

2016-12

Superficial warming and cooling of the leg affects walking speed and neuromuscular impairments in people with spastic paraparesis

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<http://hdl.handle.net/10026.1/6759>

10.1016/j.rehab.2016.04.006

Annals of Physical and Rehabilitation Medicine

Elsevier BV

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

3

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26 **ABSTRACT 210**

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

31

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

37

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

43

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

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

50

51

52 **List of Abbreviations:**

53 **MEP** – Motor Evoked Potentials

54 **MVC** – Maximal Voluntary Contraction

55 **MVCdt** – Rate of rise of torque

56 **pwSP** – people with Spastic Paraparesis

57 **TMS** – Transcranial Magnetic Stimulation

58 **BMI** – Body Mass Index

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69 **INTRODUCTION**

70 Hereditary and Spontaneous Spastic Paraparesis is a progressive condition resulting in
71 impaired balance and walking¹. In the type I or uncomplicated presentation people present

72 with lower limb paresis and spasticity due to a dying back axonal degeneration of central
73 descending and ascending tracts including the corticospinal tract, spinocerebellar tracts and
74 the dorsal columns. In the type II or complicated presentation additional signs include
75 peripheral neuropathy, cerebellar ataxia or dementia¹. Focus groups held with people with
76 Hereditary and Spontaneous Spastic Paraparesis (pwSP) in the UK (n=36 participants)
77 highlighted the perception that their walking is often slower when their legs are cold such as
78 in cold weather, this is associated with an increase in perceived lower limb stiffness.
79 Warming their lower legs by increasing layers of clothes or being in warmer environments is
80 perceived to help them walk faster and relieve increased leg stiffness.

81 In people with a stroke or an acquired brain injury a decrease in spasticity, as measured
82 clinically and electrophysiologically¹⁰⁻¹³, has been reported with periods of superficial cooling.
83 Despite this reduction in spasticity, improvements in voluntary movements and function have
84 not been clearly demonstrated¹⁰. This may reflect the associated impact of temperature
85 changes on nerve conduction velocity, passive stiffness¹⁴ and muscle strength.

86 The subjective report of an improvement of function with warming in pwSP contrasts with
87 people with Multiple Sclerosis who can also present with an upper motor neuron syndrome.
88 People with Multiple Sclerosis often report a worsening of symptoms with warming and an
89 improvement with whole body or localised cooling. This is mainly felt to be mediated by
90 inducing central nerve conduction block with warming (Uthoffs Phenomenon) secondary to
91 demyelination¹⁵. For this reason central conduction time was assessed in pwSP.

92

93 This study therefore investigated whether (a) pwSP experience changes in walking speed
94 and measures of neuromuscular impairments (movement, stiffness, strength and nerve
95 conduction velocity) with prolonged superficial cooling and warming and (b) whether these
96 changes are comparable to that seen in healthy participants. Ultimately, this study aims to

97 determine whether rehabilitation strategies should consider the functional impact of
98 temperature changes in pwSP.

99

100 **MATERIALS AND METHODS**

101 PARTICIPANTS

102 Twenty two pwSP and 19 healthy controls, matched for age, gender and body mass index
103 (BMI), participated in the study (Table 1). PwSP were recruited via advertisement in the UK
104 SP support group newsletter and controls via local advert. PwSP were included if they had a
105 diagnosis of Spastic Paraparesis with/without a family history. Other differential diagnoses
106 were excluded through appropriate imaging, clinical and laboratory tests. Participants had to
107 be able to walk at least 20m with/without a walking aid and have bilateral spasticity in the
108 ankle plantarflexors (at least grade 1 Ashworth score¹⁸). PwSP were excluded if they had
109 additional orthopaedic/neurological impairments. Exclusion factors for both groups included
110 contraindications to Transcranial Magnetic Stimulation (TMS), poor skin integrity, Raynaud's
111 disease or a fixed ankle inversion contracture. Ethical approval was provided by South West
112 Cornwall and Plymouth ethics committee (HS13/14-105). Informed consent was provided
113 by all participants.

114

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

122 according to genetic diagnosis and the presence or absence of additional signs and
123 symptoms, including peripheral neuropathy^{2,23}.

124

125 INTERVENTION

126 For pwSP the self-reported most affected side was studied, for healthy controls a similar
127 proportion of dominant and non-dominant legs were assessed. Participants were assessed
128 in a semi-reclined standardised position (Figure 1). One lower leg was cooled or warmed for
129 30 minutes using a wrap attached to a temperature controlled water bath with water
130 circulating at either 7 °C or 37 °C, (Figure 1).The order of cooling or warming was
131 randomised using a computer generated code and each condition was separated by a
132 minimum 24hr period.

133

134 MEASURES

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

138

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

142

143 Secondary outcome measures evaluated neuromuscular impairments_ in the lower leg.

144 Localised movement at the ankle was measured by foot tapping time. The time taken to tap

145 each foot 10 times was recorded with the subject in a standardised seated position. The
146 mean foot tap time was calculated for each side.

147

148 Slow and fast stretches were used to quantify passive stiffness and stretch reflex size. A 15-
149 degree amplitude, slow (peak velocity 5 °/s) and fast (peak velocity 170 °/s) ramp stretch
150 was applied at the ankle while the participant was relaxed. The ankle axis was aligned to the
151 axis of a customised servomotor (Baldor BSM, UK (Figure 1)). Each stretch was repeated 6
152 times with a 3-5 second random inter-stretch interval. Torque, position (TLSF transducer,
153 Industrial measurements UK) and surface electromyography from the tibialis anterior, medial
154 gastrocnemius and soleus muscles (2.5 cm inter-electrode distance, Digitimer D360, UK)
155 were recorded. During the 6 slow stretches, trials were omitted if the EMG was greater than
156 the mean + 2 SD of the pre-stretch relaxed level (baseline level). Torque, position and EMG
157 were digitized (2KHz Power 1401, CED Electronics, UK). EMG signals were filtered (30Hz
158 low pass 2nd Order Butterworth filtered) and rectified (MATLAB (Mathworks, USA)). Torque
159 and position were measured over a 300ms period prior to stretch onset and immediately
160 following stretch offset. Slow stretches evaluated passive stiffness²⁴.

161

162 Stiffness was normalised to body weight and defined as: $\Delta\text{Torque} / \Delta\text{position}$

163

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

166

167 Maximal isometric muscle strength (MVC) of ankle plantar- and dorsiflexors was measured
168 using the motor with the ankle in 5° plantarflexion. The participant was asked to push down

169 or pull up as hard and fast as they could and verbal encouragement was provided. The rate
170 of torque development (MVCdt) was defined as the rate torque developed between 25-50%
171 of the maximal torque as calculated using a least squares algorithm.

172

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

178

179 $\text{Inter-stimulus distance} / (\text{proximal-distal M wave latency})^{25}$

180

181 For central conduction times, motor evoked potentials (MEPs) in the abductor hallucis in
182 response to single pulse TMS were measured²⁶ (double cone coil 110mm Magstim 200
183 stimulator, Magstim company, UK). Resting threshold was determined as the stimulus that
184 produced an MEP >50 μV on at least 3 out of 5 occasions²⁶. MEP latency was measured
185 following 3 stimuli at 1.5 x resting motor threshold up to 100% machine output (2.0 T). In 2
186 pwSP MEPs at a resting threshold could not be determined therefore MEPs were recorded
187 at 100% machine output as they contracted abductor hallucis (~10% maximal voluntary
188 contraction). Lumbosacral roots were stimulated using a figure of eight coil (70 mm) that was
189 placed lateral to the L5 spinous process, oriented 45° to the vertical with the coil current
190 running in a medio-lateral direction. Stimulator intensity >80% was used to record abductor
191 hallucis MEPs²⁷.

192

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

195

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

198

199 ANALYSIS

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

207

208 RESULTS

209 Participant demographics are summarised in Table 1. There was no difference in age or BMI
210 between groups ($P > 0.05$, Table 1). Calf skin thickness was less in pwSP ($p < 0.005$, Table 1).
211 Clinical characteristics of pwSP are summarised in Table 2. When people with complicated
212 and pure presentations of spastic paraparesis were compared at baseline people with
213 complicated presentations had slower walking (t test $p < 0.001$) and foot tap times (t test
214 $p < 0.05$) but there was no difference for all other measures. Therefore both presentations
215 were analysed as one group (pwSP).

216 There were no differences between pwSP or control groups in core or room temperature
217 (Effect of Group $p>0.05$). This did not change over time (Effect of Time >0.05) and there
218 were no interaction effects. There were no Group or Time effects for skin temperature (Effect
219 of Group $p>0.05$; effect of Time $p>0.05$). There was a Time x Temperature interaction
220 ($p<0.001$, Table 3). Over 30 minutes local skin temperature decreased with cooling by $12.1 \pm$
221 2.35 °C and increased with warming by 9.37 ± 2.18 °C.

222

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

228

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

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

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

243

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

251

252 The rate of torque generation in dorsiflexor and plantarflexor muscles (MVCdt) was
253 significantly reduced in pwSP (Effect of Group $p < 0.0001$). In both groups MVCdt decreased
254 with cooling and increased with warming (Temperature x Time Interaction Dorsiflexors
255 $p < 0.001$ Plantarflexors $P < 0.001$). The reduction in MVCdt with cooling was more marked in
256 the control group (Effect of Temperature x Time x Group Dorsiflexors : $p < 0.001$,
257 Plantarflexors: $P < 0.05$, Table 3).

258

259 Data on peripheral tibial nerve conduction was obtained in 20 pwSP and 16 controls, with
260 missing data relating to perceived discomfort with the procedure. There was no difference in
261 conduction velocity between groups ($p = 0.06$). Four pwSP (20%) had a tibial nerve
262 conduction velocity over two standard deviations lower than the control mean at baseline
263 and were classified as having a peripheral neuropathy²³ (Table 2). Tibial nerve conduction
264 velocity decreased with cooling and increased with warming (Temperature x Time Interaction

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

267

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

272

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

275

276 **DISCUSSION**

277 In the current study 77% of pwSP (n=22) had a genetic diagnosis and/or family history, and
278 both complicated (n=5) and uncomplicated (n=17) presentations were seen as defined by
279 clinical presentation/genetic testing (Table 2). The proportion of pwSP with a genetic
280 diagnosis is similar to that reported in epidemiological studies²⁸⁻³⁰ and reflects the multitude
281 of genetic mutations that can cause this condition. PwSP had an increased corticospinal
282 tract conduction time in keeping with the axonal degeneration reported using MRI, diffusion
283 tensor imaging and post mortem³²⁻³⁴. At baseline increased spasticity (stretch reflex size),
284 passive stiffness, reduced MVC in dorsiflexor and plantarflexor muscles and slower walking
285 speeds were seen in pwSP compared to controls in line with previous reports^{24,3135}.

286 The level of spasticity reported could be considered to be low (median grade 1; range 1-3);
287 this could reflect a bias towards recruiting people with more mild symptoms. However, an

288 assessment of their walking ability suggests that the cohort of ambulant pwSP studied was
289 more severe with 78% using walking aids compared to 28% in population studies³⁷.

290 The impact of superficial cooling on walking speed supports subjective reports of pwSP that
291 their walking gets slower when their legs are cold. At a more local level localised ankle
292 movement measured by foot tap time increased in the targeted limb with cooling and
293 decreased with warming. Deteriorations in toe tapping time with cooling have been reported
294 previously in people with acquired brain injury¹¹. Spastic Paraparesis produces bilateral
295 spasticity and paresis; only 1 leg was targeted in this study to allow a detailed study of the
296 changes in neuromuscular impairments in that leg and assess their subsequent effects on
297 walking. More marked effects would be expected with targeting both legs although limited
298 time post cooling / warming precluded an assessment of both legs³⁶.

299

300 Group differences in the effects of temperature changes may be related to the reduction in
301 calf skin thickness in pwSP. Reductions in skin thickness have been reported in other
302 neurological conditions³⁸ and may lead to more marked changes in intramuscular
303 temperature with cooling/warming³⁹. However, there was no difference in the impact of
304 temperature on tibial nerve conduction velocity between groups suggesting that temperature
305 changes, at least at this deeper level, may be similar.

306

307 A decrease in passive stiffness was observed in both groups with cooling and warming. The
308 passive stiffness changes observed in both conditions may reflect the effects of the repeated
309 slow and fast stretches used to test stiffness and spasticity and/or the fact that the ankle was
310 held in 5° plantarflexion for the 30 minute intervention period that may have reduced the
311 viscoelastic properties of the muscle. That these changes were more marked in pwSP
312 suggests that stretching may be a useful adjunct to treatment. Cooling and warming have
313 both been reported to have effects on muscle spindle activity with changes in muscle spindle

314 sensitivity occurring alongside changes in the firing rate of Ia afferents^{6,41}. Ice has been used
315 therapeutically to reduce spasticity⁴². In contrast in this study stretch reflex size increased
316 with cooling. Noxious stimuli such as sudden superficial application of cold to the skin may
317 increase spasticity⁴⁵. However, this will only have an effect for a few seconds¹⁴. Warming
318 resulted in a reduction in spasticity; this may in part underlie the reductions in spasticity seen
319 with hydrotherapy in this patient group⁴³.

320

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

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

335

336 This study induced localised temperature changes that are more marked than usually
337 encountered in the environment. However, changes in environmental temperature would
338 affect the whole body, possibly leading to more widespread (but less marked) changes than
339 seen in the current study that may still affect functional ability³⁹. Future work could assess

340 the effects of changes in ambient temperature. This study looked at the effects of superficial
341 warming from an ambient room temperature of $22.96 \pm 1.94^\circ\text{C}$. It may be that the
342 improvements in neuromuscular impairments seen in this study with warming are more
343 marked in cooler environments.

344 The application of superficial heating or cooling has been suggested to have a depth of
345 effect of 10-30mm depth⁴⁷ although some studies have suggested changes at deeper levels
346 with superficial application of heat^{48,49}. This study used non-invasive skin temperature
347 measurement was used which has been reported to correlate to deeper intramuscular
348 temperatures^{3,50} and was a pragmatic decision in this study. In this study regardless of the
349 depth of effect changes in walking speed and neuromuscular impairments were observed
350 which suggest an effect on neuromuscular structures. Future studies could include
351 intramuscular temperature monitoring to evaluate the precise depth of temperature
352 penetration³.

353 This study highlights several implications for rehabilitation of pwSP. In pwSP, superficial
354 cooling led to a deterioration in functional ability as measured by walking speed as well as
355 changes in local neuromuscular impairments which would tend to support the observations
356 of pwSP that their walking deteriorates when their limbs are cold. Avoidance of cooling by
357 the use of insulating garments should be evaluated in pwSP. Superficial warming resulted in
358 improvements in torque generation, a reduction in spasticity and passive stiffness, as well as
359 a quicker nerve conduction speed. External passive heating or active warm up¹⁷, or
360 hydrotherapy to increase limb temperature should be explored further in pwSP. As
361 movement is impaired in pwSP it may be that maintaining and preventing heat loss or
362 increasing limb temperature using passive means may be more efficient and effective in this
363 patient group.

364

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

372

373 **CONCLUSIONS**

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

382

383 **Acknowledgements:** Acknowledgement of assistance to Julie Soane and Adam Carter for
384 assistance in building the temperature controlled wrap, Guido Bugmann and Peter Gibbons
385 for assistance in building the servomotor and the HSP support group UK for help recruiting in
386 particular Ian Bennett and Simon Hubbard. **Congresses:** Acknowledgement of oral
387 presentation of this research: European Society of Physical Rehabilitation Medicine,
388 Marseille 2014, Physiotherapy UK 2014. **Funding:** Acknowledgement of financial support for
389 this study kindly provided by the Physiotherapy Research Foundation: The Chartered
390 Society of Physiotherapy, UK.

391

392 **Conflicts of interest:** None

393

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