Contact Heat Evoked Potentials in Normal Subjects

I-An Chen[1], Steven Wu Hung[1], Yu-Hsien Chen[1], Siew-Na Lim[1], Yu-Tai Tsai[1], Cheng-Lun Hsiao[2], Hsiang-Yao Hsieh[1], and Tony Wu[1]

Abstract- Laser-evoked potentials are widely used to investigate nociceptive pathways. The newly developed contact heat stimulator for evoking brain response has the advantages of obtaining reliable scalp potentials and absence of cutaneous lesions. This study aimed to identify the most appropriate stimulation site with consistent cortical responses, and to correlate several parameters of the contact heat evoked potentials (CHEPs) with age, gender, and body height in normal subjects. CHEPs were recorded at Cz with a contact heat stimulator (Medoc, Israel) in 35 normal controls. The subjects were asked to keep eyes open and remain alert. The baseline temperature was 32 ˚C, and stimulation peak heat intensity of 51 ˚C was applied to five body sites: bilateral forearm, right dorsum hand, right peroneal area, and right dorsum foot. Reproducible CHEPs were recorded more frequently when stimulated at volar forearm (62.5%) than at the lower limbs (around 40%). The first negative peak latency (N1) was 370.1±20.3 ms, first positive peak latency (P1) was 502.4±33.0 ms, and peak to peak amplitude was 10.2±4.9 μV with stimulation of the forearm. Perceived pain intensity was not correlated with the presence or amplitude of CHEPs. No gender or inter-side differences were observed for N1 latency and N1-P1 amplitude. Also, no correlation was noted between N1 and age or body height. These results support future clinical access of CHEPs as a diagnostic tool.

Key Words: Pain, Contact heat evoked potential, Heat stimulation, Evoked potentials

Acta Neurol Taiwan 2006;15:184-191

INTRODUCTION

Evoked potentials to sensory or noxious thermal stimulation of skin constitute part of peripheral nerve and brain response to the stimulation of certain sensory fibers, and thus may provide objective information of the integrity of correlative sensory afferents. Laser-generated radiant heat pulse activation of Aδ and C nociceptors has been applied to investigate the physiology of pain. Contact heat evoked potentials (CHEPs) have recently been introduced to study nociceptive pathways by using a contact thermode which may rapidly increase skin temperature[1-4]. The morphology of the main components of CHEPs is similar to that of Laser-evoked potentials (LEPs)[3], and mapping of the scalp CHEPs resembles the topography of LEPs[1].

From the [1]Epilepsy Section, Department of Neurology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei; [2]Department of Neurology, Buddhist Tzu Chi General Hospital, Taipei.
Received February 8, 2006. Revised March 23, 2006.
Accepted April 12, 2006.

Reprint requests and correspondence to: Tony Wu, MD, PhD. Department of Neurology, Chang Gung University and Memorial Hospital, No. 199, Tung-Hwa N. Road, Taipei, Taiwan.
E-mail: tonywu@adm.cgmh.org.tw

Compared with Laser-heat stimulation, CHEPs offers the advantage of ease of obtaining reliable scalp potential and absence of cutaneous lesions[5]. Recent studies of CHEPs include 3D topographic brain mapping in pain perception by using different paradigms of nociceptive stimulation[1] and calculation of nerve conduction velocity of Aδ afferents[6]. However, few studies have examined a broad spectrum of parameters of CHEPs in normal control subjects, which is important for clinical application. The current CHEPs study thus aims to: (a) discover an appropriate stimulation site with consistent CHEPs responses in normal subjects; (b) correlate different parameters of CHEPs to the variables of age, gender, and body height.

SUBJECTS AND METHODS

Subjects

Sixteen right-handed healthy males (aged 18-32 years) and 19 right-handed healthy females (aged 23-44 years) participated in this study, conducted in Chang Gung Memorial Hospital, Linkou, Taiwan. Each subject signed a consent form after receiving a complete explanation of the study design and goals.

Stimulator

The stimulator used was a CHEP stimulator (Medoc Ltd, Ramat Yishai, Israel) with a thermode contacting a cutaneous area of 572.5 mm^2. The thermode comprised a heating thermofoil (Minco Products, Inc., Minneapolis, MN) covered with a 25 μm layer of thermoconductive plastic (Kapton®, thermal conductivity at 23 ˚C of 0.1-0.35 w/m/k). Two thermocouples were embedded 10μm within this conductive coating, which contacted the skin directly, enabling estimation of the skin temperature at the thermode surface. The thermofoil permitted a heating rate of up to 70 ˚C/s and the Peltier device permitted a cooling rate of 40 ˚C/s. Cooling began immediately after the target heat pulse temperature is achieved, and the target temperature was decided by the investigator using software provided by the manufacturer.

Procedures

Subjects sat in an armchair in a quiet room with ambient temperature of ~22 ˚C. The subjects were asked to keep their eyes open and remain alert throughout the procedure. Heat stimuli were applied at peak intensity of 51 ˚C to five sites: right volar forearm, left volar forearm, dorsum of the right hand, peroneal area of the right leg, and dorsum of the right foot. The baseline temperature was 32˚C for all stimuli. The average time from onset of heat application to the peak temperature was 250±8 ms.

Each stimulus block comprised 20 constant-intensity stimuli applied to the site at approximately five-second intervals. The subjects should withdraw from the stimulation if the stimulus became intolerable. The thermode was moved slightly between stimuli to prevent sensitization of the skin or receptor fatigue. Different body sites were stimulated in a pseudorandom order. At least two averages were obtained in each body site to ensure reproducibility. CHEPs were defined as nonreproducible if the stimulation did not produce a similar waveform and matched peak wave latency in a session of stimuli. The subjects were allowed a 3-5 min break following each stimulation block.

The subjects rated their perception of each stimulus 3 seconds following its onset. The ratings used a 0-10 level numerical ranking scale, ranging from “no sensation” at 0 to “unbearable burning sensation” at 10. A level of 4 indicated the threshold for a pinprick-like pain sensation.

Recording of contact heat evoked potential

CHEPs were recorded from the Cz (vertex) position, where the negative potential reached its maximal amplitude as indicated by the previous reports of Massimiliano Valeriani et al[1]. Linked earlobe electrodes provided a reference, and the ground electrode was placed on the forearm. The evoked potential was recorded with a band pass of 0.2 and 100 Hz and digitized at a sampling rate of 100 KHz. The data were stored on disk for off-line analysis (Nicolet Viking IV D system). Each recording epoch initiated by a TTL pulse at the beginning of the temperature increase was 500 ms before the stimulus onset.

Peri-stimulus epochs contaminated by artifacts were

excluded from signal averaging. The remaining sweeps were averaged separately for the stimulation site. At least two averages were obtained for each site to ensure response reproducibility. The first negative peak latency (N1), first positive peak latency (P1), and peak to peak amplitude of the major negative and subsequent positive peaks of the evoked potentials were identified.

Data analysis

The numbers and percentages of reproducible waveforms obtained in different stimulus sites were calculated. Independent-sample T test was applied to compare pain intensity between subjects with and without reproducible forearm wave, left and right forearm N1 latency, P1 latency and peak to peak amplitude and right forearm N1 latency, P1 latency and peak to peak amplitude in different sexes. Pearson Correlation and Linear regression were used to analyze the correlation between forearm peak to peak amplitude and pain intensity or age, as well as between forearm N1 latency and age or body height.

RESULT

Table 1 summarizes the percentage of reproducible CHEPs for each stimulation site in this study, which contain data from 16 male (mean age 27.00±6.96 years) and 19 female subjects (mean age 30.00±7.31 years). Subjects are divided into two groups based on the presence of CHEPs. Table 2 lists the average intensity ratings of pain (0-10 level numerical ranking scale) for different stimulation sites. No correlation exists between perceived pain intensity and the presence of reproducible CHEPs (P=0.618 on the right forearm; P=0.618 on the left forearm; P=0.435 on the dorsum of the hand; P=0.608 on the peroneal area; P=0.846 on the dorsum of the foot).

Fig. 1 shows the evoked waveforms in one representative subject following stimulation of the right forearm, dorsum of the hand, peroneal area of the leg, and dorsum of the right foot. Ten female and ten male subjects showed reproducible CHEPs to forearm stimulation on each side. Table 3 summarizes subject demographic data and peak latency of the first negative wave (N1 latency). Table 4 lists the other parameters of CHEPs, including N1 latency, first positive peak latency (P1 latency) and N1-P1 peak to peak amplitude. No significant difference exists for the N1 latency, P1 latency and N1-P1 peak to peak amplitude to right and left forearm stimulation in

Table 1. *Percentage of reproducible CHEPs with stimulation at different body sites*

Stimulation site	Number of cases		Number of reproducible CHEPs		Percentage (%) of reproducible CHEPs	
	Female	Male	Female	Male	Female	Male
R forearm	19	16	11	10	57.89	62.5
L forearm	19	16	11	10	57.89	62.5
Dorsum hand	19	16	8	10	42.1	62.5
Peroneal area	19	16	7	7	36.84	43.75
Dorsum foot	19	16	8	6	42.1	37.5

R: right; L: left

Table 2. *Perceived pain intensity ratings and CHEP responses to contact heat stimulation at different body sites*

Stimulation site	Pain Intensity (SD)		P value
	Patient with reproducible CHEP waveform	Patient without reproducible CHEP waveform	
Right forearm	6.0 (1.09)	6.2 (1.31)	0.618
Left forearm	6.0 (1.09)	6.2 (1.31)	0.618
Dorsum of hand	5.8 (1.38)	6.2 (1.25)	0.435
Peroneal area	6.0 (1.35)	5.7 (1.52)	0.608
Dorsum of foot	5.6 (1.42)	5.5 (1.39)	0.846

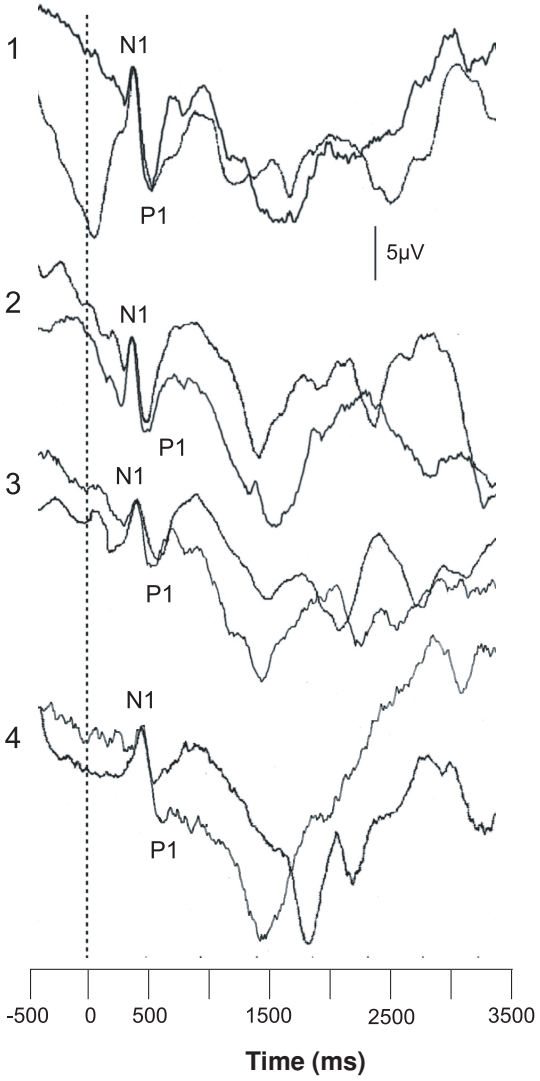

Figure 1. Contact heat evoked potential in one representative subject following 51 ˚C contact heat stimulation at different body sites: 1. right forearm; 2. right dorsum hand; 3. right peroneal area; and 4. dorsum of the foot.

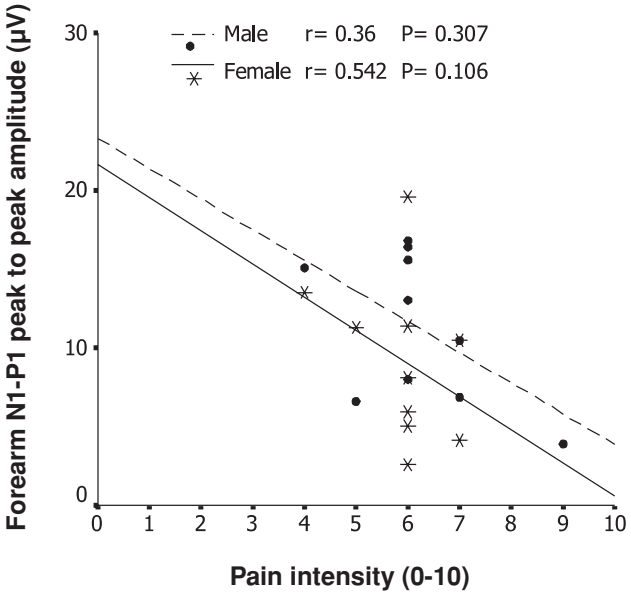

Figure 2. Correlation between pain intensity and N1-P1 peak to peak amplitude following right forearm stimulation in ten female and ten male subjects with reproducible CHEPs to forearm stimulation on each side. The regression line and correlation coefficient (r) are shown. No correlation exists between pain intensity and N1-P1 peak to peak amplitude in either female or male subjects.

the female subject group (P=0.793 for N1, P=0.092 for P1, and P=0.154 for amplitude), male subject group (P=0.862 for N1, P=0.456 for P1, and P= 0.343 for amplitude), and entire study group (P=0.775 for N1, P=0.134 for P1, and P=0.701 for amplitude). Moreover, no significant difference existed between the male and female subject groups for the forearm CHEPs parameters (P=0.222 for N1, P=0.160 for P1, and P=0.361 for amplitude).

Fig. 2 shows the correlation between pain intensity and N1-P1 peak to peak amplitude following right forearm stimulation. No correlation exists between these variables in the female (P=0.106, r=0.542), male (P=0.307, r=0.360) and total subject (P=0.075, r=0.407) groups. The correlation between N1 peak latency and age or body height is shown in figs. 3 and 4. A significant correlation exists between N1 latency and age in the female subject group (P=0.034, r=0.670), but not in the male (P=0.319, r=0.351) or total subject (P=0.288, r=0.250) groups. No significant correlation exists between N1 latency and body height in the female group (P=0.447, r=0.272), the male group (P=0.941, r=0.027), or the total subject group (P=0.178, r=0.313). No significant correlation was observed between N1-P1 peak to

Table 3. *Demographic data and N1 latency of ten female and ten male subjects with reproducible CHEPs to forearm stimulation on each side*

Subjects	Age (year)	Body height (cm)	N1 latency R forearm (ms)	N1 latency L forearm (ms)	N1 latency dorsum hand (ms)	N1 latency peroneal area (ms)	N1 latency dorsum foot (ms)
1. Female							
1	29	170	370	370	378	432	446
2	40	153	346	342	361	472	392
3	30	159	374	372	402	458	432
4	30	154	380	376	368	436	444
5	23	162	366	370	392	NA	464
6	24	160	370	360	380	412	NA
7	44	155	334	332	344	428	448
8	26	166	356	354	NA	NA	458
9	24	164	380	376	NA	458	NA
10	40	152	368	374	NA	NA	NA
Average	31	159.5	364.4	362.6	375	442.3	440.6
SD	7.6	6	14.9	15.4	19.4	21	23.7
2. Male							
11	18	173	330	338	346	356	348
12	24	171	382	378	370	430	416
13	31	173	390	388	396	NA	458
14	23	177	390	386	424	414	454
15	24	172	416	412	376	430	468
16	24	176	380	372	406	NA	NA
17	29	168	384	374	396	394	NA
18	29	171	378	386	380	NA	414
19	21	172	350	350	380	386	NA
20	32	172	358	356	376	436	NA
Average	25.5	172.5	375.8	374.0	385.0	406.6	426.3
SD	4.6	2.5	24.1	215	21.5	29.3	44.5

R: right; L: left

peak amplitude and age in the female group (P=0.382, r=0.311), the male group (P=0.321, r=0.350), or the total subject group (P=0.573, r=0.134, fig. 5).

DISCUSSION

We recorded CHEPs from five stimulation sites on the upper and lower limbs. A previous study of CHEPs demonstrated that 51 ˚C stimulation produced painful pinprick sensations over hairy skin and evoked a late potential mediated by Aδ afferents, with a mean negative peak latency of 267 ms to forearm stimulation[6]. Using a similar stimulator (Medoc, Israel) but different stimulation parameters, we had a longer N1 peak latency of approximately 360 ms to forearm stimulation. Another investigation using similar contact heat stimulator but different thermode contact area of 3.14 cm^2 yielded offset N1 peak latency around 550 ms, which presumably was also related to Aδ fiber activation[7]. We assumed that the afferent fibers responsible for the generation of CHEPs fall into the Aδ category. Discrepancies of N1 peak latency among different studies may be related to factors such as the location, temperature, duration, and surface area of the stimuli[6]. Current and previous CHEPs studies demonstrated that N1 peak latency is longer than the cortical response using CO_2-laser stimulator[8]. Adjustment of stimulation parameters was tried in a pilot study in which stimulation with peak temperature of 51 ˚C and heating rate of 70 ˚C/s produced optimal CHEP responses (data not shown). Consistent with the LEP study of Truini[7], we showed that neither the latency nor the amplitude of CHEPs differ between

Table 4. *The N1 and P1 peak latencies and N1-P1 peak to peak amplitudes in subjects with CHEP response to forearm stimulation on each side*

	Male		Female		Total	
	N	Peak latency mean ± SD (ms)	N	Peak latency mean ± SD (ms)	N	Peak latency mean ± SD (ms)
1. Peaks and stimulation sites						
R forearm N1	10	375.8 ± 24.1	10	364.4 ± 14.8	20	370.1 ± 20.3
R forearm P1	10	513.0 ± 37.2	10	491.9 ± 25.7	20	502.4 ± 33.0
L forearm N1	10	374.0 ± 21.4	10	362.6 ± 15.3	20	368.3 ± 19.0
L forearm P1	10	500.8 ± 34.2	10	472.8 ± 22.0	20	486.8 ± 31.5
Dorsum hand N1	10	385.0 ± 21.5	7	375.0 ± 19.3	17	380.8 ± 20.6
Dorsum hand P1	10	511.6 ± 49.2	7	517.4 ± 33.8	17	514.0 ± 42.4
Peroneal area N1	7	406.5 ± 29.3	7	442.2 ± 20.9	14	424.4 ± 30.7
Peroneal area P1	7	543.2 ± 38.4	7	585.1 ± 53.7	14	564.2 ± 49.8
Dorsum foot N1	6	426,3 ± 44.4	7	440.5 ± 23.7	13	434.0 ± 34.0
Dorsum foot P1	6	584.1 ± 43.6	7	569.1 ± 23.3	13	576.0 ± 33.5
2. Stimulation sites						
R forearm	10	9.2 ± 5.1	10	11.2 ± 4.7	20	10.2 ± 4.9
L forearm	10	11.0 ± 3.0	10	8.3 ± 3.9	20	9.7 ± 3.7
Dorsum hand	10	10.0 ± 5.9	7	9.9 ± 4.2	17	10.0 ± 5.1
Peroneal area	7	10.6 ± 6.6	7	8.0 ± 4.7	14	9.3 ± 5.7
Dorsum foot	6	10.9 ± 9.8	7	6.9 ± 3.5	13	8.7 ± 7.1

R: right; L: left; N: number; Amplitude: N1 to P1 peak to peak amplitude.

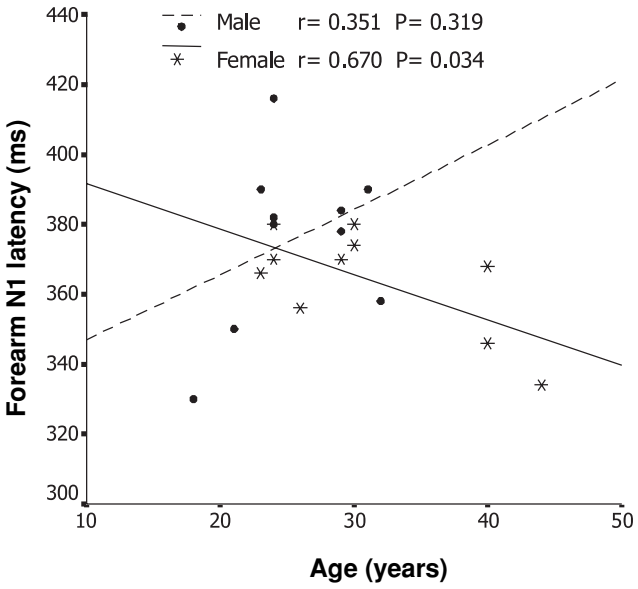

Figure 3. Correlation between age and N1 latency following right forearm stimulation in the same subject group as Fig. 2. The regression line and correlation coefficient (r) are shown. Forearm N1 latency is correlated with age in female but not in male subjects.

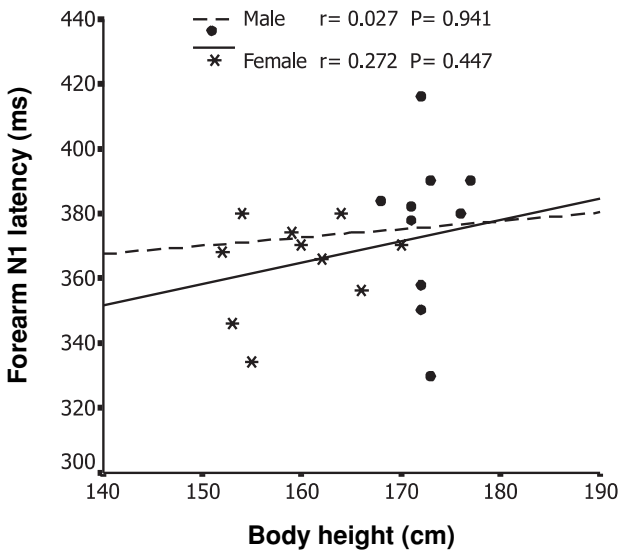

Figure 4. Correlation between body height and N1 latency following right forearm stimulation in the same subject group as Fig. 2. The regression line and correlation coefficient (r) are shown. No correlation exists between body height and right forearm N1 latency in either female or male subjects.

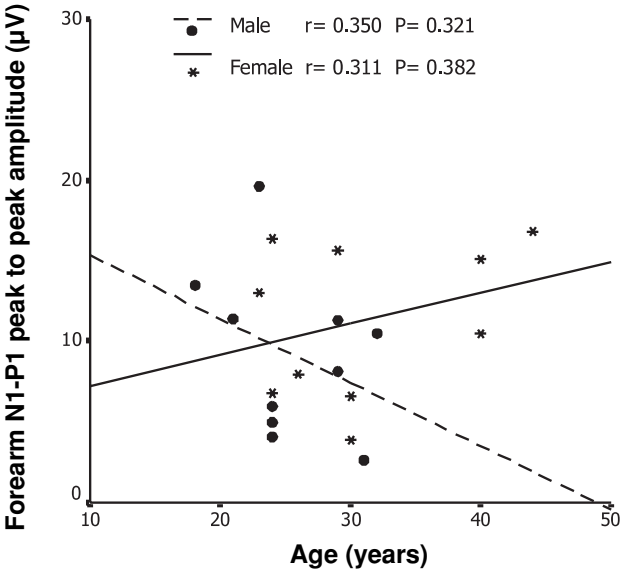

Figure 5. Correlations between age and N1-P1 peak to peak amplitude following right forearm stimulation in the same subject group as Fig. 2. The regression line and correlation coefficient (r) are shown. No correlation exists between age and N1-P1 peak to peak amplitude in either female or male subjects.

males and females[8]. In this study, we also found no significant differences in N1 latency between right and left forearm stimulation. The reproducible CHEPs were recorded more often with volar forearm stimulation (62.5%) than lower limb stimulation (around 40%), which is consistent with the report of Yelena et al.[6]. These findings indicate that the parameters of N1 latency to volar forearm stimulation may be the more preferable ones in terms of future clinical application.

Pain-evoked potentials may represent a quantitative neurophysiological correlate of peripheral nociceptive conduction and a psychological attribute of the stimulus in central nociceptive pathways[9-10]. Considerable evidence suggests that pain-evoked potentials may provide an objective assessment of peripheral small fiber pathways, including: 1) the correlation between the perceived pain intensity and the amplitude of the recorded waves in previous studies[11-13], 2) the decrease in amplitude of the evoked potential to analgesics[14], and 3) the calculation of nerve conduction velocity to differentiate the potentials medicated by Aδ from those by C fibers[6]. On the other hand, the LEPs (Laser Evoked Potentials) were found to be influenced by the consciousness level, and were closely related to the cognitive function of the subject[15]. Zaslansky et al.[9] reported that the pain related laser-evoked late potentials contained a clear non-modality-specific P300 component. The dipolar model of CHEPs topography by Massimiliano et al.[1] demonstrated the activity of anterior cingulated gyrus, which is linked to the pain-triggered attention mechanisms. The temporal and spatial shift of cortical response to different stimulation paradigms suggested that limbic affective reaction and prefrontal cognitive preparation are responsible for the integration of pain sensation[16]. This study showed no correlation between pain intensity and the presence of N1 or N1-P1 peak to peak amplitude, suggesting that pain-evoked potentials may have only indirect relation to peripheral nociceptive conduction. Some objects had longer N1 latency with forearm than with hand stimulation (subjects 4, 12, 15, 18 in Table 3), and longer N1 latency to simulation of the peroneal leg area than of the dorsum foot (subjects 2, 3, 11, 12 in Table 3). As far as future application of CHEPs in clinical neurophysiology is concerned, the results of this study indicate that central integration plays an important role in pain-evoked potentials.

A previous research on LEPs revealed that age is related to decreased LEP amplitude but not to LEP latency[8]. In this study, the female subjects exhibited a borderline significant decrease in right forearm N1 latency with increasing age (P=0.034), but no correlation between forearm N1-P1 peak to peak amplitude and age was found. Future studies recruiting both younger and older subjects may be needed to clarify the correlation of CHEPs with age. Previous study of somatosensory evoked potentials (SEPs) by transcutaneous electric stimulation of the median and posterior tibial nerves demonstrated a significant correlation between body height and SEP latencies[17]. The LEP study demonstrated a strong correlation between body height and latency of evoked cortical responses[8]. In this study, we did not find any correlation between N1 latency and body height. Although this study enrolled relatively few subjects, our

findings suggest that pain-evoked potentials to heat stimulation are more closely related to central nociceptive processing than to peripheral sensory conduction.

No universally accepted, objective, quantifiable, and physiological measure exists for pain and related symptoms[9,18-19]. Although the interpretation of pain-evoked potentials remains unsettled, the results of this CHEPs study in normal subjects may contribute to the understanding of the physiology of CHEPs and provide a valuable reference for future clinical applications.

ACKNOWLEDGEMENTS

The authors would like to thank professor Andrew Chen for the valuable discussions. We also thank Jings Instrument Corporation for the kind assistance in the establishment of recording system of contact heat evoked potentials.

REFERENCES

1. Valeriani M, Le Pera D, Niddam D, et al. Dipolar modelling of the scalp evoked potentials to painful contact heat stimulation of the human skin. Neurosci Lett 2002;318:44-8.
2. Arendt-Nielsen L, Nielsen J, Svensson P, et al. Evoked potentials to painful heat stimulation. Electroencephalogr Clin Neurophysiol Suppl 1999;49:261-6.
3. Harkins SW, Price DD, Roy A, et al. Somatosensory evoked potentials associated with thermal activation of type II Adelta mechanoheat nociceptive afferents. Int J Neurosci 2000;104:93-111.
4. Itskovich VV, Fei DY, Harkins SW. Psychophysiological and psychophysical responses to experimental pain induced by two types of cutaneous thermal stimuli. Int J of Neurosci 2000;105:63-75.
5. Nielsen J, Arendt-Nielsen L. Spatial summation of heat induced pain within and between dermatomes. Somatosens Mot Res 1997;14:119-25.
6. Granovsky Y, Matre D, Sokolik A, et al. Thermoreceptive innervation of human glabrous and hairy skin: a contact heat evoked potential analysis. Pain 2005;115:238-47.
7. Chen AC, Niddam DM, Arendt-Nielsen L. Contact heat evoked potentials as a valid means to study nociceptive pathways in human subjects. Neurosci Lett 2001;316:79-82.
8. Truini A, Galeotti F, Romaniello A, et al. Laser-evoked potentials: normative values. Clin Neurophysiol 2005;116:821-6.
9. Zaslansky R, Sprecher E, Tenke CE, et al. The P300 in pain evoked potentials. Pain 1996;66:39-49.
10. Towell AD, Boyd SG. Sensory and cognitive components of the CO2 laser evoked cerebral potential. Electroencephalogr Clin Neurophysiol 1993;88:237-9.
11. Carmon A, Dotan Y, Sarne Y. Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations. Exp Brain Res 1978;33:445-53.
12. Bromm B, Scharein E. Principal component analysis of pain-related cerebral potentials to mechanical and electrical stimulation in man. Electroencephalogr Clin Neurophysiol 1982;53:94-103.
13. Chen AC, Chapman CR, Harkins SW. Brain evoked potentials are functional correlates of induced pain in man. Pain 1979;6:365-74.
14. Kochs E, Treede RD, Schulte am Esch J, et al. Modulation of pain-related somatosensory evoked potentials by general anesthesia. Anesth Analg 1990;71:225-30.
15. Wang X, Inui K, Qiu Y, et al. Effects of sleep on pain-related somatosensory evoked magnetic fields in humans. Brain Res Cogn Brain Res 2003;17:388-99.
16. Chen AC, Niddam DM, Crawford HJ, et al. Spatial summation of pain processing in the human brain as assessed by cerebral event related potentials. Neurosci Lett 2002;328:190-4.
17. Chu NS. Somatosensory evoked potentials: correlations with height. Electroencephalogr Clin Neurophysiol 1986;65:169-76.
18. Verdugo R, Ochoa JL. Quantitative somatosensory thermotest. A key method for functional evaluation of small calibre afferent channels. Brain 1992;115(Pt 3):893-913.
19. Yarnitsky D, Sprecher E, Zaslansky R, et al. Heat pain thresholds: normative data and repeatability. Pain 1995;60:329-32.