SUPERFICIAL WARMING AND COOLING OF THE LEG AFFECTS WALKING SPEED AND NEUROMUSCULAR FUNCTIONS IN PEOPLE WITH SPASTIC PARAPARESIS

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ABSTRACT 210

Objective: People with Hereditary and Spontaneous Spastic Paraparesis (pwSP) report their legs are stiffer and walking slower when their legs are cold. This study explored the effects of prolonged superficial cooling and warming of the lower leg on walking speed and local measures of neuromuscular function.

Methods: A randomised pre and post intervention study with 22 pwSP and 19 matched healthy controls. On two separate occasions one lower leg was cooled or warmed. Measurements included walking speed and measures of lower limb impairment: ankle movement, passive muscle stiffness, spasticity, amplitude and rate of force generation and central and peripheral nerve conduction time/velocity.

Results: In both groups cooling led to a decrease in walking speed that was more marked in people with spastic paraparesis. Cooling decreased the rate and amplitude of force generation and peripheral nerve conduction velocity and increased stretch reflex size. Warming increased the rate and amplitude of force generation, nerve conduction velocity and decreased the size of the stretch reflex.

Conclusion: Superficial cooling significantly reduces walking speed. Temperature changes are associated with changes in neuromuscular impairments in spastic paraparesis and controls. Rehabilitation interventions that help to prevent heat loss (insulation) or improve limb temperature via passive or active means particularly when the legs and/or environment are cool may have benefits for people with spastic paraparesis.

Keywords: temperature, neural conduction, muscle spasticity, spastic paraparesis

List of Abbreviations:

MEP – Motor Evoked Potentials

MVC – Maximal Voluntary Contraction

MVCdt – Rate of rise of torque

pwSP – people with Spastic Paraparesis

TMS – Transcranial Magnetic Stimulation

BMI – Body Mass Index

INTRODUCTION

Hereditary and Spontaneous Spastic Paraparesis is a progressive condition resulting in impaired balance and walking[1]. In the type I or uncomplicated presentation people present with lower limb paresis and spasticity due to a dying back axonal degeneration of central descending and ascending tracts including the corticospinal tract, spinocerebellar tracts and the dorsal columns. In the type II or complicated presentation additional signs include peripheral neuropathy, cerebellar ataxia or dementia[1]. Focus groups held with people with Hereditary and Spontaneous Spastic Paraparesis (pwSP) in the UK (n=36 participants) highlighted the perception that their walking is often slower when their legs are cold such as in cold weather, this is associated with an increase in perceived lower limb stiffness. Warming their lower legs by increasing layers of clothes or being in warmer environments is perceived to help them walk faster and relieve increased leg stiffness.

In people with a stroke or an acquired brain injury a decrease in spasticity, as measured clinically and electrophysiologically[10–13], has been reported with periods of superficial cooling. Despite this reduction in spasticity, improvements in voluntary movements and function have not been clearly demonstrated[10]. This may reflect the associated impact of temperature changes on nerve conduction velocity, passive stiffness[14] and muscle strength.

The subjective report of an improvement of function with warming in pwSP contrasts with people with Multiple Sclerosis who can also present with an upper motor neuron syndrome. People with Multiple Sclerosis often report a worsening of symptoms with warming and an improvement with whole body or localised cooling. This is mainly felt to be mediated by inducing central nerve conduction block with warming (Uthoffs Phenomenon) secondary to demyelination[15,] . For this reason central conduction time was assessed in pwSP.

This study therefore investigated whether (a) pwSP experience changes in walking speed and measures of neuromuscular impairments (movement, stiffness, strength and nerve conduction velocity) with prolonged superficial cooling and warming and (b) whether these changes are comparable to that seen in healthy participants. Ultimately, this study aims to determine whether rehabilitation strategies should consider the functional impact of temperature changes in pwSP.

MATERIALS AND METHODS

PARTICIPANTS

Twenty two pwSP and 19 healthy controls, matched for age, gender and body mass index (BMI), participated in the study (Table 1). PwSP were recruited via advertisement in the UK SP support group newsletter and controls via local advert. PwSP were included if they had a diagnosis of Spastic Paraparesis with/without a family history. Other differential diagnoses were excluded through appropriate imaging, clinical and laboratory tests. Participants had to be able to walk at least 20m with/without a walking aid and have bilateral spasticity in the ankle plantarflexors (at least grade 1 Ashworth score[18]). PwSP were excluded if they had additional orthopaedic/neurological impairments. Exclusion factors for both groups included contraindications to Transcranial Magnetic Stimulation (TMS), poor skin integrity, Raynaud's disease or a fixed ankle inversion contracture. Ethical approval was provided by South West Cornwall and Plymouth ethics committee (HS13/14-105). Informed consent was provided by all participants.

Participants' baseline characteristics (height, weight, age, sex, family history, genetic diagnosis, length of symptoms and presence of anti-spasticity medication) were recorded. The abbreviated mental test score was used to screen for dementia and a self-report Barthel Index recorded functional ability. Skin fold thickness overlying the ankle plantarflexors was measured using a Harpenden calliper at the level of the mid-shank in a seated position and Body mass index (BMI) calculated from people's height and mass. The Ashworth scale was used to evaluate spasticity in the lower leg. PwSP were classified as pure or complicated according to genetic diagnosis and the presence or absence of additional signs and symptoms, including peripheral neuropathy[2,23].

INTERVENTION

For pwSP the self-reported most affected side was studied, for healthy controls a similar proportion of dominant and non-dominant legs were assessed. Participants were assessed in a semi-reclined standardised position (Figure 1). One lower leg was cooled or warmed for 30 minutes using a wrap attached to a temperature controlled water bath with water circulating at either 7 ºC or 37 ºC, (Figure 1).The order of cooling or warming was randomised using a computer generated code and each condition was separated by a minimum 24hr period.

MEASURES

Core temperature was measured in the inner ear (Tympanic membrane temperature (Omron MC 510-E2, Netherlands). Room and shank skin temperature were measured using thermocouples (type-t thermocouples (BAT-10 Physitemp, USA).

The primary outcome measure was maximal walking speed measured over a 10m walkway. Two walks were recorded with a 1 min seated rest period and the mean walking speed calculated.

Secondary outcome measures evaluated neuromuscular impairments in the lower leg. Localised movement at the ankle was measured by foot tapping time. The time taken to tap each foot 10 times was recorded with the subject in a standardised seated position. The mean foot tap time was calculated for each side.

Slow and fast stretches were used to quantify passive stiffness and stretch reflex size. A 15-degree amplitude, slow (peak velocity 5 ^{o}/s) and fast (peak velocity 170 ^{o}/s) ramp stretch was applied at the ankle while the participant was relaxed. The ankle axis was aligned to the axis of a customised servomotor (Baldor BSM, UK (Figure 1)). Each stretch was repeated 6 times with a 3-5 second random inter-stretch interval. Torque, position (TLSF transducer, Industrial measurements UK) and surface electromyography from the tibialis anterior, medial gastrocnemius and soleus muscles (2.5 cm inter-electrode distance, Digitimer D360, UK) were recorded. During the 6 slow stretches, trials were omitted if the EMG was greater than the mean + 2 SD of the pre-stretch relaxed level (baseline level). Torque, position and EMG were digitized (2KHz Power 1401, CED Electronics, UK). EMG signals were filtered (30Hz low pass 2^{nd} Order Butterworth filtered) and rectified (MATLAB (Mathworks, USA)). Torque and position were measured over a 300ms period prior to stretch onset and immediately following stretch offset. Slow stretches evaluated passive stiffness[24].

Stiffness was normalised to body weight and defined as: ΔTorque / Δ position

Stretch reflex activity was characterised by the mean rectified gastrocnemius EMG above baseline level following the fast stretch and used as a measure of spasticity.

Maximal isometric muscle strength (MVC) of ankle plantar- and dorsiflexors was measured using the motor with the ankle in 5^{o} plantarflexion. The participant was asked to push down or pull up as hard and fast as they could and verbal encouragement was provided. The rate of torque development (MVCdt) was defined as the rate torque developed between 25-50% of the maximal torque as calculated using a least squares algorithm.

Peripheral nerve conduction was measured in the tibial nerve. The latency of abductor hallucis M waves following proximal stimulation at the level of the popliteal fossa and distal stimulation at the level of the medial malleolus were recorded. The stimulation points were marked for recording following cooling/warming and the distance between distal and proximal points measured. Conduction velocity (m/s) was defined as:

Inter-stimulus distance/ (proximal-distal M wave latency)[25]

For central conduction times, motor evoked potentials (MEPs) in the abductor hallucis in response to single pulse TMS were measured[26] (double cone coil 110mm Magstim 200 stimulator, Magstim company, UK). Resting threshold was determined as the stimulus that produced an MEP >50 μV on at least 3 out of 5 occasions[26]. MEP latency was measured following 3 stimuli at 1.5 x resting motor threshold up to 100% machine output (2.0 T). In 2 pwSP MEPs at a resting threshold could not be determined therefore MEPs were recorded at 100% machine output as they contracted abductor hallucis (~10% maximal voluntary contraction). Lumbosacral roots were stimulated using a figure of eight coil (70 mm) that was placed lateral to the L5 spinous process, oriented 45^{o} to the vertical with the coil current running in a medio-lateral direction. Stimulator intensity >80% was used to record abductor hallucis MEPs [27].

The central conduction time was defined as: motor cortex MEP latency- spinal root MEP latency.

All measures were repeated before and immediately after 30 minutes of superficial cooling or warming.

ANALYSIS

Tests of normality (Shapiro-Wilks) established that data from all measures was normally distributed. Baseline characteristics were compared using unpaired t-tests. Changes in walking speed and neuromuscular measures of impairment were assessed using a between groups repeated measures analysis of variance with factors being GROUP (pwSP Vs Controls), TIME (pre vs post intervention) and TEMPERATURE (cool vs warm). An additional factor of SIDE (targeted vs non targeted) was included when assessing changes in foot tap time. Results were taken as significant if $p \leq 0.05$.

RESULTS

Participant demographics are summarised in Table 1. There was no difference in age or BMI between groups ($P>0.05$, Table1). Calf skin thickness was less in pwSP ($p<0.005$, Table 1). Clinical characteristics of pwSP are summarised in Table 2. When people with complicated and pure presentations of spastic paraparesis were compared at baseline people with complicated presentations had slower walking (t test $p<0.001$) and foot tap times (t test $p<0.05$) but there was no difference for all other measures. Therefore both presentations were analysed as one group (pwSP).

There were no differences between pwSP or control groups in core or room temperature (Effect of Group p>0.05). This did not change over time (Effect of Time >0.05) and there were no interaction effects. There were no Group or Time effects for skin temperature (Effect of Group p>0.05; effect of Time p>0.05). There was a Time x Temperature interaction (p<0.001, Table 3). Over 30 minutes local skin temperature decreased with cooling by 12.1 ± 2.35 ^{o}C and increased with warming by 9.37 ± 2.18 ^{o}C.

Walking speed was significantly slower in pwSP (Effect of Group p<0.001). Overall walking speed slowed over time (Effect of Time p<0.05) and was slower in the cooling condition (Effect of Temperature p<0.05). This reflected the fact that walking speed decreased significantly with localised cooling in both groups whilst there was no change in walking speed with localised warming (Temperature x Time Interaction (p<0.005; Figure 2A)).

Foot tap time was significantly longer in pwSP (Effect of Group P<0.0001). In both groups foot tap time significantly increased with cooling and decreased with warming (Temperature x Time Interaction p<0.001); this occurred in the targeted leg only (Temperature x Side x Time Interaction effect (p<0.001; table 3, Figure 2B). The decrease in foot tap time when the leg was warmed was significantly greater in pwSP compared to controls (Temperature x Time x Side x Group Interaction p<0.05), whilst the increase in foot tap times seen after cooling was of similar magnitude in both groups.

Passive stiffness was higher in pwSP compared to controls (Effect of Group p<0.0001). Passive stiffness decreased with cooling and warming (Effect of Time p<0.001). The decrease in passive stiffness was greater with in pwSP (Time x Group Interaction p<0.05, Table 3).

Stretch reflex size (spasticity) was higher in pwSP (Effect of Group $p<0.01$). The size of the stretch reflex significantly decreased with warming and increased with cooling (Temperature x Time interaction $p<0.05$, table 3).

Dorsiflexor MVC was significantly reduced in pwSP (Effect of Group $p<0.0001$, table 3). Dorsiflexor MVC decreased with cooling and warming (Effect of Time$p<0.0001$). The reduction in MVC with cooling was more marked than that observed with warming (Temperature x Time Interaction $p<0.0001$) and was greater in the control group (Temperature x Time x Group interaction $p<0.0001$, Table 3). Plantarflexor strength as measured by MVC was significantly reduced in pwSP ($p<0.0001$). PF MVC decreased over time (Effect of Time $p<0.05$); there were no other interaction effects.

The rate of torque generation in dorsiflexor and plantarflexor muscles (MVCdt) was significantly reduced in pwSP (Effect of Group $p<0.0001$). In both groups MVCdt decreased with cooling and increased with warming (Temperature x Time Interaction Dorsiflexors $p<0.001$Plantarflexors $P<0.001$). The reduction in MVCdt with cooling was more marked in the control group (Effect of Temperature x Time x Group Dorsiflexors : $p<0.001$, Plantarflexors: $P<0.05$, Table 3).

Data on peripheral tibial nerve conduction was obtained in 20 pwSP and 16 controls, with missing data relating to perceived discomfort with the procedure. There was no difference in conduction velocity between groups ($p=0.06$). Four pwSP (20%) had a tibial nerve conduction velocity over two standard deviations lower than the control mean at baseline and were classified as having a peripheral neuropathy[23] (Table 2). Tibial nerve conduction velocity decreased with cooling and increased with warming (Temperature x Time Interaction

($p<0.001$), Figure 3, Table 3). Changes in conduction velocity with cooling and warming were not significantly different between the groups.

Data on central conduction time was obtained in 14 pwSP (64%) and 13 Controls (68%), with dropouts being caused by perceived discomfort with the procedure. At baseline pwSP had a longer central conduction time (Effect of Group $p<0.05$). Central motor conduction time was not affected by temperature changes in either group ($p>0.05$, Table 3).

There was no effect of skin thickness on the extent of temperature-related changes in physiological or functional variables.

DISCUSSION

In the current study 77% of pwSP (n=22) had a genetic diagnosis and/or family history, and both complicated (n=5) and uncomplicated (n=17) presentations were seen as defined by clinical presentation/genetic testing (Table 2). The proportion of pwSP with a genetic diagnosis is similar to that reported in epidemiological studies[28–30] and reflects the multitude of genetic mutations that can cause this condition. PwSP had an increased corticospinal tract conduction time in keeping with the axonal degeneration reported using MRI, diffusion tensor imaging and post mortem[32–34]. At baseline increased spasticity (stretch reflex size), passive stiffness, reduced MVC in dorsiflexor and plantarflexor muscles and slower walking speeds were seen in pwSP compared to controls in line with previous reports[24,3135].

The level of spasticity reported could be considered to be low (median grade 1; range 1-3); this could reflect a bias towards recruiting people with more mild symptoms. However, an assessment of their walking ability suggests that the cohort of ambulant pwSP studied was more severe with 78% using walking aids compared to 28% in population studies[37].

The impact of superficial cooling on walking speed supports subjective reports of pwSP that their walking gets slower when their legs are cold. At a more local level localised ankle movement measured by foot tap time increased in the targeted limb with cooling and decreased with warming. Deteriorations in toe tapping time with cooling have been reported previously in people with acquired brain injury[11]. Spastic Paraparesis produces bilateral spasticity and paresis; only 1 leg was targeted in this study to allow a detailed study of the changes in neuromuscular impairments in that leg and assess their subsequent effects on walking. More marked effects would be expected with targeting both legs although limited time post cooling / warming precluded an assessment of both legs[36].

Group differences in the effects of temperature changes may be related to the reduction in calf skin thickness in pwSP. Reductions in skin thickness have been reported in other neurological conditions[38] and may lead to more marked changes in intramuscular temperature with cooling/warming[39]. However, there was no difference in the impact of temperature on tibial nerve conduction velocity between groups suggesting that temperature changes, at least at this deeper level, may be similar.

A decrease in passive stiffness was observed in both groups with cooling and warming. The passive stiffness changes observed in both conditions may reflect the effects of the repeated slow and fast stretches used to test stiffness and spasticity and/or the fact that the ankle was held in 5^{o} plantarflexion for the 30 minute intervention period that may have reduced the viscoelastic properties of the muscle. That these changes were more marked in pwSP suggests that stretching may be a useful adjunct to treatment. Cooling and warming have both been reported to have effects on muscle spindle activity with changes in muscle spindle sensitivity occurring alongside changes in the firing rate of Ia afferents[6,41]. Ice has been used therapeutically to reduce spasticity[42]. In contrast in this study stretch reflex size increased with cooling. Noxious stimuli such as sudden superficial application of cold to the skin may increase spasticity[45]. However, this will only have an effect for a few seconds[14]. Warming resulted in a reduction in spasticity; this may in part underlie the reductions in spastcity seen with hydrotherapy in this patient group[43].

A reduced MVC was seen in dorsiflexors but not plantarflexors with cooling. This may reflect the fact that the common peroneal nerve supplying the ankle dorsiflexors is more superficial than the tibial nerve supplying the ankle plantarflexors. The rate of torque generation in the dorsiflexor muscles (MVCdt) decreased significantly with cooling and increased with warming in both groups. This has not been reported previously in people with neurological conditions. The ability to rapidly generate force in the dorsiflexor muscles is key in the gait cycle for swing through and to reduce tripping. For pwSP the prevention of cooling of these muscles may therefore also be important for risk of falls measurement of falls could be incorporated into future studies.

Superficial cooling or warming was applied to the lower leg and therefore both the flexor and extensor muscle compartments were targeted. In future it would be interesting to target either compartment. This could, for example, help differentiate between the functional impact of plantarfexor spasticity and dorsiflexor paresis in causing foot drop that is reported to lead to trips and falls in pwSP.

This study induced localised temperature changes that are more marked than usually encountered in the environment. However, changes in environmental temperature would affect the whole body, possibly leading to more widespread (but less marked) changes than seen in the current study that may still affect functional ability[39]. Future work could assess the effects of changes in ambient temperature. This study looked at the effects of superficial warming from an ambient room temperature of 22.96±1.94°C. It may be that the improvements in neuromuscular impairments seen in this study with warming are more marked in cooler environments.

The application of superficial heating or cooling has been suggested to have a depth of effect of 10-30mm depth[47] although some studies have suggested changes at deeper levels with superficial application of heat[48,49]. This study used non-invasive skin temperature measurement was used which has been reported to correlate to deeper intramuscular temperatures[3,50] and was a pragmatic decision in this study.   In this study regardless of the depth of effect changes in walking speed and neuromuscular impairments were observed which suggest an effect on neuromuscular structures. Future studies could include intramuscular temperature monitoring to evaluate the precise depth of temperature penetration[3].

This study highlights several implications for rehabilitation of pwSP. In pwSP, superficial cooling led to a deterioration in functional ability as measured by walking speed as well as changes in local neuromuscular impairments which would tend to support the observations of pwSP that their walking deteriorates when their limbs are cold. Avoidance of cooling by the use of insulating garments should be evaluated in pwSP. Superficial warming resulted in improvements in torque generation, a reduction in spasticity and passive stiffness, as well as a quicker nerve conduction speed. External passive heating or active warm up[17], or hydrotherapy to increase limb temperature should be explored further in pwSP. As movement is impaired in pwSP it may be that maintaining and preventing heat loss or increasing limb temperature using passive means may be more efficient and effective in this patient group.

As discussed above limitations include the impact of difference in skin thickness and the lack of recordings of temperature in subcutaneous tissues. Further, although order effects were minimised by randomising the order of presentation the assessors were not blinded to the type of intervention. Future work could therefore assess the effects of more clinically feasible methods of cooling/warming and/or the impact of environmental changes. Blinded outcome measurement of not only neuromuscular impairment but also subjective and objective measures of functional ability should be included.

CONCLUSIONS

Superficial cooling of a limb affects both walking speed and localised measures of neuromuscular impairments (ankle movement, dorsiflexor strength, passive stiffness, spasticity and nerve conduction speed) in pwSP and control participants. Warming does not have an effect on walking speed but it does result in improvements in neuromuscular functions: localised ankle movement, nerve conduction speed, passive stiffness, spasticity and ability to rapidly generate force in dorsiflexor muscles. Rehabilitation interventions that help to prevent heat loss or increase limb temperature via passive means may have functional benefits for pwSP.

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