conditioning can suppress the flexion reflex, and that the spinal stretch reflex can be operantly conditioned to decrease, we speculate that repeated TENS applications over a period of time (weeks) could result in a significant cumulative reduction of the flexion reflex. It should be note that possible long-term effect of TENS on the flexion reflex has not been investigated in either human or animal studies.

Also as mentioned earlier, Chan and Dallaire (1989) demonstrated that the VAS score is linearly correlated with the FR area under control conditions (i.e. without any conditioning).

Furthermore, the FR amplitude was found to be modulated in parallel with that of pain sensation by the same mental task or morphine administration (Willer et al., 1979, 1980). In addition, Hui-Chan and Mah (1992) reported a high positive linear correlation between the VAS and the FR *during* and *after* electroacupuncture to the contralateral leg alone (r=0.89) and with simultaneous electroacupuncture to the contralateral arm (r=0.93), in subjects showing a decrease in the FR area. However, it is not clear whether such a relationship between subjective pain sensation and FR responses will change with reference to possible cumulative effects of TENS. Thus, the *third* objective of our study was to investigate whether the linear relationship between VAS scores and FR area was modifiable by long-term TENS application.

In summary, the objectives of the present study were threefold:

(1) to determine whether the influence of a single TENS application on subjective pain sensation followed a similar or different time course as that of the FR;

(2) to determine whether the effects of repeated daily TENS on subjective pain sensation and FR would cumulate over time;

(3) to investigate whether the relationship between subjective pain sensation and FR responses was modifiable by long-term afferent conditioning via repeated TENS applications.

CHAPTER 2*

TENS exerts a prolonged and parallel inhibition of electrically induced pain sensation and flexion reflex in man

* This chapter is modified from a paper with the same title by Hui-Chan, C.W.Y. and Liu, J. in preparation for submission to *Pain*.

SUMMARY

Our previous study showed that low intensity, high frequency TENS produced a progressive and prolonged inhibitory influence on the lower limb flexion reflex (FR) in man. The *first* objective of our present study was to determine if the influence of TENS on subjective pain sensation followed a similar or different time course from that on the FR. The *second* objective was to examine whether the linear relationship previously observed between subjective pain estimates and FR areas was modifiable by such prolonged (60 min) afferent conditioning.

Twenty young healthy subjects were randomly assigned to a TENS or a placebo group, with 10 in each group. Sixty minutes of TENS or placebo stimulation was applied to the lumbro-sacral region. The FR was elicited by electrically stimulating the sole of subject's right foot at maximally tolerable intensity, and recorded electromyographically from the ipsilateral biceps femoris (BF) and tibialis anterior (TA) muscles. Subjective pain sensation was measured using the visual analog scale (VAS). ANOVA and planned comparison tests were employed to analyze the data obtained *before*, *during*, and up to 60 min *after* TENS or placebo stimulation.

Four main findings emerged. *Firstly*, the group mean VAS score reduced progressively *during* TENS, and reached statistical significance during the *after* stimulation period in the TENS (to 85.2% of control value, $p < 0.05$) but not placebo group (to 102.9%; $p > 0.05$). *Secondly*, the group mean TA FR area decreased significantly during the *after* stimulation period in both TENS (75.3% of control value; $p < 0.01$) and placebo groups (88.2%; $p < 0.05$). In comparison with placebo stimulation, however, TENS did produce a statistically greater amount of inhibition ($p < 0.05$). The group mean BF FR area decreased significantly during the *after* stimulation period in both TENS (78.2% of control value; $p < 0.01$) and placebo groups (85.8%; $p < 0.05$). However, a between-group comparison

showed that TENS did not produce significantly greater effects on BF FR area than placebo stimulation. *Thirdly*, the inhibitory influence of TENS on VAS scores followed a similar time course as that on FR area, with post-stimulation effects lasting over 60 min. *Fourthly*, 60 min of TENS did not modify the linear relationship between the VAS score and FR area and showed a correlation coefficient (r) of 0.93 and 0.95 respectively for TA and BF FR areas.

Our results suggest that prolonged stimulation of large diameter fibers, such as 60 min of low intensity, high frequency TENS, produced inhibitory influence on both subjective pain sensation and flexion reflex that had a similar time course. Such similar effects are probably the results of comparable processing at both cortical and spinal levels. The finding of a persistent post-stimulation effect is consistent with previous results showing the involvement of endogeneous opioids in TENS analgesia.

Key words: transcutaneous electrical nerve stimulation (TENS); flexion reflex; visual analog scale (VAS); subjective pain sensation; experimental pain

Introduction

Transcutaneous electrical nerve stimulation (TENS) has been demonstrated to be effective in treating a number of pain conditions. Some examples are low back pain (Fox and Melzack, 1976; Long et al., 1979; Marchand et al., 1993; Melzack et al., 1980, 1983), myofacial pain (Griaff-Radford et al., 1989), rheumatoid arthritis (Mannheimer and Carlsson, 1979), and postoperative pain (Smith et al., 1986, Warfield et al., 1985). The analgesic effects produced by low intensity, high frequency TENS were reported by some investigators to be immediate (Sweet and Law, 1983) or within 10 to 15 min (Erikson and Sjolund, 1976), showing a relatively rapid offset after stimulation (Andersson and Holmgren, 1976; Hughes et al., 1984). Indeed, Willer et al. (1982) found that this type of TENS induced a rapid depression of the blink reflex, which manifested no post-stimulation effect and was not reversed by naloxone.

In a previous study using the flexion reflex (FR) as a quantitative pain measure, we found the opposite: TENS produced a progressive rather than immediate depressing action that *outlasted* the stimulation for more than 50 min (Chan and Tsang, 1987). Such contradictory results on the FR and subjective reports of clinical pain are puzzling. A possible explanation could be that TENS produces *different* rather than *similar* depressing influences on the FR processed at the *spinal cord* and the subjective pain sensation processed at the *cortical* level. In other words, TENS could have induced progressive and persistent inhibition of the FR, but immediate and brief inhibition of pain sensation. An alternative

explanation could be that clinical pain is different from experimental pain. Thus, the *first* objective of our study was to examine whether the antinociceptive influence of TENS on subjective pain sensation followed a similar or different time course from that of the FR induced by the *same* maximally tolerable electrical stimulation.

Now, subjective pain sensation has been assessed using the visual analog scale (VAS). The latter was found to be reliable and sensitive to small changes in pain (Huskisson, 1974; Scott and Huskisson, 1976), and highly correlated (r = 0.62 to 0.98) with other pain scales such as numerical rating scales, simple descriptive scales and graphic rating scales (Downie et al., 1978). Of relevance to the present study is our own finding that the EMG area of the FR generated in a lower limb flexor (the biceps femoris) is linearly correlated (r = 0.84) with the subjective pain sensation assessed by VAS scores (Chan and Dallaire, 1989). This latter finding corroborated with those observed by Bromm and Treede (1980) in an upper limb extensor, and by Willer et al. (1984) using a numerical rating. A *second* question therefore arises: Is the linear relationship between the FR and subjective pain modifiable by prolonged afferent conditioning through low intensity, high frequency TENS?

In other words, the objectives of the present study were twofold: 1) to determine whether the influence of TENS on the subjective pain sensation followed a similar or different time course as that on the FR recorded in the lower limb flexors; and 2) to

determine whether the linear relationship between VAS scores and the FR was modifiable by prolonged afferent conditioning such as 60 min of TENS.

Methods

Subjects

Twenty-six paid, healthy university students with no existing neurological and neuromuscular disorder or pain syndrome were recruited for a screening test. Twenty of them (aged 19-24, 11 males and 9 females) who showed a stable FR over an hour of recording participated in the main study. They were randomly assigned to either a TENS (5 males, 5 females) or a placebo group (6 males, 4 females). Subjects were advised not to take any food/fluid containing caffeine prior to the experiment, because chemicals such as caffeine had been found to block the antinociceptive effects of opioids (Yashpal and Henry, 1992). None of the subjects had experienced TENS before, and everyone signed an "Informed Consent Form" approved by the local ethics committee.

TENS and Placebo Stimulation

A dual channel portable TENS unit (Staodyn MAXIMA III) provided electrical stimulation of 140 μsec square pulses at 80 Hz to the subject's low back for 60 minutes. Two skin electrodes (Staodyn Lo-back electrode) measuring 16.5 x 3.2 cm each were placed in parallel over the lumbro-sacral region (L4-S2)

paraspinally. This particular site was selected because it receives similar segmental innervation as the area antero-lateral to the median arch of the foot (L4-S2) where the painful FR stimulus was applied. The intensity was adjusted to produce a tingling sensation, and was approximately 2-3 times the sensory threshold. *Placebo stimulation* was delivered in the same fashion using sham units which were identically looking, but whose internal circuit had previously been disconnected. All subjects were told that they might or might not feel the stimulation over time. These procedures controlled psychological factors such as stress or subject bias, which had been shown to influence outcome (Willer and Able-Fessard, 1980). The results of stimulation were assessed using both the FR and VAS scores described below.

FR Recording

Details for eliciting and recording the FR have been described elsewhere (Chan and Dallaire, 1989; Chan and Tsang, 1985, 1987) They are now presented below.

To elicit the FR, the cathode (Graphic Control Medi-Trace pellet electrode) was strapped under pressure over the area anterio-lateral to the median arch of the right foot. The anode (a silver plate) was placed over the dorsal aspect of the foot. Once all the electrodes were affixed, the subject lay comfortably in a semi-inclined position (Fig. 2.1). The right knee and ankle articulations were fixated by partial casts in a relatively extended position to enhance the FR excitability (Baxendale and Farrell, 1981; Faganel, 1973).

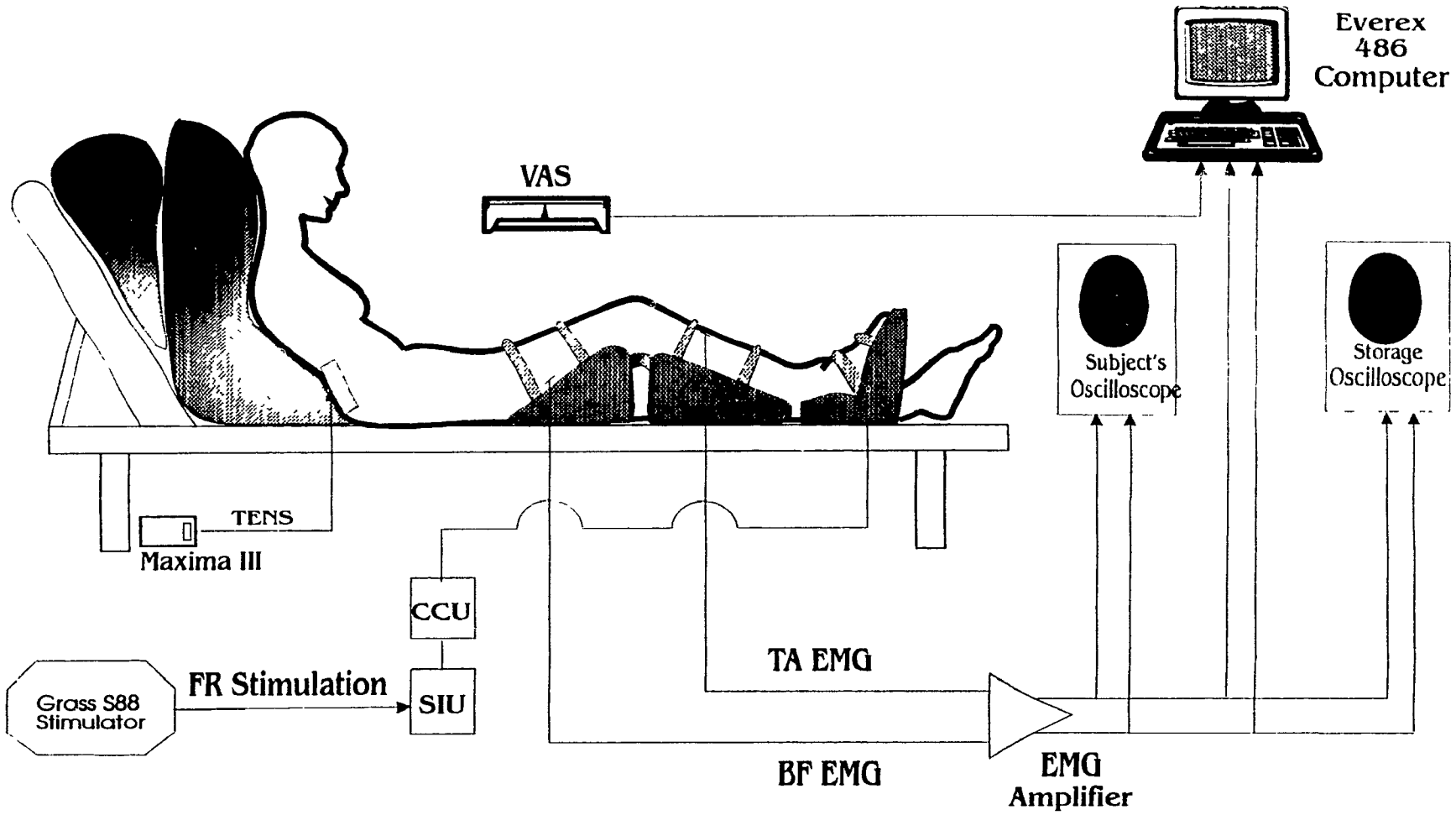

Fig 2.1 Experimental set-up.

The electrical stimulation used to elicit the FR consisted of a 30 msec train of 6 x 1 msec square pulses with an internal frequency of 200 Hz. It was delivered from a Grass S88 stimulator via a stimulus isolation unit (Grass SIU5) and a constant current unit (Grass CCU1). The current intensity was adjusted to the maximum level that the subject was able to tolerate, usually about 4 times the sensory threshold. It was measured by connecting a passive current probe for on-line recording throughout the experimental session. Fig. 2.2 shows its stability over the period of FR recording (see **Results**).

To avoid habituation of the FR, the electrical stimulation was applied with an inter-stimulus interval varying between 10 and 20 sec (Dimitrijevic et al., 1972), as well as during a tonic background contraction of the relevant muscles (Desmedt and Godaux, 1976; Kearney and Chan, 1979). It should be noted that the latter procedure has been shown to enhance the FR (Jenner and Stephens, 1982). Subjects were instructed to maintain a constant tonic background contraction of the tibialis anterior (TA) and biceps femoris (BF) at around 10% of the respective MVC, aided by the display of the filtered and smoothed EMG on an oscilloscope (Tektronix 2213). Because it was important to monitor the same type of motor neurons in terms of their size (Henneman et al., 1965), on-line computer control via a Everex computer (486 IBM compatible PC) ensured that the stimuli were delivered only when the subject's tonic EMG activity reached the desired level $\pm$ 15% for 1 sec.

To record raw EMG activities from the TA and BF of the right lower extremity, bipolar surface electrodes (Graphic Control Med-Trace pellet electrode) were attached 4 cm apart to scratched and degreased skin over the respective motor points (Basmajian and Blumenstein, 1980). For the BF, the ground electrode was placed over the lateral epicondile of the femur. For the TA, it was placed over the upper 1/3 bony shaft of the tibia. The EMG signals were amplified with a gain of 2,000, and band-pass filtered (10-500 Hz) with Disa (15 C 01) EMG amplifiers. They were then sampled on-line by an Everex computer at a frequency of 4 kHz, for 100 msec prior to and 400 msec after the FR stimuli. For averaging purposes, 15 response ensembles of the FR were recorded at 10 min intervals *before*, and 20 min intervals *during* and up to one hour *after* 60 min of TENS or placebo stimulation.

Subjective Pain Evaluation

Subjective pain sensation was measured using the visual analogue scale (VAS), which consisted of a horizontal 20 cm line anchored at the left end by "threshold intensity" (no pain) and the right end by "maximal tolerable intensity" (pain as bad as it could be) (Jensen et al., 1986). The VAS was attached to a linear potentiometer connected to the Everex computer for readout and storage. Each subject's sensory threshold was determined, and the maximal tolerable intensity ascertained by gradually increasing stimulus intensity until pain tolerance was reached. Immediately following each FR recording, the subject was asked to give an estimation of the intensity of the pain elicited by the electrical

stimulation, by moving the cursor on the VAS. Afterwards, they were instructed to return the cursor to the left end of the scale (i.e. the "threshold intensity" position). This was done to eliminate the potential bias resulting from comparison to previous estimations (c.f. Chan and Dallaire, 1989; Dallaire and Chan, 1987).

Data Analysis

Matlab and SPSS professional statistics packages were used to analyze the EMG data and VAS scores. EMG signals were rectified, then FR areas were computed by integrating the areas underneath the EMG curves over windows ranging from 40 to 200 msec according to individual FR response pattens. FR area values and VAS scores were pooled for each of the 3 time periods *before*, *during*, and *after* TENS or placebo stimulation, and then normalized to the mean of their respective control value (i.e. the pooled data obtained *before* the stimulation). The effects of 60 min of TENS on both FR areas and VAS scores were compared with those of placebo stimulation using two-way mixed design analysis of variance (ANOVA), followed by planned comparison post hoc tests with Bonferronic correction (Olson, 1987). Pearson's correlation coefficient tests and linear regression analyses were employed to determine the relationship between VAS scores and FR areas as a result of TENS application. A statistical significance level of $p < 0.05$ was set for all tests.

Results

Stability of Electrical Stimuli Eliciting the FR

Fig. 2.2 shows that the electrical current intensity used to elicit the FR was stable throughout the recording period in one subject each from the TENS (left plot) and placebo group (right plot). Note the similarity in current intensity applied to these 2 subjects, which was typical of the TENS (mean = 18.6 $\pm$ 1.6 mA) and placebo group (mean = 18.1 $\pm$ 3.5 mA).

Influence of TENS and Placebo Stimulation on Subjective Pain Sensation

Fig. 2.3 shows the effect of 60 min of TENS (left plot) and placebo stimulation (right plot) on subjective pain sensation in one subject from the respective group. Each data point represents the mean of 15 VAS scores $\pm$ 1 S.D., expressed as a percentage of the mean control value (average of 3 ensembles of 15 VAS scores recorded at 10 min intervals *before* stimulation). Note that VAS scores progressively decreased *during* TENS and reached a maximum value at 60 min *after* TENS was turned off. In contrast, placebo stimulation produced a negligible influence on the VAS scores.

Fig. 2.4 illustrates the effects of TENS and placebo stimulation on group means VAS scores. Each histogram column represents a mean of 10 x 45 VAS scores (10 subjects; 45 trials per subject), expressed as a percentage of the mean control value obtained *before* stimulation. Note that the group mean VAS score was

reduced during TENS and reached statistical significance during the 60 min *post*-stimulation period in the TENS (to 85.2% of control value; $p<0.05$), but not in the placebo group (to 102.9%; $p<0.05$). Moreover, a between-group comparison revealed that TENS produced statistically greater *post*-stimulation effects on VAS scores than placebo stimulation ($p<0.05$).

Effects of TENS and Placebo Stimulation on Flexion Reflex

Fig. 2.5 illustrates the effects of 60 min of TENS (left plots) and placebo stimulation (right plots) on the TA FR responses in one subject from each group. Each plot represents the mean of 15 rectified FR EMG signals. Fig. 2.5 (A-C) on the left shows the control responses obtained respectively at 30, 20, and 10 min *before* TENS. Fig. 2.5 (D-F) illustrate the progressive inhibition of the FR responses at 20, 40, and 60 min *into* TENS. Interestingly, the FR responses became even more inhibited during the 3 x 20 min intervals *after* TENS was turned off (Fig. 2.5.G-I). In contrast, placebo stimulation produced only negligible inhibitory effects on the TA FR (right plots in Fig. 2.5). Note that there were differences in the FR pattens between the two subjects. The subject in the TENS group displayed an FR with a double peak, while the subject in the placebo group showed an FR with a single peak. Off-line calculation revealed that the FR in Fig. 2.5.A on the left had a latency of 60 ms and a duration of 110 ms (i.e. it lasted from 60 to 170 ms), while the other one on the right had a latency of 61 ms and a duration of 47 ms (i.e. it lasted from 61 to 108 ms). A close check of all the subjects' data

showed that the two pattens of FR were found in both TENS and placebo groups.

Fig. 2.6.A shows the effects of TENS and placebo stimulation on the TA FR area. Each histogram column represents a mean of 10 x 45 FR area values (10 subjects; 45 trials per subject), expressed as a percentage of the mean control value obtained *before* stimulation. The group mean TA FR area was significantly decreased during the *after* stimulation period in both TENS (to 75.3% of control value; $p<0.01$) and placebo groups (to 88.2%; $p<0.05$). In comparison with placebo stimulation, however, TENS did not produce a significantly greater amount of inhibition ($p<0.05$).

Fig. 2.6.B shows the effects of TENS and placebo stimulation on the BF FR area. The group mean BF FR area was significantly reduced to 78.0% of control value ($p<0.01$) during the *after* stimulation period in the TENS group, and to 85.8% ($p<0.05$) in the placebo group. However, despite the tendency towards greater inhibition, a between-group comparison showed that TENS did not produce significantly greater effects on the BF FR area than placebo stimulation.

*Relationship between VAS Scores and FR Areas **Before, During** and **After** TENS*

Fig. 2.7 shows the linear regression line drawn between VAS scores and FR area values. The 9 data points in each graph were obtained at 3 x 10 min intervals *before* and 3 x 20 min intervals *during* and *after* TENS. Each of the 9 data points represents a mean

of 10 x 15 trials (10 subjects with 15 trials per subject), and is expressed as a percentage of the group mean control value (average of 3 ensembles of 15 trials in the TENS group recorded *before* TENS for the 10 subjects). It is evident that VAS scores were highly correlated with both TA FR area and BF FR area values, with a correlation coefficient (r) of 0.93 and 0.95 and a slope of 0.55 and 0.61 respectively.

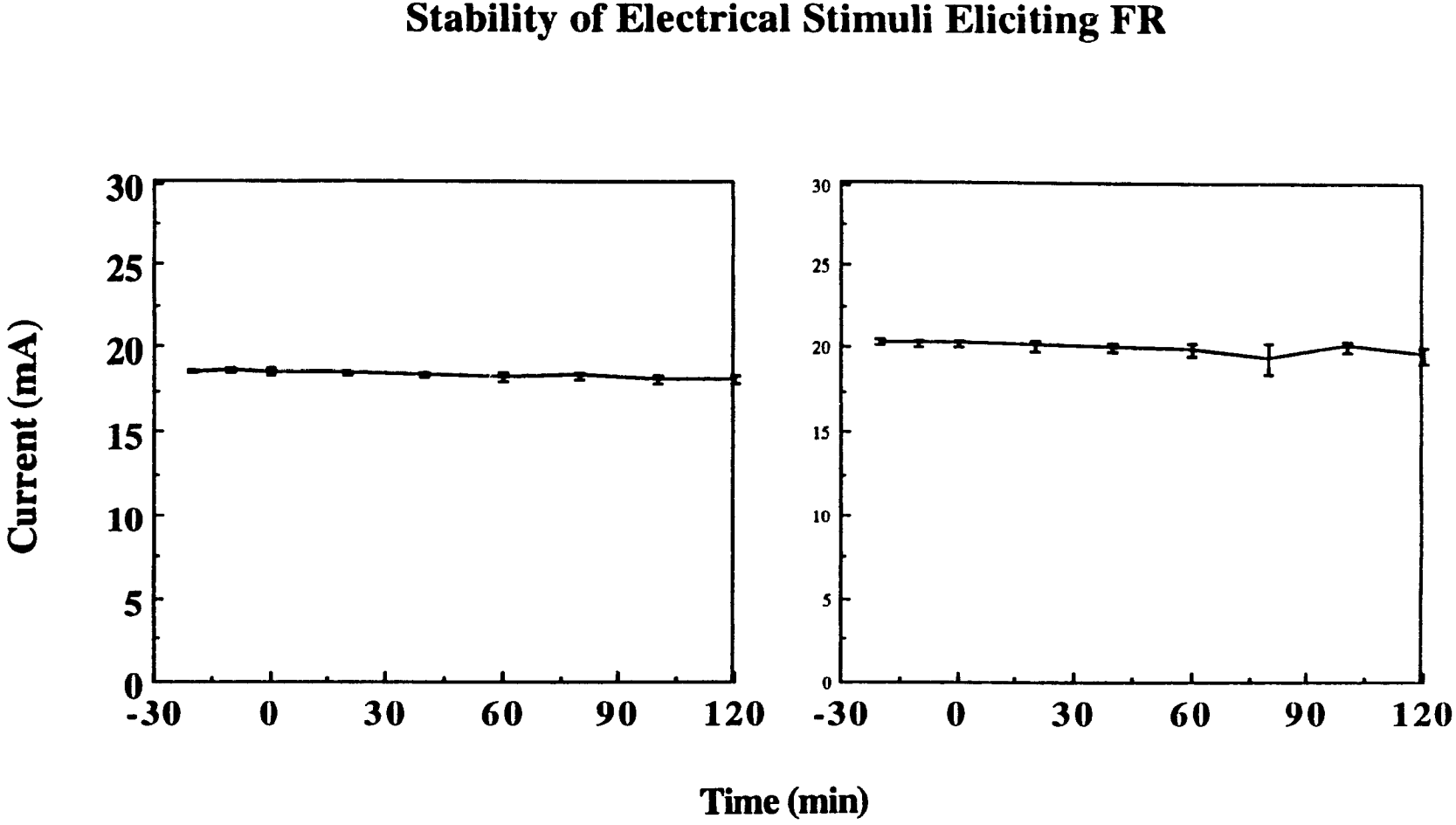

Fig. 2.2 Intensity of the electrical current that elicited the FR in one subject from each of the TENS (left) and placebo group (right). Each data point represents the mean of 15 trials ± 1 S.D.

Influence of 60 min of TENS and Placebo Stimulation on Subjective Pain Sensation

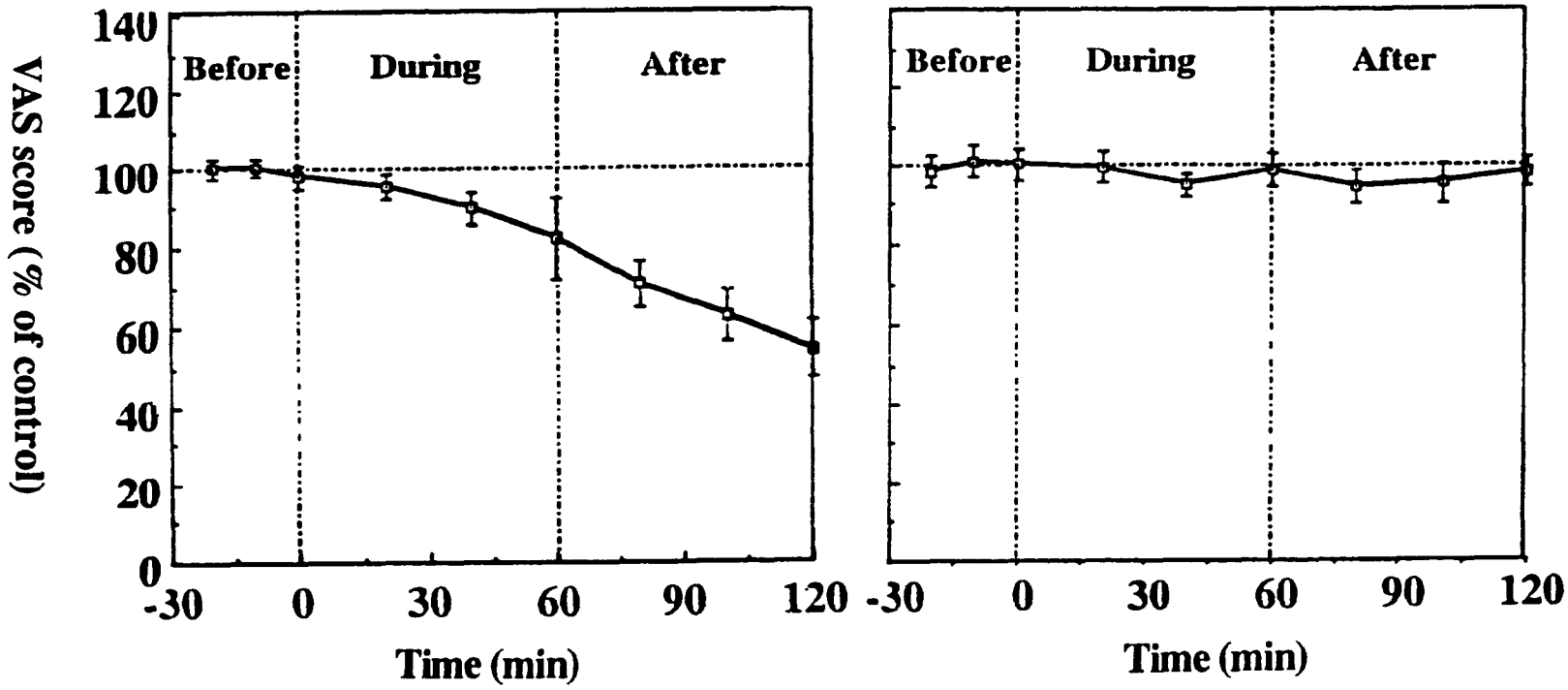

Fig. 2.3 Influence of 60 min of TENS (left plot) and placebo stimulation (right plot) on VAS scores in 2 different subjects. Each data point represents the mean of 15 VAS scores ± 1 S.D., expressed as a percentage of the mean control value (average of 3 ensembles of 15 VAS scores obtained at 10 min interval *before* stimulation).

Effects of TENS and Placebo Stimulation on VAS Score

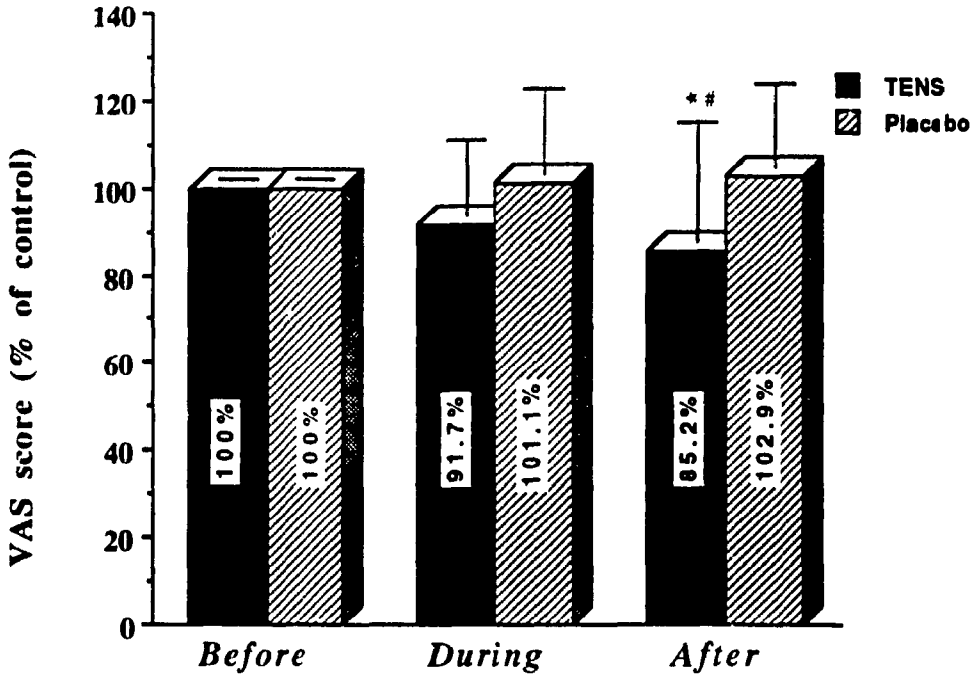

Fig. 2.4 Effects of 60 min of TENS (black columns) and placebo stimulation (striped columns) on group means of VAS scores. Each column represents a mean of 10 x 45 VAS scores (10 subjects with 45 trials per subject) expressed as a percentage of the mean control value obtained *before* stimulation.

* denotes the within group comparison between the period *before* and *after*. and represents $p<0.05$.

# denotes comparison between TENS and placebo group, and represents $p<0.05$.

Influence of 60 min of TENS and Placebo Stimulation on Tibialis Anterior FR

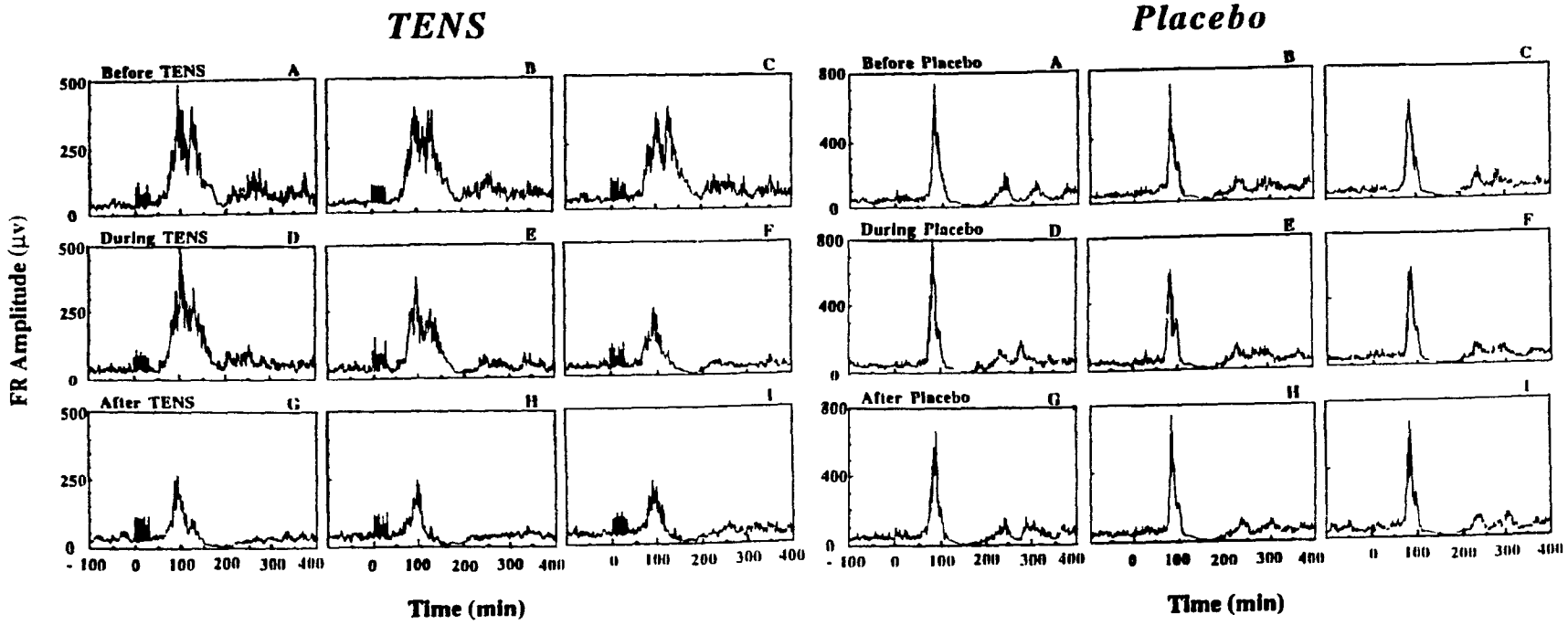

Fig. 2.5 Effects of 60 min of TENS (left plots) and placebo stimulation (right plots) on the TA FR responses in 2 different subjects. Each of the graphs represents the mean of 15 rectified FR EMG signals. (A - C). Control responses recorded at 10 min intervals *before* stimulation; (D - F). Responses recorded at 20 min intervals *during* stimulation; (G - I). Responses recorded at 20 min intervals *after* stimulation.

Effects of TENS and Placebo Stimulation on FR Area

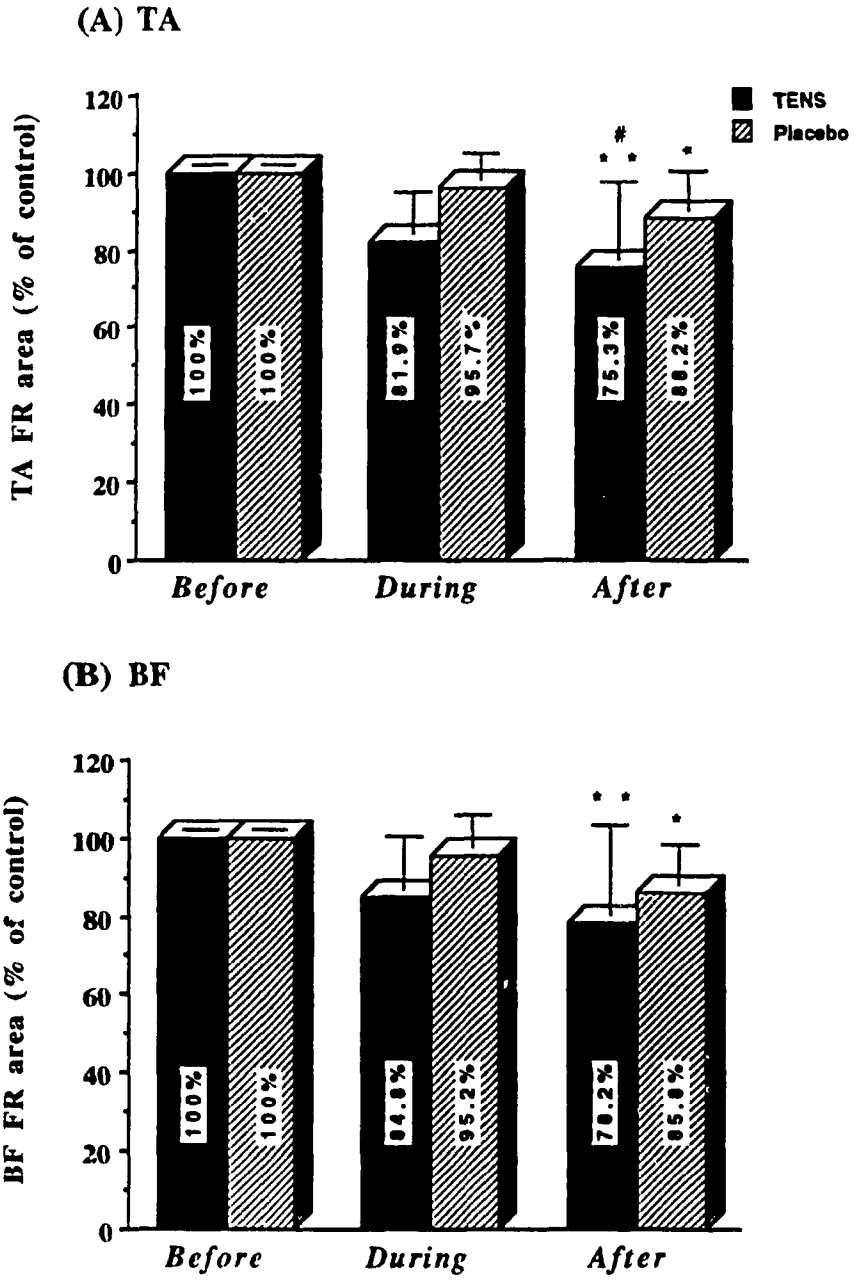

Fig. 2.6 Effects of 60 min of TENS (black columns) and placebo stimulation (striped columns) on group means of the (A) TA and (B) BF FR area. Each column represents a mean of 10 x 45 FR area values (10 subjects with 45 trials per subject) expressed as a percentage of the mean control value obtained *before* TENS or placebo stimulation.
* and ** denote the within group comparison between the period *before* and *after*, and represent $p<0.05$ and $p<0.01$ respectively.
# denotes the comparison between the TENS and placebo group, and represents $P<0.05$.

Influence of 60 min of TENS on the Relationship between VAS Scores and FR areas

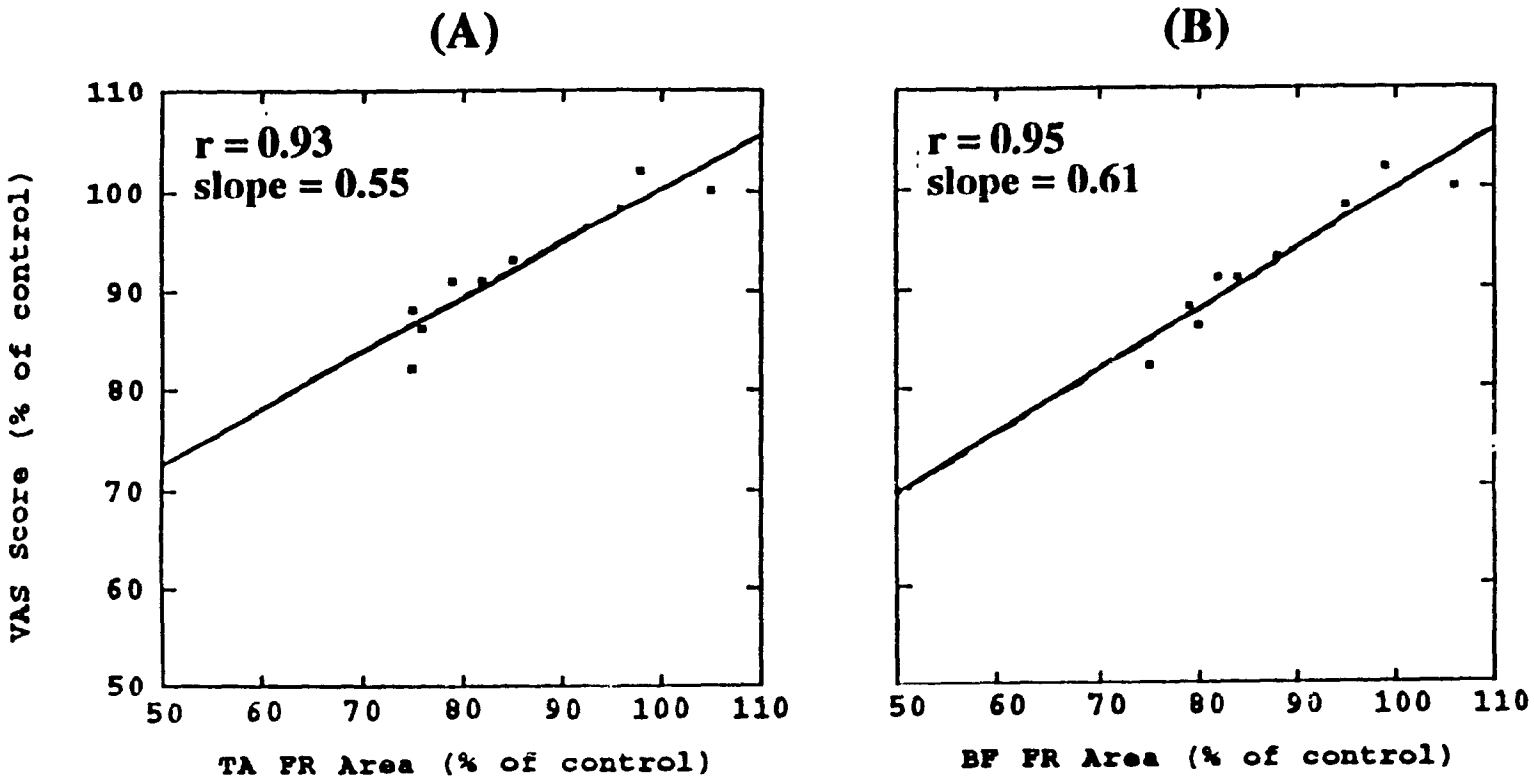

Fig. 2.7 Linear regression lines drawn between VAS scores and (A) TA and (B) BF FR areas obtained at 3 x 10 min intervals *before* and 3 x 20 min intervals *during* and *after* TENS. Each of the 9 data points represents a mean of 10 x 15 trials (10 subjects; 15 trials per subject) expressed as a percentage of the group mean control value (average of 3 ensembles of 15 trials recorded before TENS for the 10 subjects).

Discussion

Depressing Effect of TENS on Subjective Pain Sensation

In contrast to placebo stimulation, low intensity, high frequency TENS progressively depressed the subjective pain sensation as measured by VAS scores *during* the 60 min treatment period (Fig. 2.3). After TENS was turned off, the depressing effect further increased instead of recovering, and reached statistically significant depression during the 60 min period *after* TENS was turned off (Fig. 2.4, black column). It should be interesting to document how long this antinociceptive post-stimulation effect lasts. However, since the 2 $^1/_2$ hours of recording required by our protocol was already at the limit of our subjects' tolerance level, we were not in a position to further prolong our post-stimulation recording period because of ethical considerations.

The mechanism underlying TENS analgesia is not entirely understood yet. It is commonly accepted that TENS analgesia can be at least partly explained by the gate control theory (Melzack and Wall, 1965), which states that stimulation of low threshold large myelinated primary afferent fibers can decrease the response of dorsal horn neurons to small nociceptive fibers. A recent study from our laboratory showed that both conventional (i.e. low intensity, high frequency) and acupuncture-like TENS (i.e. high intensity, low frequency) activated similar afferent fibers, predominantly in the Aαβ range (Levin and Hui-Chan, 1993). Accordingly, the stimulation parameters used in the present study

should likewise activate large diameter fibers. Thus, it could be argued that stimulation of large diameter fibers could reduce the transmission of pain signals by the small nociceptive fibers, leading to the depression of VAS scores *during* TENS stimulation in our study (Fig. 2.3 and the middle shaded column of Fig. 2.4). What then could account for the post-stimulation effects observed in our experiment?

It is generally agreed that acupuncture-like TENS analgesia is probably mediated by the endogenous pain inhibitory system first proposed by Basbaum and Fields (1978, 1984). This is based on studies which showed that acupuncture-like TENS produced gradual onset and long-lasting analgesic effects (Andersson et al. 1973; Pomeranz and Cheng, 1979), that were blocked by the administration of naloxone, an opiate antagonist (Cheng and Pomeranz, 1979; Sjolund and Eriksson, 1979). Indeed, a direct increase of opioid peptides in the cerebrospinal fluid (CSF) has been found after acupuncture-like TENS by a number of researchers (e.g. Sjolund et al., 1977; Han et al., 1991).

However, low intensity, high frequency (the so-called *conventional*) TENS was used in our present study rather than acupuncture-like TENS, In this context, there has been some controversies regarding the mechanism responsible for mediating conventional TENS analgesia. For sometime, it was thought to involve non-opioids systems, since a few studies had demonstrated that the analgesic effects generated by conventional TENS were not blocked by naloxone (e.g. Freeman et al., 1983; Sjolund and Eriksson, 1979).

In contrast, Woolf et al. (1977) showed that the depressing effect generated on the tail immersion test by low intensity TENS was antagonized by naloxone in rats. Han et al. (1991) further demonstrated that whereas acupuncture-like TENS (2 Hz) significantly increased met-enkephalin-arg-phe from the preproenkephalin, conventional TENS (100 Hz) produced a significant increase of dynorphin A from preprodynoephin. These authors proposed that proenkephalin-derived peptides acted on the *mu* receptors; whereas preprodynorphin-derived peptides worked on the *kappa* receptors which were relatively resistant to naloxone blockage (Fei et al., 1987; Goldstein et al., 1979; Han et al., 1984). Therefore, insufficient dosage of naloxone used and/or failure to employ specific *kappa* antagonists in the previous studies (Freeman et al., 1983; Sjolund and Eriksson, 1979) could explain why they failed to show that conventional TENS analgesia was naloxone reversible.

As mentioned in the Introduction, some investigators have reported that conventional TENS produced on instant pain relief (Andersson et al., 1977; Eriksson and Sjolund, 1976). In contrast, our present study showed that conventional TENS analgesia had a gradual onset and that the effect was even greater during the 60 min *post*-stimulation period (Fig. 2.3 and the right black column of 2.4). The reason behind these conflicting findings is not clear, but one possible explanation could be that we used a longer duration of stimulation. This issue will be further discussed in the section below.

Inhibitory Effect of TENS on Flexion Reflex

As illustrated in Fig. 2.5 and Fig. 2.6.(right black column), 60 min of TENS also produced a progressive and prolonged inhibition on both TA and BF FR, that reached statistical significance ($p<0.05$ for both muscles) during the period *after* TENS was turned off. This result is consistent with our previous findings (Chan and Tsang, 1987). Both studies demonstrated that TENS exerted a gradual and prolonged inhibitory effect on FR, and thus favored the view that the antinociceptive effects generated by low intensity, high frequency TENS could involve, at least in part, the release of endogenous opioids. In addition to the evidence mentioned above, this speculation was supported by Facchinetti et al. (1984) who found a concomitant increase in nociceptive flexion reflex threshold and plasma opioids following conventional TENS. Furthermore, the present study showed that the FR became even more inhibited for up to an hour *after* TENS was turned off (Fig. 2.5 and 2.6), in contrast to our previous study which reported that the maximum inhibition occurred *during* TENS and that the FR recovered somewhat *after* TENS was turned off (Chan and Tsang, 1987). The fact that FR responses were further inhibited *after* TENS in the present study may be attributed to a longer duration of TENS (60 min) being used in the present than the previous study (30 min). Garcia-Larrea et al. (1989) investigated the effects of 5 min of dorsal column stimulation (DCS) and TENS in patients with intractable pain, and found that the FR depression was rapidly reversed after stimulation. The short duration (5 min only) they used could account for the

rapid recovery of the FR. Thus, it appeared that the longer the duration of TENS, the longer the post-stimulation effect.

Our finding of a significant inhibition of the FR in both TA and BF muscles by placebo stimulation ($p<0.05$; Fig. 2.6.A and B, right stripped columns) raises an interesting point. It could be argued that such an inhibition may not be a pure placebo influence, that at least part of it could be due to the effect of repeating a constant stimulus over time. It is known that the FR is subject to habituation (Dimitrijevic et al., 1972). Therefore, we had taken some steps to minimize habituation, such as varying inter-stimulus interval and subjects being instructed to maintain a constant tonic background contraction of the muscle being tested. Furthermore, only subjects showing stable FRs over an hour of recording during the screening test were recruited for the study (see **Methods**). Nevertheless, our experimental session lasted 2 $^1/_2$ hours. Thus, possible habituation of the FR could not be entirely excluded. This is why we included a placebo group in our protocol design to take account of not only the placebo effect but also possible time effect. Whether there were real placebo or purely time effects, findings from the present study did show that TENS produced a significantly greater inhibitory effect than placebo stimulation on the TA FR area. Although similar findings had not yet been confirmed for the BF FR area, a tendency for it to be more inhibited both *during* and *after* TENS than placebo stimulation was shown in Fig. 2.6.B (black column). Such a lack of statistical significance may be due to the wide variability of BF FR area values and the small sample size. We speculate that the

difference between the effect of TENS and placebo stimulation might become significant for the BF FR area, if the duration of stimulation were longer. Further study is needed to confirm this conjecture.

Relationship between Subjective Pain Sensation and Flexion Reflex

As discussed above, 60 min of TENS produced progressive inhibitory effects on both subjective pain sensation and FR - both *during* and *after* the stimulation was turned off. In other words, TENS appeared to produce parallel inhibition of the two pain indices. This was illustrated in Fig. 2.7, which showed that the decrease of VAS scores was linearly correlated with both TA and BF FR area values *before*, *during*, and *after* TENS treatment. This finding was consistent with that of Willer et al. (1979, 1980), who reported that the amplitude of FR could be depressed (or facilitated) in parallel with subjective pain report by a single session of morphine or mental task conditioning. These findings indicated that the linear relationship observed between subjective pain sensation and FR under control conditions in our previous study (Chan and Dallaire, 1987), was not modified by a single session of afferent conditioning in normal subjects. Such inhibitory effects of TENS on subjective pain sensation and FR were probably the results of parallel processing at both cortical and spinal levels.

In conclusion, 60 min of TENS produced a similar inhibitory influence on both subjective pain sensation and flexion reflex that reached statistical significance during the post-stimulation period. Such parallel effects are probably the results of parallel processing

at both cortical and spinal levels. The finding of progressive antinociceptive and long-last post-stimulation effects is consistent with previous results showing the involvement of endogenous opioids in mediating low intensity, high frequency TENS analgesia.

Acknowledgements

This work was supported by a grant from the *Fonds de la Recherche en Santé du Québec*. The authors wish to thank the subjects for their participation and in particular, Ahmed Alfat, who developed the computer programs for on-line experimental control, data collection and analysis.

CHAPTER 3*

Antinociceptive Effects of TENS on Experimental Pain and Flexion Reflex Will Cumulate over Time

* This chapter is modified from a paper with the same title by Liu, J. and Hui-Chan, C.W.Y. in preparation for submission to *Pain*.

SUMMARY

Previous studies in our laboratory showed that a single 30 min application of TENS produced a progressive and prolonged inhibition of both biceps femoris (BF) and tibialis anterior (TA) flexion reflex (FR) in the majority of the human subjects examined. In Chapter 2, we demonstrated that the decrease in subjective pain sensation was linearly correlated with the decrease in lower limb FR area *during* and *after* 60 min of TENS. The *first* objective of our study was to determine whether such suppressing influence on subjective pain sensation and FR would cumulate over a two-week period with repeated applications of daily TENS. We then set out to delineate whether progressive changes in the relationship between subjective pain sensation and FR could have resulted from such long-term afferent conditioning.

Twenty young healthy subjects were randomly assigned to a TENS or a placebo group, with 10 in each. TENS or placebo stimulation was applied to the lumbro-sacral region for 60 minutes on 10 treatment days over a two-week period. The FR was elicited by electrically stimulating the sole of subject's right foot and recorded electromyographically from BF and TA muscles *before*, *during* and *after* TENS or placebo stimulation. Subjective pain sensation was measured using the visual analog scale (VAS). ANOVA and planed comparison tests were used to compare the data obtained *before* TENS or placebo stimulation on Day_1 with those of Day_{10} and between the two groups. Pearson's correlation coefficient tests and linear regression analyses were employed to determine the relationship between VAS scores and FR areas on Day_1, Day_5 and Day_{10}.

A significant reduction of the pre-stimulation VAS control value from Day_1 to 67.2% was found on Day_{10} in the TENS ($p < 0.01$) but not the placebo group (104.2%). For the TA FR area, the pre-stimulation control value was decreased from Day_1 to 68.6% on Day_{10} in the TENS group ($p < 0.01$), but not in the placebo group (92.5%; $p > 0.05$). For the BF

FR area, both TENS and placebo stimulation significantly depressed the pre-stimulation control value from Day_1 to 63.8% ($p < 0.01$) and 84.8% ($p < 0.05$) respectively on Day_{10}. In comparison with placebo stimulation, however, TENS produced greater inhibitory effects ($p < 0.01$) on both VAS scores and FR areas of the two muscles examined. In addition, the VAS scores were highly correlated with both TA and BF FR areas, with correlation coefficients (r) of 0.93 and 0.95, 0.95 and 0.97, 0.78 and 0.68 respectively for Day_1, Day_5, and Day_{10}.

The above findings indicated that repeated daily TENS applications produced cumulative inhibitory influence on both subjective pain sensation and FR over a two-week period. Such a gradual development probably implicated that plastic changes could have been induced in the neural pathway. The similar effects of TENS on the two pain indices were probably the results of similar processing at both cortical and spinal levels.

Key words: transcutaneous electrical nerve stimulation (TENS); experimental pain; flexion reflex; subjective pain sensation; visual analog scale (VAS)

Introduction

Perception of pain in humans involves the transmission of neural signals via many synapses connecting various neurons. These synapses could be subject to plastic changes (Nakata et al., 1979; Raisman and Field, 1973; Starr and Wolpaw, 1993) besides pharmacological manipulation. Indeed, evidence is accumulating to indicate that even the hard-wired, monosynaptic spinal stretch reflex can be modified over time as a result of mental conditioning. More specifically, Wolpaw and colleagues (1983; 1985; Wolpaw and Carp, 1990; Wolpaw and O'Keefe, 1984) reported that both the spinal stretch reflex and the H reflex could be operantly conditioned to increase or decrease their magnitude over a training period of several weeks in monkeys. Similar changes have also been found in normal human subjects (Evatt et al., 1989; Segal et al., 1989). In stead of mental training, Levin and Hui-Chan (1992) demonstrated that repeated daily application of TENS but not placebo stimulation for 3 weeks decreased the magnitude of stretch reflex in hemiparetic patients. In other words, plastic changes in the stretch reflex pathway have been shown to occur after prolonged mental conditioning in monkeys and normal humans or afferent conditioning in patients.

Now, immediate changes in the flexion reflex (FR) have been reported to occur after a single session of afferent conditioning in both animal and human studies. Chung et al. (1983) showed that the flexion reflex was maximally inhibited to 40.1% and 42.7% of the control value after 15 or 30 min of peripheral nerve stimulation

respectively in decerebrate and spinal cats. The inhibitory effects lasted from less than 10 min to over an hour after termination of the conditioning stimuli in 27 decerebrate and spinal cats. In human studies, Chan and Tsang (1987) demonstrated that 30 min of TENS applied to the low back produced a gradual inhibition of the FR in the biceps femoris (BF) and tibialis anterior (TA) muscles in the majority of 11 normal subjects, and the effects lasted for up to 50 min after TENS. Garcia-Larrea et al. (1989) reported that FR was depressed or suppressed by 5 min of dorsal column stimulation (DCS) or TENS in 11 of 21 patients with chronic intractable pain, but the depression was rapidly reversed after stimulation.

In view of the modifiability of the stretch reflexes by long-term afferent conditioning, an interesting question arises: would the inhibitory effect on the FR due to a single session of TENS cumulate after repeated applications over time? To our best knowledge, possible long-term effect of TENS on the FR has not been investigated in either human or animal studies.

Now, subjective pain sensation, as measured by the visual analog scale (VAS), has been found to correlate with FR parameters such as threshold, amplitude and/or area values (Bromm and Seide, 1982; Brown and Treede, 1980; Chan and Dallaire, 1989, Willer et al., 1979; 1980; 1983; 1984). More specifically, Chan and Dallarie (1989) showed that VAS scores were linearly correlated with the FR areas recorded from the BF under control conditions ($r = 0.84$). In the previous Chapter, we reported our finding that 60 min of TENS produced similar and prolonged inhibition on both VAS scores and

FR areas, and that these 2 pain indices were highly correlated for both the TA (r = 0.93) and the BF muscles (r = 0.95) even in the presence of afferent conditioning. However, it was not clear whether such a systematic relationship was modifiable by possible cumulative effects of long-term TENS application. Consequently, the *first* objective of our present study was to determine whether the suppressing effects of repeated daily TENS on subjective pain sensation and FR would cumulate over a two-week period in humans. We then set out to investigate whether there were progressive changes in the relationship between VAS scores and FR areas as a result of such long-term stimulation.

Methods

Subjects

Twenty-six paid, healthy university students with no existing neurological and neuromuscular disorder or pain syndrome were recruited for a screening test. Twenty of them (aged 19-24, 11 males and 9 females) who showed a stable FR over an hour of recording were selected to complete the full study. None of them had any experience of TENS before, and everyone signed a "Informed Consent Form" approved by the local ethic committee.

Experimental Protocol

The twenty subjects were randomly assigned to either a TENS group (5 males, 5 females) or a placebo group (6 males, 4 females).

Both groups came to the laboratory to receive either conventional TENS or placebo stimulation that lasted for 60 minutes on 10 treatment days over a two-week period. There was a two days' break between Day_5 and Day_6. Stimulation outcome in the two groups was assessed using both the VAS and the FR on the first, fifth and tenth treatment day, termed Day_1, Day_5 and Day_{10} henceforth. Because of known circadian variation of human FR (Sandrini et al., 1986), every subject was assessed during the same period of the day for the 3 testing sessions.

TENS and Placebo Stimulation

A dual channel portable TENS unit (Staodyn MAXIMA III) provided electrical stimulation of 140 μsec square pulses at 80 Hz to the subject's low back for 60 minutes on each of the 10 treatment days. Two skin electrodes (Staodyn Lo-back electrode) measuring 16.5 x 3.2 cm each, were placed in parallel over the lumbro-sacral region (L4-S2) paraspinally. This particular site was selected because it receives similar segmental innervation as the area anterio-lateral to the median arch of the foot (L4-S2) where the painful FR stimulus was applied. The intensity was adjusted to produce a tingling sensation and was approximately 2-3 times the sensory threshold. *Placebo stimulation* was delivered in the same fashion using sham units which looked identical, but whose internal circuit had previously been disconnected. All subjects were told that they might or might not feel the stimulation over time. These procedures controlled psychological factors such as stress or

subject bias, which had been shown to influence outcome (Willer and Albe-Fessard, 1980).

FR Recording

Details for eliciting and recording the FR have been described elsewhere (Chan and Dallaire, 1989; Chan and Tsang, 1985, 1987). They are now presented below.

To elicit the FR, the cathode (Graphic Control Medi-Trace pellet electrode) was strapped under pressure over the area anterio-lateral to the median arch of the right foot. The anode (a silver plate) was placed over the dorsal aspect of the foot. Once all the electrodes were affixed, the subject lay comfortably in a semi-inclined position (Fig. 2.1 in Chapter 2). The right knee and ankle articulations were fixated by partial casts in a relatively extended position to enhance the FR excitability (Baxendale and Farrell, 1981; Faganel, 1973).

The electrical stimulation used to elicit the FR consisted of a 30 msec train of 6 x 1 msec square pulses with an internal frequency of 200 Hz. It was delivered from a Grass S88 stimulator via a stimulus isolation unit (Grass SIU5) and a constant current unit (Grass CCU1). The current intensity was adjusted to the maximum level that the subject was able to tolerate, usually about 4 times the sensory threshold. It was measured by connecting a passive current probe for on-line recording throughout the experimental session. Fig. 2.2 shows its stability over the period of FR recording (see **Results** in Chapter 2).

To avoid habituation of the FR, the stimulation was applied with an inter-stimulus interval varying between 10 and 20 sec (Dimitrijevic et al., 1972), as well as during a tonic background contraction of the relevant muscles (Desmedt and Godaux, 1976; Kearney and Chan, 1979). It should be noted that the latter procedure has been shown to enhance the FR (Jenner and Stephens, 1982). Subjects were instructed to maintain a constant tonic background contraction of the tibialis anterior (TA) and biceps femoris (BF) at around 10% of the respective MVC, aided by the display of the filtered and smoothed EMG on an oscilloscope (Tektronix 2213). Because it was important to monitor the same type of motor neurons in terms of their size (Henneman et al., 1965), on-line computer control via a Everex computer (486 IBM compatible PC) ensured that the stimuli were delivered only when the subject's tonic EMG activity reached the desired level $\pm$ 15% for 1 sec.

To record raw EMG activities from the TA and BF of the right lower extremity, bipolar surface electrodes (Graphic Control Med-Trace pellet electrode) were attached 4 cm apart to scratched and degreased skin over the respective motor points (Basmajian and Blumenstein, 1980). For the BF, the ground electrode was placed over the lateral epicondile of the femur. For the TA, it was placed over the upper 1/3 bony shaft of the tibia. In an attempt to keep identical sites for EMG recording on Day_1, Day_5 and Day_{10}, each electrode location was marked on the skin using a permanent ink pen at the end of the experiments on Day_1 and Day_5. The EMG

signals were amplified with a gain of 2,000, and band-pass filtered (10-500 Hz) with Disa (15 C 01) EMG amplifiers. They were then sampled on-line by an Everex computer at a frequency of 4 KHz, for 100 msec prior to and 400 msec after the FR stimuli. For averaging purposes, 15 response ensembles of the FR were recorded at 10 min intervals *before*, and at 20 min intervals *during* and up to one hour *after* 60 min of TENS or placebo stimulation.

Prior to the FR recording, 3 maximum voluntary isometric contractions (MVC) were recorded in both TA and BF muscles. The electromyography (EMG) activity generated by the MVCs of both the TA and BF will be used for normalization of the FR response. Several researchers have reported reproducible results with surface EMG recording during MVC. Viitasalo and Komi (1975) investigated the reliability and constancy of MVC of the rectus femoris muscle in 10 normal subjects (aged 13-15). They found that the within-day reliability coefficient was 0.88 and the between-day constancy coefficient was 0.73, in terms of integrated EMG area recorded by surface electrodes at the motor point of the muscle. Therefore, we feel justified to normalizing the FR with regard to each subject's own MVC for comparison across subjects and/or sessions in our study.

Subjective Pain Evaluation

Subjective pain sensation was measured using the visual analogue scale (VAS), which consisted of a horizontal 20 cm line anchored at the left end by "threshold intensity" (no pain) and the right end by "maximal tolerable intensity" (pain as bad as it could

be) (Jensen et al., 1986). The VAS was attached to a linear potentiometer connected to the Everex computer for readout and storage. Each subject's sensory threshold was determined, and the maximal tolerable intensity ascertained by gradually increasing stimulus intensity until pain tolerance was reached. Immediately following each FR recording, the subject was asked to give an estimation of the pain intensity induced by the electrical stimulation, by moving the cursor on the VAS. Afterwards, they were instructed to return the cursor to the left end of the scale (i.e. the "threshold intensity" position). This was done to eliminate the potential bias that could result from comparison with previous estimates (c.f. Chan and Dallaire, 1989; Dallaire and Chan, 1987).

Data Analysis

Madlab and SPSS professional statistics packages were used to analyze the EMG data and VAS scores. EMG signals were rectified, then FR areas were computed by integrating the areas underneath the EMG curves over windows that ranged from 40 to 200 msec according to individual FR response patterns. VAS scores were pooled for each of the 3 time periods *before*, *during* and *after* TENS or placebo stimulation on Day_1, Day_5 and Day_{10}, respectively, and then normalized to the mean of the pooled data obtained *before* stimulation on Day_1. FR areas were first pooled for each of the 3 time periods *before*, *during*, and *after* the stimulation on Day_1, Day_5 and Day_{10}, respectively. Mean values of these pooled data on each of the 3 testing days were then normalized with respect to the corresponding mean MVC EMG area values computed over a window

of 100 ms. These 9 normalized FR/MVC area ratios and VAS scores, Obtained *before, during* and *after* stimulation per each of the 3 testing days were again normalized to their corresponding value recorded *before* stimulation on Day_1. Note that such normalization procedures permitted valid comparisons across subjects and testing sessions.

The effects of 10 daily 60 min of TENS on both FR/MVC area ratios (abbreviated as FR areas henceforth) and VAS scores were compared with those of placebo stimulation using three-way mixed design analysis of variance (ANOVA), followed by planned comparison post hoc tests with Bonferronic correction (Olson, 1987). Pearson's correlation coefficient tests and linear regression analyses were employed to determine the relationship between FR areas and VAS scores on Day_1, Day_5 and Day_{10}. A statistical significance level of $p<0.05$ was set for all tests.

Results

Reproducibility of Maximum Voluntary Isometric Contraction

Fig. 3.1 shows the EMG areas computed over a time window of 100 ms during the MVC that was recorded in the TA (Fig. 3.1.A) and BF (Fig. 3.1.B) muscles of the TENS (black columns) and placebo group (striped columns) on the 3 testing sessions. Statistical analysis showed that there were no significant differences in these values between TENS and placebo group, or among the different

testings days for both TA and BF muscles. We therefore normalized the FR areas to their respective MVC EMG areas for comparison across the different groups and testing sessions (c.f. Data analysis above).

Cumulative Effects of TENS on Subjective Pain Sensation

Fig. 3.2 compares the results of stimulation on the VAS scores in a subject receiving TENS (left plots) with another one receiving placebo stimulation (right plots). Each data point represents the mean of 15 VAS scores $\pm$ 1 S.D., expressed as a percentage of the mean of the 3 ensembles of 15 VAS scores obtained at 10 min intervals *before* TENS on Day_1. As reported in the previous Chapter, the VAS scores were progressively suppressed during 60 min of TENS but not placebo stimulation. On Day_1, Day_5 and Day_{10}, these scores were further suppressed during the *after* period of TENS. Even more interesting is the finding that the VAS scores obtained *before* TENS were progressively decreased from Day_1 through Day_5 to Day_{10}. In contrast, placebo stimulation did not produce such a progressively suppressing effect on VAS scores.

Fig. 3.3 shows the cumulative effects of TENS (black columns) and placebo stimulation (striped columns) on group mean VAS scores. Each histogram column represents a mean of 10 x 45 pre-stimulation VAS scores (10 subjects with 45 trials per subject) obtained *before* TENS or placebo stimulation on Day_1 or Day_5 or Day_{10}, and expressed as a percentage of the mean pre-stimulation value on Day_1. Note that TENS but not the placebo stimulation

(104.2%, $p>0.05$) significantly decreased the pre-stimulation VAS score from Day_1 to 67.2% on Day_{10} ($p<0.01$). Furthermore, a between-group comparison showed that on Day_{10}, the pre-stimulation VAS value of the TENS group was significantly lower than that of the placebo group.

Cumulative Effect of TENS on Flexion Reflex

Fig. 3.4 illustrates the cumulative effects of 10 x daily 60 min of TENS (left plots) or placebo stimulation (right plots) on the TA FR responses in one subject from each group. Each graph plots the mean of three ensembles of 15 trials (n = 45). Note that, from Day_1 (top row) through Day_5 (middle row) to Day_{10} (bottom row), the FR responses during the pre-stimulation period were progressively reduced in terms of both EMG amplitude and area in the subject who received TENS (first column of left plots in Fig. 3.4). However, no such dramatic change was observed in the subject who received placebo stimulation (first column of right plots in Fig. 3.4). The difference in the FR patterns between the two subjects has been discussed in Chapter 2. These two patterns of FR were found in both TENS and placebo groups.

Fig. 3.5.A shows the cumulative effects of TENS (black columns) or placebo stimulation (striped columns) on the group means of TA FR area. Each histogram column represents a mean of 10 (subjects) x 45 pre-stimulation (trials) of FR area value obtained *before* TENS or placebo stimulation, and expressed as a percentage of the mean pre-stimulation value on Day_1. It should be noted that from Day_1 to

Day_{10}, the pre-stimulation TA FR area value was significantly decreased to 68.6% ($p<0.01$) in the TENS group, but not in the placebo group (92.5%, $p>0.05$). A between-group comparison further showed that on Day_{10} the pre-stimulation value TA FR area value of the TENS group was significantly lower than that of the placebo group ($p<0.01$).

Fig. 3.5.B shows the cumulative effects of TENS (black column) and placebo stimulation (striped column) on the group means of BF FR area. Both TENS and placebo stimulation significantly depressed the pre-stimulation BF FR area value from Day_1 to 63.8% ($p<0.01$) and 84.8% ($p<0.05$) respectively on Day_{10}. When compared with placebo stimulation, however, TENS produced greater depressing effects ($p<0.01$) on the pre-stimulation BF FR area.

Changes in the Relationship between FR and VAS

Fig. 3.6 shows the linear regression line drawn between VAS scores and (A) TA (left plots) and (B) BF (right plots) FR areas obtained from the TENS group on Day_1, Day_5, and Day_{10}. The 9 data points in each of the graph were obtained at 3 x 10 min intervals *before*, and at 3 x 20 min intervals *during* and *after* TENS. Each of the 9 data points represents a mean of 10 x 15 trials (10 subjects with 15 trials per subject), and is expressed as a percentage of the group mean control value on Day_1 (i.e. average of the 3 x 15 trials recorded *before* TENS on Day_1 for the 10 subjects in the TENS group). Note that VAS scores were highly correlated with both TA and BF FR areas on Day_1, Day_5 and Day_{10}, with correlation

coefficients (r) of 0.93 and 0.95, 0.95 and 0.97, 0.78 and 0.68, and slopes of 0.55 and 0.61, 0.68 and 0.90, 1.05 and 1.39, respectively.

Reproducibility of MVC

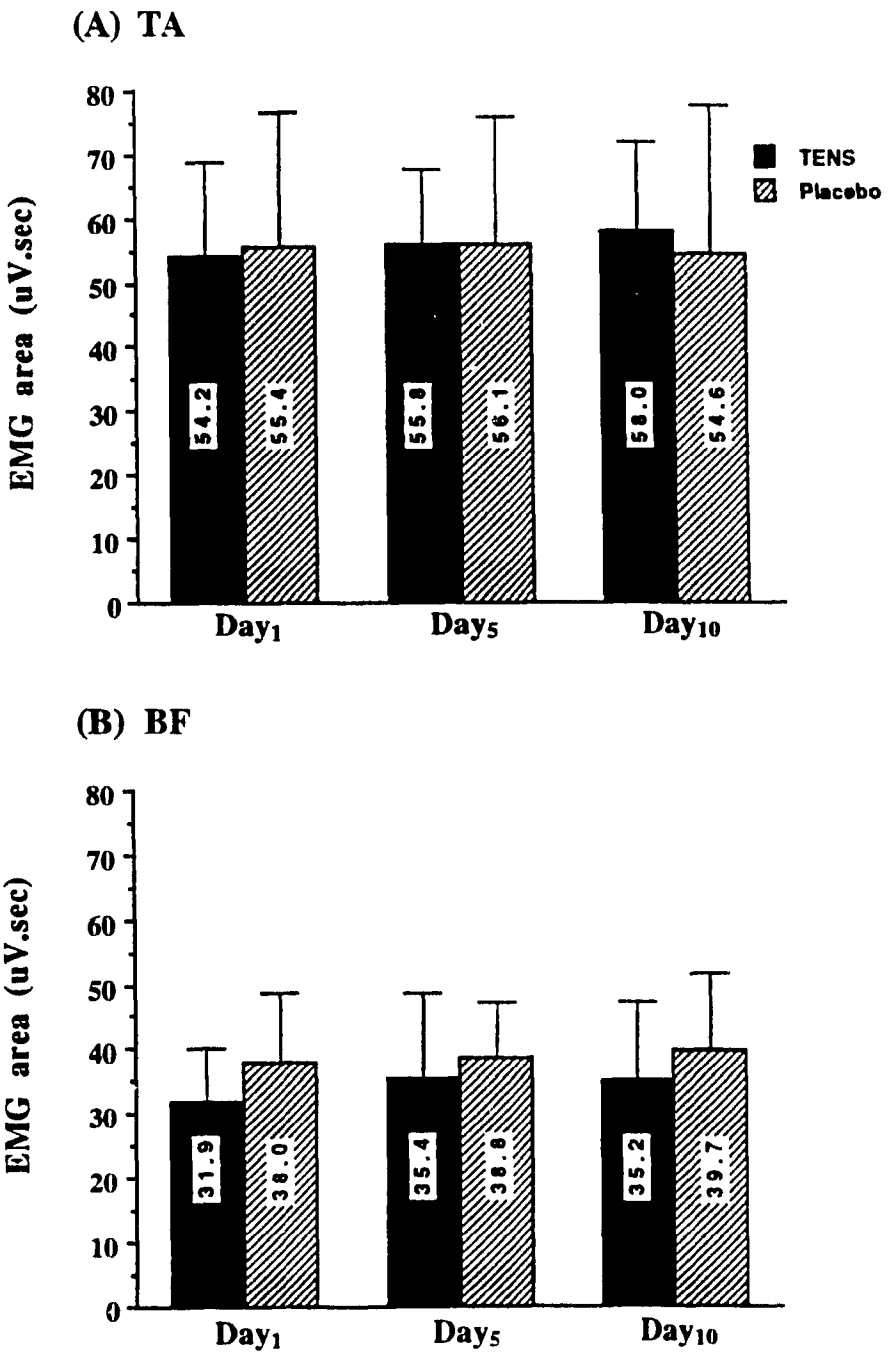

Fig. 3.1 Reproducibility of (A) TA MVC and (B) BF MVC EMG values recorded in the TENS (black columns) and placebo group (striped columns) on Day_1, Day_5 and Day_{10}. Each column represents a mean of 10 x 3 MVC EMG area values (10 subjects with 3 trials per subject) computed over a window of 100 ms during the MVC.

Cumulative Effects of TENS and Placebo Stimulation on Subjective Pain Sensation over a Two Week Period

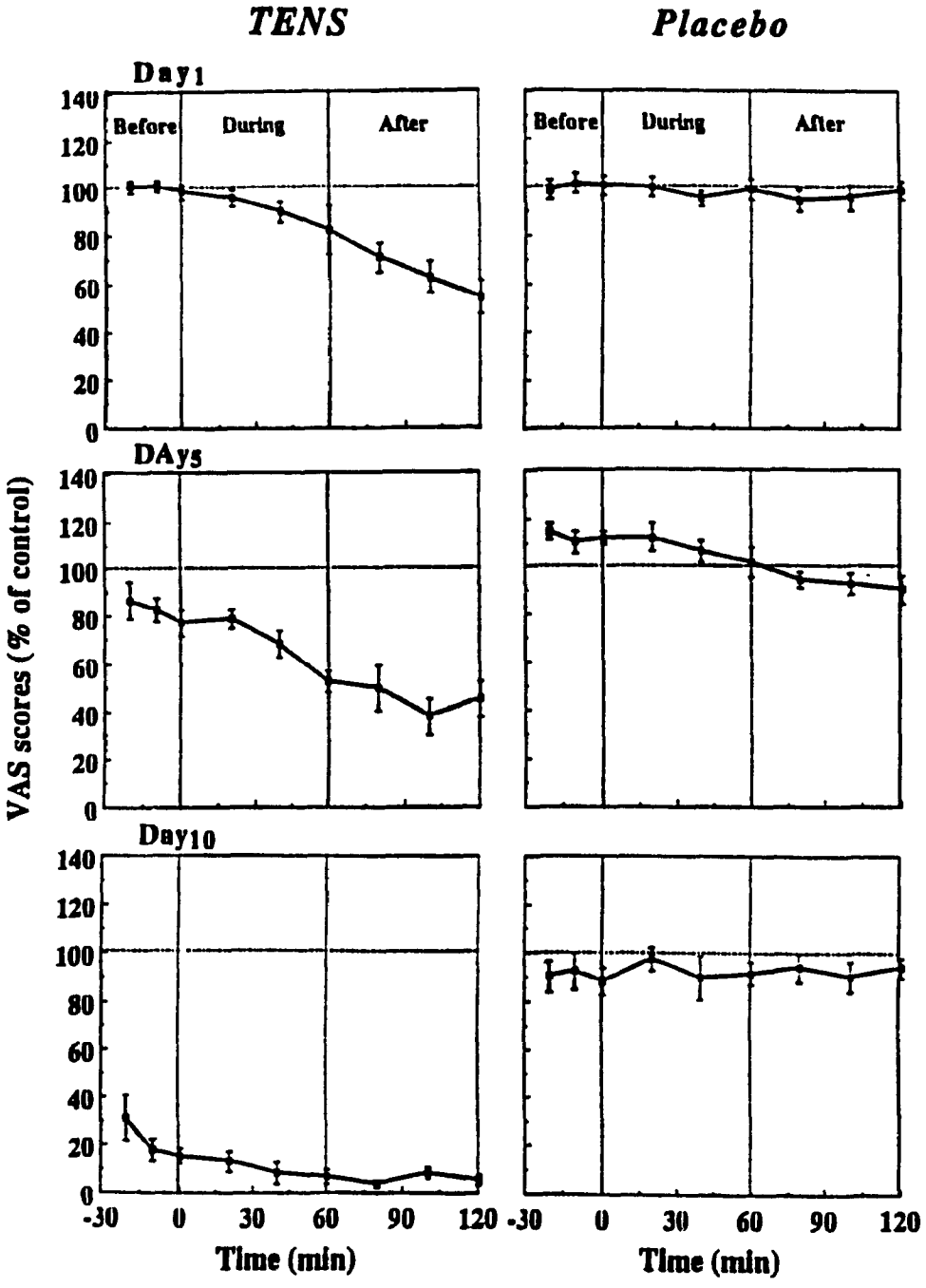

Fig. 3.2 VAS scores progressively decreased in a subject receiving 10 x daily 60 min of TENS (left plots) but not in the one receiving placebo stimulation (right plots). Each data point represents a mean of 15 VAS scores ± 1 S.D., expressed as a percentage of the mean of 3 ensembles of 15 VAS scores obtained at 10 min intervals *before* TENS or placebo stimulation on Day_1.

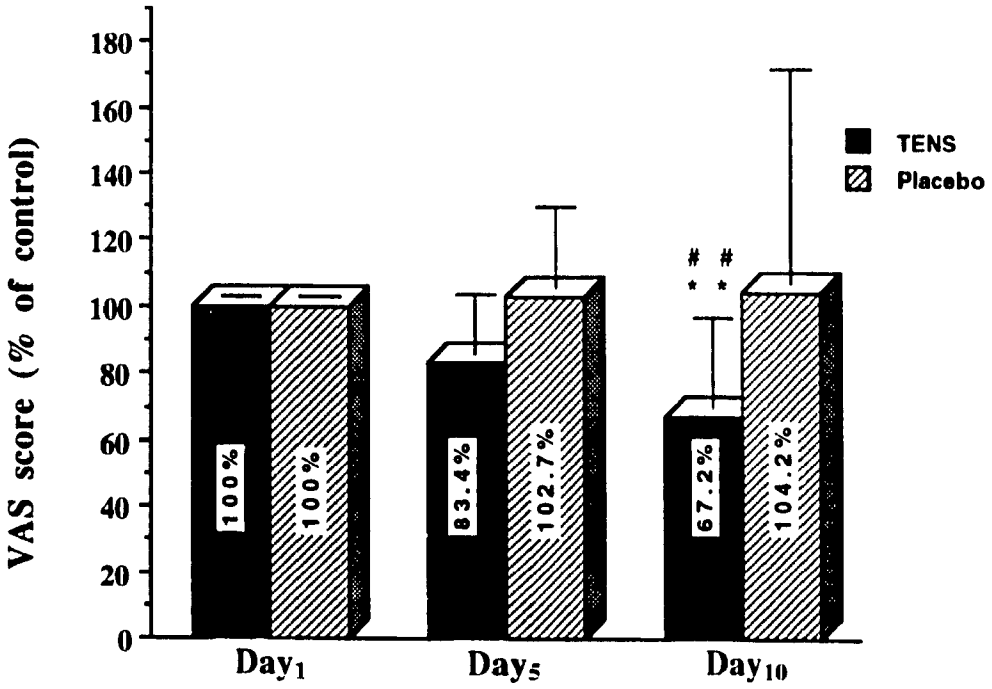

Fig. 3.3 Cumulative effects of TENS (black columns) and placebo stimulation (striped columns) on group mean VAS scores. Each column represents a mean of 10 x 45 VAS scores (10 subjects with 45 trials per subject) obtained *before* TENS or placebo stimulation and expressed as a percentage of the mean on Day_1.

** denotes the within group comparison between Day_1 and Day_{10}, and represents $p<0.01$.

denotes the comparison between the two groups on Day_{10}, and represents $p<0.01$.

Cumulative Effects of TENS and Placebo Stimulation on Tibialis Anterior FR over a Two Week Period

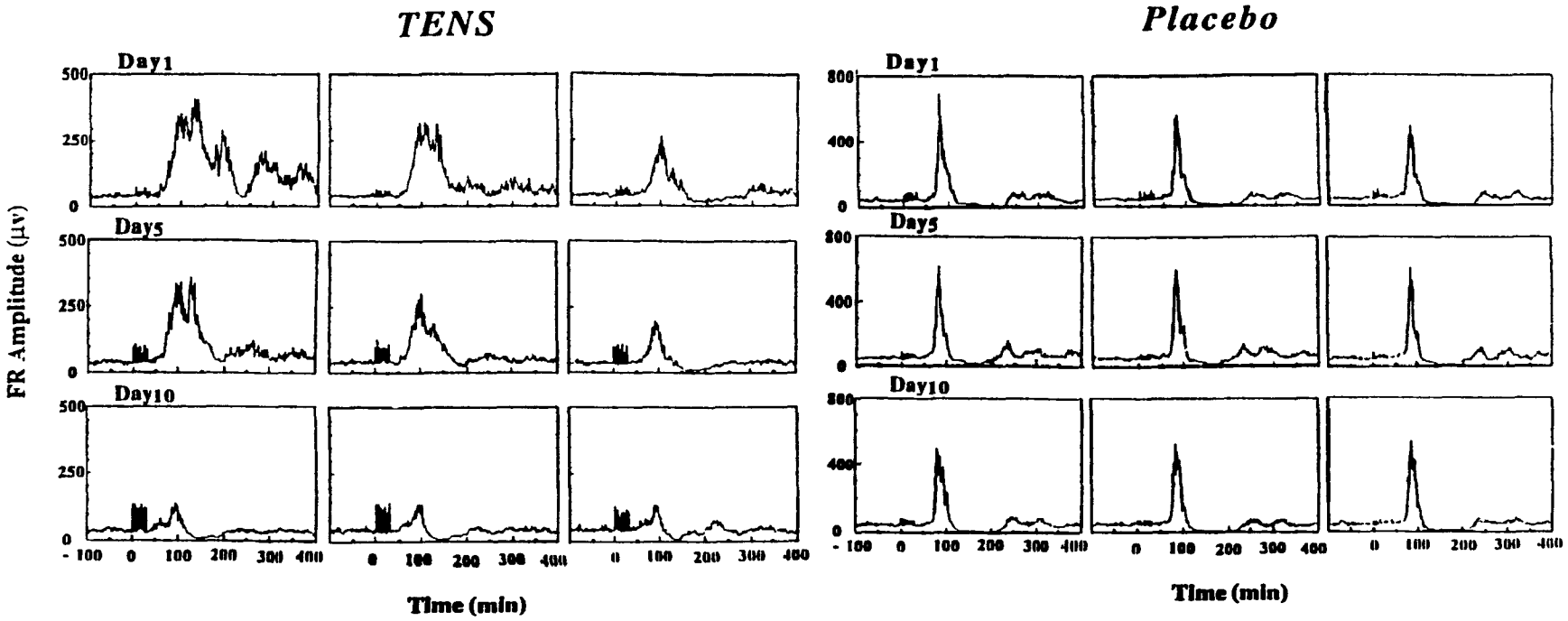

Fig. 3.4 Cumulative effects of 10 x daily 60 min of TENS (left plots) and placebo stimulation (right plots) on the TA FR responses in two different subjects. Each graph plots the mean of three ensembles of 15 trials (n = 45). Top row = Day_1; middle row = Day_5; and bottom row = Day_{10}. Left column = a 30 min period *before* stimulation; middle column = a 60 min period *during* stimulation; and right column = a 60 min period *after* stimulation.

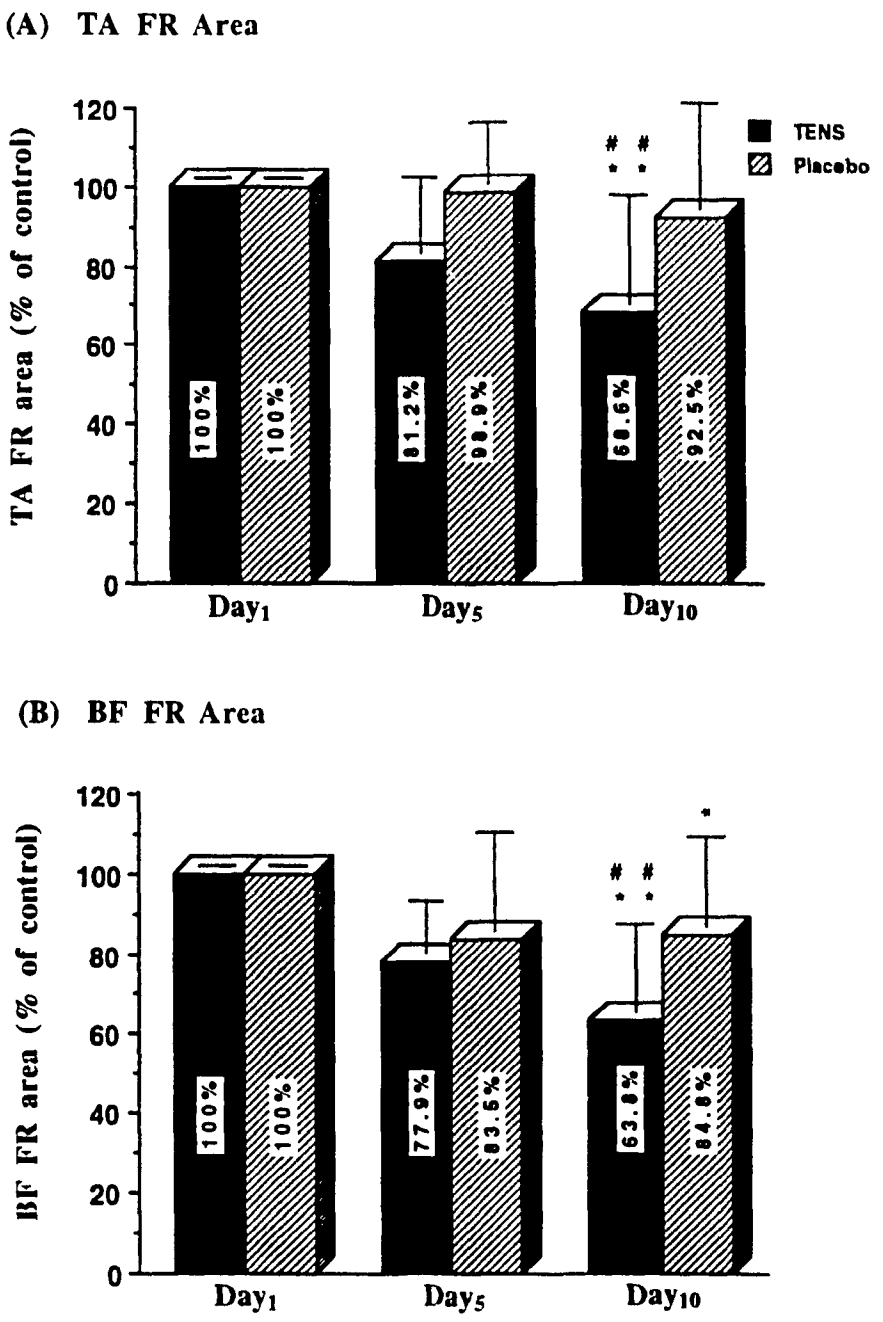

Fig. 3.5 Cumulative effect of TENS (black columns) or placebo stimulation (striped columns) on group mean (A) TA and (B) BF FR areas. Each column represents a mean of 10 x 45 FR area values obtained *before* stimulation and expressed as a percentage of the mean on Day_1.
* and ** denote the within group comparison between Day_1 and Day_{10}, and represent $p<0.05$ and $p<0.01$ respectively.
denotes the comparison between the two groups on Day_{10}, and represents $P < 0.01$

Influence of TENS on the Relationship between VAS Scores and FR Areas over a Two Week Period

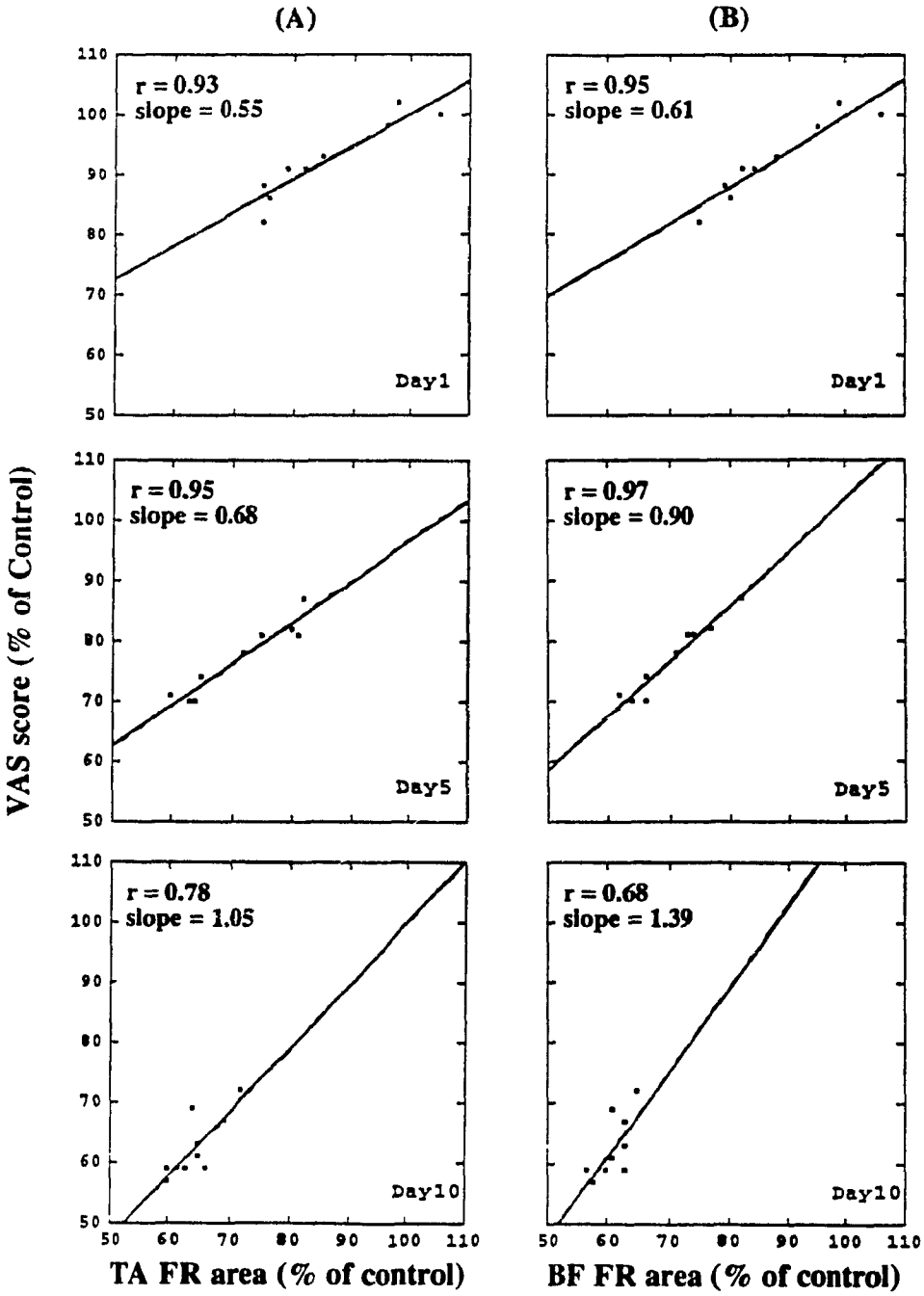

Fig. 3.6 Linear regression lines drawn between VAS scores and (A) TA (left plots) and (B) BF FR areas (right plots) obtained from the TENS group on Day_1, Day_5 and Day_{10}. The 9 data points in each graph were obtained at 3 x 10 min intervals *before*, and at 3 x 20 min intervals *during* and *after* TENS. Each of the 9 data points represents a mean of 10 x 15 trials (10 subjects with 15 trials per subject) and expressed as a percentage of the pre-stimulation group mean on Day_1.

Discussion

Cumulative Effects of TENS on Subjective Pain Sensation

As illustrated in Fig.3.2, 10 repeated daily applications of TENS but not placebo stimulation progressively suppressed the VAS score within each of the 3 testing sessions. Furthermore, such long-term afferent conditioning produced a progressive inhibitory influence on the *pre*-stimulation VAS scores *across* the 3 testing sessions of Day_1, Day_5 and Day_{10}. Note that there was a two-day break between Day_5 and Day_6, but this break did not appear to influence the gradual and cumulative suppressing effects of TENS on the VAS scores. Of interest is that these cumulative effects reached statistical significance when the group mean *pre*-stimulation VAS score was compared between Day_1 and Day_{10}, as well as across the two groups (Fig. 3.3). N.B. To avoid too many repeated comparisons, data on Day_5 had not been statistically compared to either Day_1 or Day_{10}.

Our results thus showed that repeated TENS but not placebo stimulations over a two week period produced significant cumulative effects on subjective pain sensation in normal human subjects. To the best of our knowledge, no previous studies have ever examined the possible cumulative effects of long-term TENS application on experimental pain. At the moment, we make no presumption that this result could be generalized to all clinical pain conditions. Among other considerations, electrically induced experimental pain is likely mediated by Aδ fibres, whereas chronic pain is probably mediated by C fibres. Nevertheless, our findings

are in agreement with a recent clinical study. More specifically, Marchand et al. (1993) demonstrated that TENS but not placebo stimulation had a cumulative analgesic effect on low back pain. The mechanisms underlying this cumulative TENS analgesia is not clear, but such a gradual development implicated possible plastic changes in the neuronal pathway.

Cumulative Inhibitory Effect of TENS on Flexion Reflex

As illustrated in Fig. 3.4 (left plots), 10 daily repeated applications of TENS not only progressively suppressed the TA FR within each of the 3 testing sessions, but also across the sessions. In contrast, placebo stimulation produced negligible effects. Between-group comparisons of the group mean values showed that TENS, but not placebo stimulation, produced a significant inhibitory influence on both TA and BF FR areas (Fig. 3.5). This finding is similar to the cumulative effects of TENS on the VAS scores presented above. To our knowledge, this is the first study demonstrating that long-term TENS conditioning had a cumulative suppressing effect on FR over time. In other words, plastic changes of the flexion reflex could have been induced after repetitive afferent conditioning in normal young human subjects.

The mechanisms of this plastic change are not clear. However, evidence is accumulating to indicate that neural plastic changes could be due to morphological, physiological and biochemical alternations in the central nervous system. As early as 1911, Cajal suggested that prolonged morphological and physiological changes

in synaptic connections between nerve cells could occur following lesions in the central nervous system. A recent study (Starr and Wolpaw, 1993) suggested that an operantly conditioned decrease in the primate triceps surae H-reflex was associated with type-specific changes in motoneuron synaptic covering. Specifically, they found that the proportion of F-type terminals (flattened or pleomorphic vesicles) increased in H-reflex↓ motoneurons (66 ± 5%) as compared to naive (control) motoneurons (50 ± 4%), whereas the proportions of C-type terminals (postsynaptic subsurface cisterns) decreased in H-reflex↓ motoneurons (9 ± 4%) as compared to naive motoneurons (19 ± 5%). Carp et al. (1993) reported a more positive firing threshold and a reduced axonal conduction velocity of primate motoneurons after an operantly conditioned decrease in H-reflex amplitude. It is not known whether similar plastic changes could have been induced in the flexion reflex neural pathway after 2 weeks of afferent conditioning as studied in our present project. Further experiments are certainly needed to explore the mechanisms underlying the gradual changes of the flexion reflex.

Influence of TENS on the Relationship between Subjective Pain Sensation and Flexion Reflex

As described above, repetitive daily TENS produced similar inhibitory effects on subjective pain sensation and FR. That the decrease in the two pain indices bore a systematic relationship with each other is further presented in Fig. 3.6. Briefly, statistical analysis showed that the decrease in VAS scores was linearly related to the decrease in TA and BF FR areas on each of the 3 testing days.

The high correlation coefficients on Day_1 and Day_5 ($r \geq 0.93$) indicated that the linear relationship was not modified during the first 5 days of 60 min of TENS. Even after 10 days of TENS, the correlation coefficients ($r = 0.78$ and 0.68 respectively for TA and BF) remained fairly high. Previous studies already showed that subjective pain sensation was linearly correlated with FR under control conditions (i.e. in the absence of afferent conditioning; Chan and Dallaire, 1989), as well as during a mental task or morphine administration (Willer et al., 1979, 1980). The results of the present study demonstrated that such a linear relationship was maintained despite 10 repeated daily TENS applications. Therefore, it further confirmed that flexion reflex can be accepted as a good testing tool for studies addressing the understanding of pain treatments in human.

Interestingly, the slopes of the linear regression lines between the VAS scores and FR areas changed progressively from Day_1 (Fig. 3.6, top row), through Day_5 (middle row), to Day_{10} (bottom row). Such progressive changes of the slope could be explained by the difference between amount of reduction of VAS scores and FR area values during two different testing periods: the first 5 days from Day_1 to Day_5 and the second 5 days from Day_6 to Day_{10}. Specifically, the VAS score were reduced by the same amount in the two periods: 16.6% during the first 5 days and 16.2% during the second 5 days (Fig. 3.3). On the other hand, the FR area values were depressed by 18.8% and 22.1% respectively for TA and BF during the first 5 days, but 12.6% and 14.1% respectively during the second 5

days (Fig. 3.5). In other words, it appeared that the rate of decrease in the FR areas was greater than that of VAS scores during the first 5 days, then slowed down during the second 5 days; while the rate of VAS scores decrease remained the same. It is not clear why the rate of FR decrease was different during the two 5-day periods. Wolpaw and O'Keefe (1984) observed that the operantly conditioned spinal stretch reflex (SSR) change had a rapid initial jump (phase I) within the first 6 hours, followed by a slow gradual change (phase II). The authors proposed that the rapid initial jump suggested that the monkey quickly responded to the training with an immediate alteration in suprasegmental influence on the segmental arc of SSR pathway, whereas the phase II slow change indicated long-term plasticity. Based on our finding, one could argue that FR responded quicker to the afferent conditioning during the first 5 days as compared to the second 5 days, but further study is needed to investigate whether the inhibitory effects of TENS do show 2 phases of changes. For example, one could attribute the different rate of FR decrease partly if not entirely to different amount of possible time and/or placebo effect on the FR area during the two time periods. As reported in Chapter 2, we found that a single session of 60 min of placebo stimulation produced certain inhibitory effects on FR area (Fig. 2.6), but had no effect on the VAS scores (Fig. 2.4).

In summary, repetitive TENS applications over a two week period produced significant cumulative inhibitory effect on both subjective pain sensation and flexion reflex in normal human subjects. Furthermore, the decrease in the two pain indices bore a

linear relationship with each other. The gradual cumulation of the suppressing influence probably implicates plastic changes in the neural pathway. The similar time course of the cumulative influence on the two pain indices suggest that similar processing might take place at cortical (subjective pain) and spinal (flexion reflex) levels as a result of long-term TENS conditioning.

Acknowledgements

This work was supported by a grant from the *Fonds de la Recherche en Santé du Québec*. The authors wish to thank subjects who participated in the study, and particularly A. Alfat who developed the computer programs for on-line experimental control, data collection and analysis.

CHAPTER 4

Summary and Conclusions

Summary and Conclusions

To our knowledge, this is the first study that investigated the possible cumulative effects of 10 repeated daily TENS applications on experimental pain and flexion reflex (FR) in humans.

Prior to this study, Chan and Tsang (1987) demonstrated that lower limb FR was significantly inhibited by a single 30 min application of TENS in the majority of subjects examined, and that the inhibition lasted for up to 50 min after TENS. Subjective pain sensation, as measured by the visual analog scale (VAS), was subsequently found to be linearly correlated ($r = 0.84$) with FR area in the absence of any conditioning stimuli (Chan and Dallaire, 1989). Thus, two questions arose: First, would the influence of TENS on subjective pain sensation follow a *similar* or *different* course from that of the FR elicited by the *same* maximally tolerable electrical stimulation? Secondly, was the linear relationship between the two pain indices *modifiable* by a single session of prolonged (60 min) TENS? The objectives of our *first study* were to answer these two questions (Chapter 2). Our *second study* (Chapter 3) was set out to examine whether repeated daily TENS could produce *cumulative* inhibitory effect on both subjective pain sensation and FR over a two-week period, and to investigate whether there were *progressive changes* in the relationship between subjective pain sensation and FR as a result of long-term TENS application.

Twenty young healthy subjects were randomly assigned to a TENS or placebo group, with 10 in each. Low intensity, high frequency (80 Hz) TENS or placebo stimulation was applied to the lumbro-sacral region for 60 minutes on 10 treatment days over a two-week period. The FR was elicited by electrically stimulating the sole of subject's right foot and recorded electromyographically from BF and TA muscles. Subjective pain sensation was measured using the VAS. ANOVA and planned comparison tests with Bonferronic correction were used to analyze the data obtained *before*, *during*, and up to 60 min *after* TENS or placebo stimulation, and to compare the control data obtained *before* stimulation on Day_1 with those of Day_{10} of the treatment period and between the two groups. A summary of our findings are highlighted below:

On Day_1: (1) The group mean VAS score was significantly reduced to 85.2% of control value ($p<0.05$) during the 60 min of post-stimulation period in the TENS group, but not placebo group (102.9%).

(2) For TA FR area, the group mean decreased to 75.3% of control value ($p<0.01$) during the post-stimulation period in the TENS group, and to 88.2% ($p<0.05$) in the placebo group. In comparison with the placebo stimulation, however, TENS produced greater inhibitory effect ($p<0.05$) on the TA FR area.

(3) For BF FR area, the group mean decreased to 78.2% of control value ($p<0.01$) during the post-stimulation

period in the TENS group, and to 85.8% ($p<0.05$) in the placebo group. A between-group comparison showed that TENS did not produce significantly greater effect on the BF FR area.

(4) *Before*, *during*, and up to 60 min *after* TENS, the VAS scores and FR areas were highly correlated with each other, with a correlation coefficient (r) of 0.93 for TA and 0.95 for BF.

A comparison of the control values obtained *before* stimulation between Day_1 and Day_{10} revealed a significant decrease in:

(1) VAS control value to 67.2% on Day_{10} in the TENS ($p<0.01$), but not placebo group (104.2%);

(2) TA FR area control value to 68.6% on Day_{10} in the TENS ($p<0.01$), but not placebo group (92.5%);

(3) BF FR area control value to 63.8% ($p<0.01$) and 84.8% ($p<0.05$) on Day_{10} respectively for both TENS and placebo stimulation.

(4) In comparison with placebo stimulation, however, TENS produced greater inhibitory effects ($p<0.01$) on *both* VAS scores and FR areas of the two muscles examined.

(5) The VAS scores were highly correlated with both TA and BF FR areas in the TENS group on all 3 testing days ($Day_{1, 5, 10}$), with correlation coefficients (r) of 0.93 and 0.95, 0.95 and 0.97, 0.78 and 0.68, respectively.

In contrast to the reports of some researchers (Andersson et al., 1977; Eriksson and Sjolund, 1976) that low intensity, high frequency TENS only produced instant pain relief, the above findings demonstrated that a single session of 60 min TENS exerted prolonged inhibition on both subjective pain sensation and FR. Such a persistent post-stimulation effect is consistent with our previous result (Chan and Tsang, 1987) and other studies (Facchinetti, et al., 1984; Salar et al., 1981) which showed the involvement of endogenous opioids in TENS analgesia. Note that a shorter duration of TENS could have accounted for some of those studies (Garcia-Larrea et al., 1989) which failed to show a prolonged effect of TENS.

Between Day_1 and Day_{10}, the inhibitory effect of TENS on subjective pain sensation and FR were found to follow a similar time course. Such predominantly parallel effects on the two pain indices were probably due to similar processing at both cortical and spinal levels, as a result of long-term afferent conditioning via repeated TENS applications.

The most interesting finding in our study was that 10 daily repeated TENS applications produced significantly greater cumulative inhibitory effect on both subjective pain sensation and FR over a two-week period than placebo stimulation. Such a gradual

development probably implicated that plastic changes could have been induced in the neural pathway by long-term afferent conditioning.

Results from this study may provide clinicians with some more theoretical bases for repeating TENS applications in the treatment of pain conditions. Such a strategy could be considered for pain patients who do not respond to the first couple of TENS treatments, since TENS may produce cumulative analgesic effects over time. On the other hand, we caution that the results of this study should not be generalized to all clinical pain conditions, because electrically induced experimental pain is likely mediated by Aδ fibres. For example, the induced sensation is obviously different from the "quality" of chronic pain which is usually mediated by C fibres.

In conclusion, this is the first study which demonstrated that repeated TENS applications produced similar and cumulative inhibitory influences on both subjective pain sensation and flexion reflex over a two week period. Such a gradual development indicated that plastic changes could have been induced in the neural pathway. The linear relationship between the decrease in VAS and FR area that persisted from Day_1 to Day_{10} of stimulation suggested that comparable processing and plastic changes could have occurred at both cortical and spinal levels. Further studies are needed to investigate how long (probably in terms of hours) the post-stimulation effects of 60 min of TENS may persist; and how long (probably in terms of days) the cumulative effects of the 10 daily repeated TENS will last without further conditioning.

APPENDIX I

Informed Consent Form For Pain Study

I ....., understand the following explanation of this research study and consent to participate in the experiment.

(a) Purpose and Design of the Study

The purpose of this study is to determine the possible effects of transcutaneous electrical nerve stimulation (TENS) on the subjective pain sensation and the flexion reflex, in an attempt to understand mechanisms of TENS analgesia. After an orientation, the experiment will consist of 10 sessions within two consecutive weeks, with three sessions (day_1, day_5 and day_{10}) lasting approximately two to three hours each and the rest an hour each. I am informed that the TENS will be applied on my low back for 10 times on 10 weekdays, and each TENS "treatment" session will last for 60 min. The stimulation will not be painful. I know I will be tested on day1, day5 and day10. Each of the three testing sessions will start with five maximum voluntary contractions of my right leg muscles. I am also aware that I shall receive electrical stimulation, which will be within my pain tolerance, to the sole of my right foot. The electrical activity elicited in my right leg muscles will be recorded with surface electrodes. The skin underlying the electrodes will be shaved and cleaned prior to applying the electrodes. Immediately following each test electrical stimulation, I will estimate the intensity of each stimulus by moving a cursor along a horizontal scale. This testing procedure will be repeated prior to, during and up to one hour after 60 min of TENS on experiment day_1, day_5 and day_{10}.

(b) Disadvantages of Participation in the Study

The main discomfort will be that the electrical stimuli to my sole of right foot may cause pain sensation, but its intensity will be

within my pain tolerance. In the occasional subjects, possible side-effects could be local skin allergic reactions and irritations.

(c) Advantage of Participation in the Study

There are no personal benefits to be gained from participating in these experiments, except for a small payment for participation in the study. However, the results from this study will contribute to our understanding of how electrical conditioning of the nerve fibers could influence human pain perception and flexion reflex.

(d) Inquiries Concerning the Study

I have been informed that the experiment will be conducted by Mr. Jiaqiang Liu under the supervision of Dr. C.W.Y. Hui-Chan. In addition, I have been assured that all my personal data will be confidential I understand that any inquiries that I may have about this study will be answered. I can direct my questions to Mr. Liu and/or Dr. Hui-Chan who can be reached at the School of Physical and Occupational Therapy, McGill University, 3630 Drummond St., Montreal, Quebec, H3G 1Y5 or via telephone at (514) 398-5035.

(e) Withdrawal from the Study

I understand that my participation in this research experiment is strictly voluntary, and that I may withdraw at any time. I am told I am entitled to keep a copy of this consent form for my future references.

Signature of Subject: ..... Date: .....

Witness: ..... Date: .....

I, Jiaqiang Liu, hereby certify that I have explained to the above mentioned subject the purpose, methods and potential risks involved in the study, and he/she has the option of withdrawing from the experiment at any time.

Signature: ..... Date: .....

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