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EFFECT OF COOLING SUIT TREATMENT IN PATIENTS WITH MULTIPLE SCLEROSIS EVALUATED BY EVOKED POTENTIALS

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The aim of the present study was to determine whether any significant alterations of evoked potentials could be detected after treatment of patients with multiple sclerosis with a cooling suit. All patients had previously experienced a positive effect of this treatment. Six patients were investigated with visual, sensory and motor evoked potentials and six further patients with only motor evoked potentials. All patients had relevant clinical lesions. The mean values for the group of patients were similar before and after cooling, but a few individuals showed a substantial improvement of motor evoked potentials after cooling, with increased amplitude and/or shortened central motor conduction time. There was also a weak, but significant, correlation between temperature decrements and the reduction of central motor conduction time. However, since the central motor conduction times of most patients were only slightly affected, this effect could explain only a small part of the beneficial effect of cooling. Effects on cognition and executive ability or improvement of spasticity may be of greater importance.

Key words: multiple sclerosis, cooling-suit, evoked potentials.

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INTRODUCTION

Heat-intolerance and a beneficial reaction to cooling are frequently reported phenomena in multiple sclerosis (MS) (for review, see 14). To date, there are several reports of symptomatic improvement after the use of a cooling suit (4, 5, 8, 15). A possible mechanism for this effect could be improved conduction through demyelinated segments of the nerve fibres. The aim of the present investigation was to determine whether investigations with evoked potentials of patients with MS, previously found to be cold-responsive, could discern measurable cooling effects on nerve impulse transmission.

PATIENTS AND METHODS

Patients with MS

Twelve patients with MS (6 females, 6 males), aged 35–62 years (median 46 years) were included in the study. All patients were responsive to treatment with the cooling suit, i.e. they had shown improvement in at least one motor test in a previously described test battery (8). The duration of the disease varied from 10 to 24 years (median 16 years). One patient had an Extended Disability Status Score (EDSS) (10) of 4.0 (walked without aid), one of 8.0 (confined to wheelchair), while all the other ten patients had an EDSS between 6.0 and 7.5 (walked with unilateral or bilateral support). All patients fulfilled the criteria for clinically definitive or laboratory supported clinically definitive MS proposed by Poser et al. (11). All investigated patients had lesions with clinical symptoms relevant to the performed investigations with evoked potentials.

The cooling system

The cooling garment comprises a vest and a head cap, with channels through which a liquid mixture of water and glycol circulates (Mark VII Microclimate Cooling suit, Life Support Systems Inc., Mountain View, CA, USA). A pump system driven by chargeable batteries is connected to a cooling box, in which the circulating fluid is cooled in an ice water chamber at 10°C.

Temperature recordings

Rectal temperature was used as a measure of core temperature. The thermometer (in Celsius) was validated against a reference thermometer in a water-bath. The deviation, expressed as the standard error of the mean, was 0.003°C. Oral temperature was measured in parallel.

Evoked potentials

Evoked potentials were recorded before and after the patients wore the cooling suit. The recordings started at 10.00 h and were then repeated at around 13.00 h. Between the recording sessions the patients ate lunch and then wore their cooling garments for 40 minutes. The recordings started again 30 minutes after the garments had been taken off. In six of the patients, the recordings included motor evoked potentials (MEP), somatosensory evoked potentials (SEP) and visual evoked potentials (VEP). In the other six, only MEPs were recorded. In half of the patients in whom all three modalities were recorded, the recordings started with MEP and VEP and in the other half with SEP. The recordings were performed in the same order after the cooling. All recordings were made on a Nicolet Viking equipment (Nicolet Biomedical Inc. Madison, WI, USA).

MEP

MEPs were recorded from m. abductor digiti minimi and m. tibialis anterior bilaterally. The responses were recorded simultaneously from all four positions (Fig. 1). MEPs were elicited by cortical magnetic stimulation (CMS) (Novametrix, Magstim 200) and when recorded from the intrinsic hand muscles also by magnetic stimulation over the lower cervical spine. The subjects were comfortably seated in a reclining chair during the examination. CMS was first performed with the subjects relaxed. After the position of the coil had been adjusted at least five stimulations were performed at maximal output (100%). The coil was then reversed for stimulation of the other hemisphere. The same procedure was then carried out with the muscles under slight voluntary activation. If no MEP could be elicited, at least 10 stimulations were delivered. Finally, with the subjects relaxed, the coil was positioned over the seventh cervical vertebra for stimulation of the nerve roots.

Latencies to all responses (first deviation from baseline) recorded

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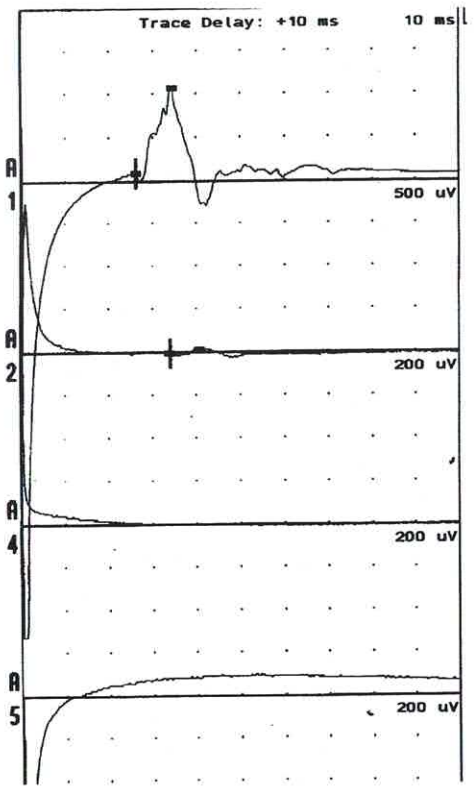

Fig. 1. Example of motor evoked potential recording. Recordings are from right m. abductor digiti minimi (first trace), left m. abductor digiti minimi (second trace), right m. tibialis anterior (third trace) and left m. tibialis anterior (fourth trace). The recording is made with coil position optimal for right m. abductor digiti minimi.

during rest were measured. Central motor conduction time (CMCT) was defined as the difference in latency between the earliest occurring response to CMS and the response to cervical stimulation. Amplitudes of all responses elicited by CMS were measured. For analysis, the response with the highest amplitude (max amplitude) was used, as well as the mean value of the three highest MEPs (mean amplitude).

SEP

SEPs were recorded over the cortex between Cz' (2 cm behind Cz) and Fz after stimulation of the left and right tibial nerve. The stimulus intensity was adjusted to produce a small muscle twitch and the stimulus frequency was set at 3.1 Hz. The filter settings were 0.5 Hz and 500 Hz, respectively. The average response to 1000 stimulations was recorded. From each nerve, two recordings were performed to check the reproducibility. Peak latency to the first positive peak (P40) and the following negativity (N50) were measured. The amplitude of P40 was measured from the preceding baseline and the amplitude of N50 from the preceding peak (P40).

VEP

VEPs were recorded from the occipital area overlying the visual cortex, 4 cm above the inion, in the midline, referred to a frontal reference electrode. A black and white, high-contrast chequerboard pattern was reversed at 1.1 Hz. The pattern was displayed on a TV-monitor, 150 cm in front of the subjects. The field size was 9.5° × 6.9° and each square subtended 1.2°. The filter settings were 0.5 and 200 Hz, respectively. The average response to 100 stimulations was recorded and the recording was repeated at least twice. Each eye was stimulated separately. The subjects were instructed to fixate the centre of the pattern. The latency to and amplitude of the most prominent positive peak (P100) were measured.

Statistics

Spearmans non-parametric correlation coefficient was used in finding associations between temperature-decrements and results of evoked potential recordings.

RESULTS

Core temperature

After 40 minutes in the cooling suit, the rectal temperature fell in all patients, on average 0.27°C (range 0.05–0.55°C). The oral temperature decreased in all patients except one, on average 0.39°C (range 0.00–1.00°C).

VEP

Reproducible VEPs with an identifiable P100 could be recorded in only two of the six patients. The latency was prolonged on stimulation of both eyes in both subjects. There were no significant changes of either latency or amplitude in the recordings made after cooling.

SEP

In two of the patients, no cortical responses could be identified, either before or after cooling. In two other patients, spasms occurred in one leg when the nerve was stimulated, which made the examination impossible. When stimulating the other leg, one of the patients had no detectable cortical response, while the other had a delayed response of low amplitude. The remaining two patients both had clearly delayed cortical responses bilaterally. There were no significant changes in any of the recordings after cooling.

MEP

CMS elicited detectable MEPs from m. tibialis anterior in only six patients and in only two of the patients at rest. Amplitudes were generally low and variable and latencies were difficult to determine due to background activity when the recordings were made during slight voluntary activation.

MEPs were obtained from both m. abductor digiti minimi in all subjects, in one of them only during voluntary activation. The results are presented in Table I. All patients except one had abnormal MEP latencies and abnormal CMCTs bilaterally, with CMCT values ranging between 10.8 and 34.9 milliseconds. One patient had an increased CMCT on one side, and a borderline value on the other. The mean values of both latencies and amplitudes for the group of patients were very similar before and after cooling.

In individual patients there were small increases or decreases in MEP latency and in CMCT, bilaterally or unilaterally, after cooling. The CMCT was longer (0.2–2.6 milliseconds) after cooling in 9 of the examined pathways and shorter in 13. In the majority of cases, the degree of decrease in CMCT was of the same order as the increases. In two patients (three pathways) the shortening after cooling was more marked, 3.6–5.9 milliseconds. In one of these patients, the amplitude also increased (maximum amplitude 0.1–0.6 mV and mean amplitude 0.1–

Table I. *Mean values and SDs for latencies and amplitudes of motor evoked potentials before and after cooling*

	Latency (milliseconds) rest	CMCT (milliseconds) rest	Max. ampl. (mV) rest	Mean ampl. (mV) rest	Max. ampl. (mV) activation	Mean ampl. (mV) activation
Before cooling	30.4 (7.08)	17.0 (6.62)	1.20 (1.35)	1.07 (1.31)	2.29 (1.52)	2.02 (1.45)
After cooling	30.3 (7.17)	16.4 (6.89)	1.16 (0.86)	1.02 (0.78)	2.44 (1.19)	2.20 (1.21)
Difference	−0.12 (2.21)	−0.60 (2.14)	−0.04 (0.68)	−0.05 (0.71)	0.15 (0.99)	0.18 (0.78)

CMCT: central motor conductive time.

0.4 mV), in the other, the amplitude decreased. In the recordings performed during voluntary activation there were no amplitude increases or shortening of latency after cooling, but the onsets of the MEPs were difficult to define due to the presence of background activity.

In three further patients, the amplitude increased after cooling. In one patient there was an unilateral increase both at rest (maximum amplitude 0.3–1.2 mV, mean amplitude 0.2–1.2 mV) and during voluntary activity (maximum amplitude 0.8–3.1 mV, mean amplitude 0.7–2.5 mV). In the other two the increases in amplitude (128–257%) were only seen during rest. Amplitude reductions were seen in six patients (eight muscles), at most 49%.

Amplitude-alterations were not significantly correlated to temperature-decrements.

Decreases in CMCT, recorded in the hand with longest latencies, were significantly correlated with temperature decrements ($k = 0.74$, $p = 0.010$, Fig. 2). In the other hand, this correlation was close to statistical significance ($k = 0.60$, $p = 0.053$).

DISCUSSION

All the patients included in this study had a long-standing disease and had moderate to severe symptoms. As a consequence, all recorded evoked potentials were abnormal, either delayed or not detectable. The high proportion of missing responses concerning VEP, SEP and MEP from m. tibialis anterior precluded any purposeful analysis of these data. With respect to MEP from m. abductor digiti minimi, there were no significant differences in latencies or amplitudes before and after cooling when group comparisons were carried out. Latencies and CMCT in individual patients became either somewhat shorter or somewhat longer after cooling and amplitudes showed a similar variation. The alterations in latency were, in the majority of cases, less than 2 milliseconds, but in two patients a decrease in CMCT of 3.6–5.9 milliseconds was seen after cooling. No increases in latency of the same order were noted. Moreover, there was a statistically significant correlation between the decrement in rectal temperature and the change in CMCT.

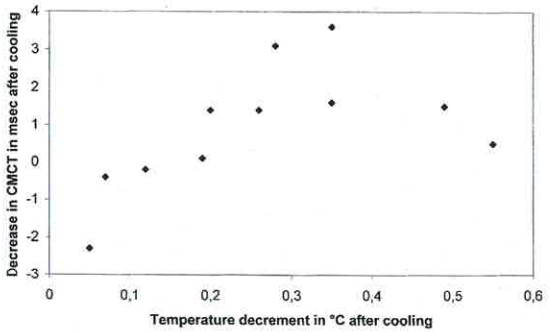

Fig. 2. Influence of temperature decrements on central motor conduction time (CMCT) in 11 patients with MS. MEPs were recorded from m. abductor digiti minimi and the results from the side with the slowest nerve-conduction are shown.

In experimental conditions, normal nerve-fibres react with block of conduction at high, non-physiological temperatures (13). One effect of demyelination is that the critical temperature, at which conduction block occurs, is lowered and may lie within the range of normal body temperature. Patients with MS often exhibit fluctuations in symptoms related to changes in temperature, compatible with a temperature dependent variation in the number of blocked axons in various central afferent and efferent pathways. An increase in amplitude of the MEP, reflecting an increase in the number of conducting axons, and a decrease in latency would be the expected findings of enhanced conduction through central motor pathways. However, if mainly slowly conducting axons are unblocked, the effect on latency and amplitude of the evoked CMAP would probably be negligible. Of importance in this context also is a methodological problem. There is a normal variability in both amplitude and latency of MEPs when repetitive cortical stimulation is performed. This variation is probably caused by small changes in facilitation and by technical factors, such as small shifts in coil position. The interstimulus variability is probably also more prominent in demyelinated pathways. This makes interpretation of our data more difficult.

It could not be ruled out that the changes seen in this study are caused by the above-mentioned factors and, thus, do not reflect actual improvement of nerve impulse transmission. The group comparison and the lack of concomitant changes in latency and amplitude in all patients except one give support to this alternative. The small changes in temperature that were measured after cooling are notable in this context and it is not known to what extent these changes are transmitted to the CNS. On the other hand, there are three findings worth considering: the increase in amplitude and shortening of latency seen in one patient, the decrease in latency of 3.6 milliseconds or more seen

in two patients and the correlation between decrement in temperature and change in latency. These findings suggest that some effect on central transmission could be present, at least in some of the patients. However, in the majority of patients, the beneficial effect on performance could probably not be attributed to this change.

Cooling may have several effects on motor performance, other than reducing axonal blocking in demyelinated nerve-fibres. Many studies have confirmed a positive effect of cooling on spasticity (2, 3, 9). However, in some patients the presence of spasticity may aid standing and walking by providing a pillar function. If leg weakness is severe, reduced spasticity may deteriorate these functions. This was not seen in our patients. In patients, in whom weakness is relatively less pronounced than spasticity, reduced spasticity may improve standing and walking without influencing MEP or SEP. However, reduced spasticity could not be the only explanation, since patients with MS without spasticity also have been shown to improve after cooling (8). An unspecific adrenergic effect as a response to the challenge of cooling could also be discussed. However, with the exception of a slight decrease in heart rate, no cardiovascular manifestations have as yet been documented (own observations and 7). There is no shock-effect when using the cooling suit: the cooling effect and shivering gradually increase. Local cooling of the head and neck has recently been reported to decrease intracranial blood flow (16), supporting the concept of a cooling effect on the core temperature. A redistribution of the blood flow from the cooled skin to the central nervous system has also been proposed as an explanation for the cooling effect in patients with MS (1). Fatigue or tiredness is reported in a high percentage of patients with MS (6). In a previous study (8) 9 out of 13 patients with MS stated less fatigue after cooling. This effect may contribute to enhanced motor performance.

Although the clinical impression of improvement after cooling is widely recognized, few attempts to measure the effect of conduction in central pathways have been published. Robinson et al. (12) recorded SEP following stimulation of median- and tibial-nerve before and after cooling but did not find any significant changes. In the study by Capello et al. (4) VEP, SEP as well as MEP were recorded in six patients with MS before and after cooling. They reported a significant shortening of tibial nerve SEP latency after cooling, although the results, presented as mean values and standard deviations, do not fully support this conclusion. They also noted an "improvement in CMCT" in three of the patients, but no data were presented. This finding could be in agreement with our results. The core temperatures were measured differently in these studies. In our study temperatures were recorded rectally and orally, with an average decrease of 0.27°C and 0.39°C, respectively. In comparison, the decrease in temperature in the study by Robinson et al. (12) was on average 0.46°C (tympanic temperature) and in the study by Capello et al. (4) 0.7°C (oral temperature).

In conclusion we found small changes in MEP from m. abductor digiti minimi after cooling, changes that could reflect improvement in central efferent conduction, although the beneficial effect of cooling is probably mainly related to other factors. However, the results are far from unequivocal and further studies are needed to clarify the mechanisms behind the positive effect of cooling on motor performance in MS. A more detailed examination of MEPs, including determination of stimulation-thresholds for evoking motor responses, could be of interest.

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