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Research Article

Positive Effect of a Cooling Cap on Functional Performance in Thermosensitive People with Multiple Sclerosis: A Randomized Controlled Trial

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Background. Up to 80% of people with MS experience worsening of their condition upon an increase in body temperature. Therefore, various options of cooling are being evaluated to help improve physical performance in people with MS. Most previous studies used active cooling methods. Our aim was to study the effect of simple device providing passive cooling. *Methods*. A randomized crossover study was conducted in 21 thermosensitive people with mild to moderate disability. Subjects were tested immediately before and after intervention (experimental or sham cooling). The assessment included timed 25-foot walk test, the 2- and 6-minute walk test, nine-hole peg test, and symbol digit modalities test. *Results*. A significant improvement was found in the experimental group in timed 25-foot walk test ($p = 0.011$) and in nine-hole peg test for dominant hand ($p = 0.033$). No significant improvement was found in the control group (sham cooling). *Conclusions*. Wearing cooling cap can improve short-term functional performance (walking and fine motor skills) in thermosensitive people with MS. This passive cooling method can be considered as a symptomatic treatment for some people with MS. This trial is registered with ISRCTN56350227.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system with various symptoms, including gait disorders, balance impairment, sensory impairment, sphincter dysfunctions, fatigue, vision impairment, muscle weakness, spasticity, and depression. These symptoms are highly variable among patients but may also fluctuate in time in individual patients [1]. However, up to 80% of people with MS experience worsening of their condition upon an increase in body temperature or ambient temperature [2]. This heat sensitivity is a common symptom in MS. Symptom deterioration usually appears after 8 minutes of heating, when the body temperature has increased by 0.8°C and is reduced approximately after 15 minutes after heating is ended [3].

Worsening of neurological symptoms due to impaired conduction of impulses on demyelinated fibres with increased body temperature is called the Uhthoff phenomenon. In 1890, the German ophthalmologist first described this phenomenon of temporary deterioration of vision in patients after optic neuritis [2]. In addition to demyelinated fibres, the presence of inflammatory lesions in the areas of brain responsible for body temperature regulation can also contribute to thermoregulation disorders. This causes changes in the function of the sweat glands and sudomotor pathway, which is why people with MS may experience a decrease in sweating [4]. A slightly higher body temperature in people with MS compared to the healthy population has also been described, apparently due to impaired thermoregulation [5, 6]. Due to this worsening of disease symptoms after an increase in body temperature, most people with MS do not tolerate sauna sessions, which can temporarily lead to deterioration in their physical and mental function [7, 8].

An increase in body temperature is a problem and limitation, especially while performing physical activities [9]. This is also the reason why patients were rather discouraged from exercising in the past. However, many studies have recently shown the benefit of regular exercise [10, 11]. Since the body temperature increases more during aerobic exercise, it is recommended for more thermosensitive people to perform resistance exercise or a slower type of exercise activity instead [12]. An alternative to preventing temperature rise is to cool down or take a cold bath before exercise [13, 14].

Especially during the hot summer months, an increase in body temperature can cause difficulties in normal daily functioning. In previous studies, different techniques and equipment have been used to provide cooling. Active cooling techniques (usually a vest or other liquid condition garment) achieve a greater effect than passive ones [15], while active cooling mainly uses cooled fluid flowing to the body surface (and can therefore achieve a higher degree of cooling of the body surface but require more complex equipment). The main limitations of these garments are the lack of transportability and large power source. Other options represent passive cooling based on the principle of evaporation [15]. In most cases, cooling the centre of the body, i.e., the torso area, is achieved with various types of vests [16–18]. However, it is also possible to cool the limbs, e.g., forearms or thighs [19–21]. Head and neck cooling is also an alternative, as cooling this relatively small area of the skin also results in reduction in core temperature [22]. In clinical practice, we sometimes meet patients who have had a positive experience with simple (passive) cooling devices based on the principle of evaporation (manufactured, for example, for athletes or motorcyclists).

The aim of this study was therefore to verify whether these simple and cheap cooling aids can really affect functional performance in thermosensitive people with MS.

2. Methods

2.1. Participants. Participation in the study was offered to patients treated at the MS centre of the Neurological Clinic of the 1st Faculty of Medicine and General University Hospital in Prague who suffered from subjectively perceived thermosensitivity. Thus, a convenience sampling technique was used to select the sample. Patients who expressed interest had to meet the following criteria to be included in the study.

The inclusion criteria were as follows: (a) clinically stable MS (at least 60 days since the last attack), (b) with stable medication (no changes in treatment in last 90 days), (c) without the presence of another serious somatic disease (disease of musculoskeletal system, internal disease, etc.), and (d) without significant limitation of cognitive function.

The study was approved by the Ethics Committee of the General University Hospital in Prague and registered with number ISRCTN56350227. All participants were informed about the course of the study and had provided signed informed consent. For randomization, the random number generator was used.

2.2. Cooling Procedure

2.2.1. Cooling Aid. Local negative thermotherapy was implemented through a cooling cap. This simple, commercially available cooling aid is a one-size-fits-all accessory made of multilayer polyester, able to retain moisture, with the process of evaporation cooling the wearer. Among the advantages of the cooling cap are its low cost and low weight. It weighs only a few grams, so it does not limit the wearer's mobility (Figures 1(a) and 1(b)). This simple device is used to cool the body temperature, for example, in industry, the armed forces or by motorcyclists (they use it to cool down under the helmet). For the study, we used a more common type of such tool (purchased at a job shop), which is made of polyester and has a purchase value of less than 10 euros. According to the manufacturer's instructions, the device can be used repeatedly and worn for several hours a day if the user is comfortable with it (with the need to rewet it as it dries to ensure evaporation). The aid could probably be used repeatedly by several people, but for hygiene reasons, each patient in this study got his own cap.

2.2.2. Procedure. Participants were examined during warm summer days (with a temperature ≥ 20°C, average temperature 25°C) using functional tests commonly used in clinical practice. To evaluate the effect of local cooling, the participants were randomly divided into the experimental and control groups. The experimental group underwent an assessment first with local cooling and then with sham cooling. The control group (with sham cooling) completed the same in reverse order. The assessment took place on two different days. The study procedure is schematically displayed in Figure 2.

During the local cooling (true-negative thermotherapy), the cooling cap was soaked in cold water and wrung out according to the manufacturer's instructions. In the sham cooling group, the cap was only placed into the freezer for a few seconds (without soaking in water). This only gave to the participants in the control group a short-term cooling sensation, but there was no cooling effect by the gradual slow evaporation of water from the fabric. The effect of both real and sham-negative thermotherapy lasted at least for 15 minutes each time; during that time, the participants were at rest (sitting in the waiting room).

2.3. Assessment. A crossover study design with randomized assignment to the experimental or control group was conducted between July and August 2020. All study participants completed both the experimental and the control intervention. The experimental group underwent an assessment first with local negative thermotherapy and then with sham cooling. The control group (with sham cooling) completed the same in reverse order. The assessment of effect these two different conditions took place on two different days. To evaluate the effect of local negative thermotherapy, the following tests commonly used in clinical trials with MS were chosen: the

(a) (b)

Figure 1: (a, b) Cooling cap.

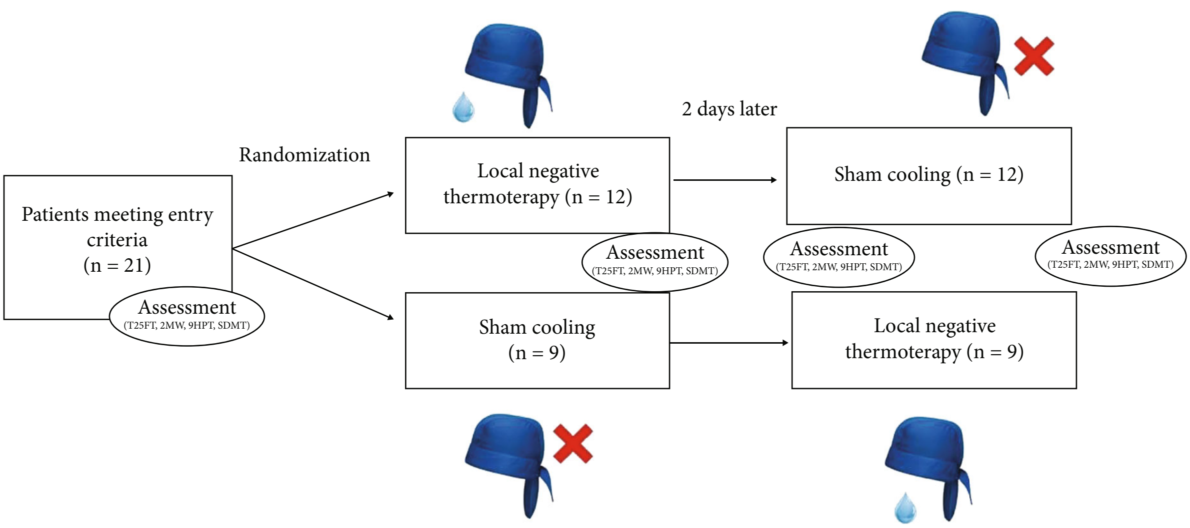

Figure 2: Study procedure.

timed 25-foot walk test (T25FW) [23] and the endurance walking test for 2 minutes (2MWT) [24] to evaluate functional mobility. To assess fine motoric function, the nine-hole peg test (9HPT) [25] was selected. Cognitive functions were assessed using the symbol digit modalities test (SDMT) [26]. After each assessment, the participants were given a study-specific questionnaire to report subjective perceived effect. All assessments were performed in the Department of Neurology. The baseline assessment of patients was performed before and immediately after the 15-minute cooling procedure (during the assessment procedure, they were still wearing the cap).

2.4. Statistical Analysis. The data were evaluated using SPSS. A within-subject comparison of the two conditions was performed, and the difference between performance after local negative thermotherapy (baseline assessment versus after procedure) and sham cooling (baseline assessment versus after procedure) was compared. Since the differences were not normally distributed, nonparametric tests were used for comparison between the experimental and the control assessment, specifically the Wilcoxon signed ranked test. The threshold for significance was set at $p < 0.05$, and differences with $p < 0.010$ were described as "trends."

3. Results

A total number of 21 people with MS with mild to moderate disability participated in the study. Most participants were women (19 (90.5%). The mean age of the participants was 46.8 years, the mean disease duration was 13.8 years, and

Table 1: Demographic characteristics of the 21 participants.

Parameter	Mean (SD)	Median (range)
Age (years)	46.8 (8.17)	45 (34-66)
Disease duration (years)	13.8 (9.33)	10 (1-34)
Neurological disability (EDSS—Expanded Disability Status Scale)	4.2 (1.56)	4.5 (2-6.5)
MS type (RR/SP/PP)	18/2/1	

MS type: RR = relapsing remitting MS; SP = secondary progressive MS; PP = primary progressive MS.

the median neurological disability assessed by EDSS was 4.5 points. Detailed characteristics of the participants are displayed in Table 1.

When comparing neurological performance after local cooling of the head versus sham cooling, a significant improvement was found in the short brisk walking tests assessed by T25FW ($p = 0.011$) and in the functional mobility of the dominant upper limb assessed by 9HPT ($p = 0.033$) (Figure 3). There was also a trend for improvement in 2-minute walk test ($p = 0.086$). Other parameters were without significant changes between the groups. A total of 4 subjects in the experimental group achieved clinically significant improvement in the short fast walk test (T25FW) and 3 in the 9HPT in the dominant hand. In contrast, only 1 patient achieved improvement in the short fast walk test in sham cooling. The mean values of the investigated parameters in both groups are shown in Table 2.

A total of 14 participants (74%) subjectively perceived a positive effect of experimental cooling to reduce fatigue. Wearing a cooling cap was well tolerated, without any complications. No side effects have been reported with the use of the aid. Hair wetting or possible water dripping (if the device was not wrung out sufficiently) could be considered an adverse event, but none of the participants complained about this. In total, 16 participants (84%) would recommend the purchase of a cooling cap to other patients as well.

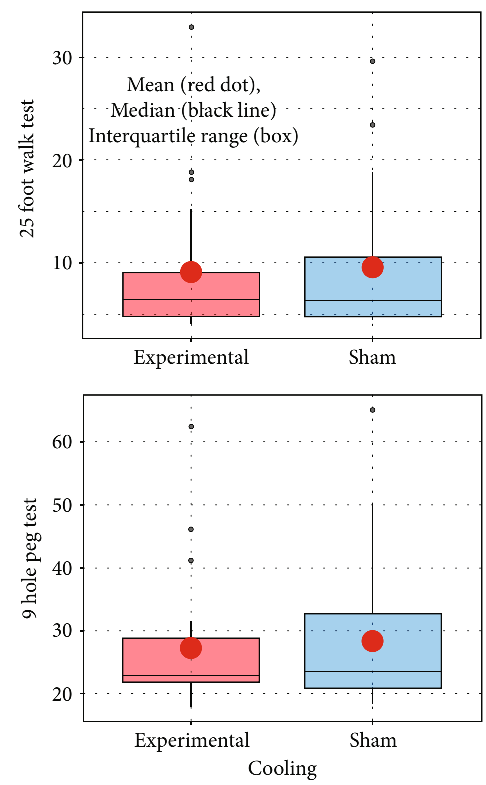

Figure 3: Parameters with significant changes.

4. Discussion

Our study brings the novel finding that even a simple cooling aid (cooling the head area by evaporation) can improve short-term performance in functional mobility such as walking and fine motor skills in thermosensitive people with MS.

Another study that also examined the effect of head and neck cooling on gait performance (6-minute walking test), grip strength, and visual acuity in six patients (a study by Reynolds et al.) found a significant improvement in gait performance after 60 minutes of active cooling only in the walking test [22]. A significant improvement in short walking tests (10- and 30-meter walk test) was also found in a study using a cooling vest in 43 thermosensitive people with MS. The largest study to date investigating the effect of cooling demonstrated an improvement in the timed 25-foot walk test, but not in the 9-hole peg test. In this study, an active cooling system for the head and upper body [17] was used. Another Swiss study also mentions a positive effect of active cooling of the thigh area on the timed 25-foot walk test and the nine-hole peg test [20]. In contrast to our results, no positive effect of cooling on fine motor skills was noted in a previous study [27]. Similarly to our work, a study by Gossman et al. using cooling with a vest did not improve cognitive functions [28]. In addition, a positive effect of local cooling on subjectively perceived fatigue reported in previous studies is in agreement with our results [16–18].

In was shown that cooling can help patients not only in better daily functioning, but it seems that training with a cooling vest can have a more significant training effect, e.g., in terms of improving walking distance and reducing fatigue, as demonstrated in a study on 18 patients after 7 weeks of training [29]. In general, training in a cooler, ideally air-conditioned environment is recommended for people with MS [30]. It is also described in non-MS people that training in a hot environment reduces voluntary power input [31]. Cooling down in a cold bath or with active cooling vest and cap before exercise can also be an option, to limited increase of body temperature during exercise. This is followed by better gait performance after exercise load [13, 14]. Peripheral cooling of the forearm may also help people with ataxia to reduce limb tremor [19, 21].

TABLE 2: Comparison of experimental and sham cooling.

Parameter	Local negative thermotherapy (experimental) $N = 21$			Sham cooling (control) $N = 21$			Comparing the differences
	Baseline mean (SD)	After intervention mean (SD)	Difference mean (SD)	Baseline mean (SD)	After intervention mean (SD)	Difference mean (SD)	p value
T25FW (sec)	9.67 (7.84)	8.53 (5.87)	1.19 (2.33)	9.53 (7.59)	9.55 (6.48)	-0.02 (2.6)	**0.011**
2MWT (meters)	121.70 (42.31)	129.37 (39.21)	9.1 (12.2)	119.91 (40.46)	123.83 (41.09)	4.9 (7.3)	0.086
9HPT-dominant (sec)	28.74 (13.98)	25.79 (8.68)	3.1 (6.5)	28.88 (12.98)	28.29 (12.12)	0.5 (2)	**0.033**
9HPT-non dominant (sec)	28.01 (13.15)	26.64 (12.87)	1.3 (1.1)	29.21 (15.01)	28.78 (14.36)	0.4 (2.5)	0.156
SDMT (points)	50.19 (11.45)	57.09 (11.83)	6.9 (4.0)	51.1 (10.27)	55.7 (11.85)	4.6 (3.8)	0.371

Values in bold indicate significantly meaningful change.

Negative thermotherapy is also used in a cryochamber, where patients undergo a stay at a temperature of -110°C for 2-3 minutes. After 10 therapies, a significant improvement in fatigue and mobility was found [32]. However, there are only a few studies evaluating the effect of cryotherapy [33]. Therefore, nowadays the cryotherapy is not a common nonpharmacological treatment for people with MS. It is worth mentioning that not only major reduction in body temperature but also mild lowering of body temperature by 0.5°C can help to alleviate the symptoms of the disease in heat-sensitive people. In our sample, we did not measure the effect of cooling on the core temperature, but it has been reported that 30 minutes of head and neck cooling can reduce rectal temperature by 0.26°C [22].

Compared to previous studies using different methods of cooling, such as active cooling with liquid immersion [34] or liquid condition garments [15, 16, 18, 20, 28], a cooling bath [13, 21, 35], or simple passive cooling with evaporation [27], our study brings new knowledge to clinical practice and demonstrates that even a simple cooling cap based on the principle of evaporation can help to improve physical performance in people with MS.

Limitations of the study include a smaller sample of patients, lack of blinding of investigators, and absence of body temperature measurements. The disadvantage of this aid can also be considered the relatively fast evaporation, so repeated soaking of the cap is necessary. Some patients may also find it uncomfortable to get their hair wet when using the device (although none of the probands in our study complained of this). On the other hand, the strength of this study compared to the previous research is inclusion of the control group and a randomized crossover study design. Some previous studies did not include cooling [14, 15, 35] or use warmer water in the control group [17, 28]. Apart from the two studies [17, 27], most previous works included a smaller number of participants than our study.

5. Conclusion

Wearing a cooling cap is a simple, well-tolerated method that can help people with heat-sensitive MS improve short-term functional performance. In contrast to sham cooling, local negative thermotherapy (cooling via evaporation) improved walking and fine motor skills in heat-sensitive people with MS. Cooling aids, especially portable ones, can therefore be considered a simple means of symptomatic treatment for thermosensitive people with MS.

Data Availability

Data are available on request.

Conflicts of Interest

The authors declare that they have no financial or other interests in this study.

Acknowledgments

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References

[1] R. Dobson and G. Giovannoni, “Multiple sclerosis–a review,” *European Journal of Neurology*, vol. 26, no. 1, pp. 27–40, 2019.

[2] T. C. Guthrie and D. A. Nelson, “Influence of temperature changes on multiple sclerosis: critical review of mechanisms and research potential,” *Journal of the Neurological Sciences*, vol. 129, no. 1, pp. 1–8, 1995.

[3] D. A. Nelson and F. McDowell, “The effects of induced hyperthermia on patients with multiple sclerosis,” *Journal of Neurology, Neurosurgery, and Psychiatry*, vol. 22, no. 2, pp. 113–116, 1959.

[4] S. L. Davis, T. E. Wilson, A. T. White, and E. M. Frohman, “Thermoregulation in multiple sclerosis,” *Journal of Applied Physiology*, vol. 109, no. 5, pp. 1531–1537, 2010.

[5] J. F. Sumowski and V. M. Leavitt, “Body temperature is elevated and linked to fatigue in relapsing-remitting multiple sclerosis, even without heat exposure,” *Archives of Physical Medicine and Rehabilitation*, vol. 95, no. 7, pp. 1298–1302, 2014.

[6] V. Leavitt, E. De Meo, G. Riccitelli, M. A. Rocca, and G. Comi, “Elevated body temperature is linked to fatigue in an Italian sample of relapsing–remitting multiple sclerosis patients,” *Journal of Neurology*, vol. 262, no. 11, pp. 2440–2442, 2015.

[7] P. Hamalainen, A. Ikonen, A. Romberg, H. Helenius, and J. Ruutianen, “The effects of heat stress on cognition in persons with multiple sclerosis,” *Multiple Sclerosis*, vol. 18, no. 4, pp. 489–497, 2012.

[8] A. Romberg, A. Ikonen, J. Ruutianen, A. Virtanen, and P. Hamalainen, “The effects of heat stress on physical functioning in persons with multiple sclerosis,” *Journal of the Neurological Sciences*, vol. 319, no. 1-2, pp. 42–46, 2012.

[9] C. Fjeldstad, D. R. Brittain, A. S. Fjelstadt, and G. Pardo, “Fatigue and thermo sensitivity affect physical activity in multiple sclerosis,” *Journal of Applied Research*, vol. 10, no. 3, p. 109, 2010.

[10] U. Dalgas, M. Langeskov-Christensen, E. Stenegar, M. Riemenschneider, and L. G. Hvid, “Exercise as medicine in multiple sclerosis-time for a paradigm shift: preventive, symptomatic, and disease-modifying aspects and perspectives,” *Current Neurology and Neuroscience Reports*, vol. 19, no. 11, p. 88, 2019.

[11] R. Kalb, T. R. Brown, S. Coote et al., “Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course,” *Multiple Sclerosis Journal*, vol. 26, no. 12, pp. 1459–1469, 2020.

[12] A. G. Skjerbaek, A. B. Moller, E. Jensen et al., “Heat sensitive persons with multiple sclerosis are more tolerant to resistance exercise than to endurance exercise,” *Multiple Sclerosis*, vol. 19, no. 7, pp. 932–940, 2013.

[13] A. White, T. E. Wilson, S. L. Davis, and J. H. Petajan, “Effect of precooling on physical performance in multiple sclerosis,” *Multiple Sclerosis Journal*, vol. 6, no. 3, pp. 176–180, 2000.

[14] B. Op’t Eijnde, C. Keytsman, I. Wens, and D. Hansen, “Whole-body cooling does not compromise muscle oxidative capacity in subjects with multiple sclerosis,” *NeuroRehabilitation*, vol. 35, no. 4, pp. 805–811, 2014.

[15] J. Kinnman, U. Andersson, L. Wetterquist, Y. Kinnman, and U. Andersson, “Cooling suit for multiple sclerosis: functional improvement in daily living?,” *Scandinavian Journal of Rehabilitation Medicine*, vol. 32, no. 1, pp. 20–24, 2000.

[16] G. Flensner and C. Lindencrona, “The cooling-suit: a study of ten multiple sclerosis patients’ experiences in daily life,” *Journal of Advanced Nursing*, vol. 29, no. 6, pp. 1444–1453, 1999.

[17] NASA/MS Cooling Study Group, “A randomized controlled study of the acute and chronic effects of cooling therapy for MS,” *Neurology*, vol. 60, no. 12, pp. 1955–1960, 2003.

[18] E. Capello, M. Gardella, M. Leandri et al., “Lowering body temperature with a cooling suit as symptomatic treatment for thermosensitive multiple sclerosis patients,” *The Italian Journal of Neurological Sciences*, vol. 16, no. 7, pp. 533–539, 1995.

[19] P. Feys, W. Helsen, X. Liu et al., “Effects of peripheral cooling on intention tremor in multiple sclerosis,” *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 76, no. 3, pp. 373–379, 2005.

[20] A. Meyer-Heim, M. Rothmaier, M. Weder, J. Kool, P. Schenk, and J. Kesslering, “Advanced lightweight cooling-garment technology: functional improvements in thermosensitive patients with multiple sclerosis,” *Multiple Sclerosis Journal*, vol. 13, no. 2, pp. 232–237, 2007.

[21] H. Albrecht, M. Schwecht, W. Pollmann, D. Parag, L. P. Erasmus, and D. Konig, “Lokale Eisapplikation in der Therapie der gliedkinetischen Ataxie Klinischer Nachweis positiver Behandlungseffekte bei Patienten mit multipler Sklerose,” *Der Nervenarzt*, vol. 69, no. 12, pp. 1066–1073, 1998.

[22] L. F. Reynolds, C. A. Short, D. A. Westwood, and S. S. Cheung, “Head pre-cooling improves symptoms of heat-sensitive multiple sclerosis patients,” *Canadian Journal of Neurological Sciences*, vol. 38, no. 1, pp. 106–111, 2011.

[23] R. W. Motl, J. A. Cohen, R. Benedict et al., “Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis,” *Multiple Sclerosis*, vol. 23, no. 5, pp. 704–710, 2017.

[24] D. Gijbels, B. Eijnde, and P. Feys, “Comparison of the 2- and 6-minute walk test in multiple sclerosis,” *Multiple Sclerosis Journal*, vol. 17, no. 10, pp. 1269–1272, 2011.

[25] P. Feys, I. Lamers, G. Francis et al., “The nine-hole peg test as a manual dexterity performance measure for multiple sclerosis,” *Multiple Sclerosis Journal*, vol. 23, no. 5, pp. 711–720, 2017.

[26] R. H. Benedict, J. De Luca, G. Philips, N. LaRocca, L. D. Hudson, and R. Rudick, “Validity of the symbol digit modalities test as a cognition performance outcome measure for multiple sclerosis,” *Multiple Sclerosis Journal*, vol. 23, no. 5, pp. 721–733, 2017.

[27] Y. Nilsagård, E. Denison, and L.-G. Gunnarsson, “Evaluation of a single session with cooling garment for persons with multiple sclerosis–a randomized trial,” *Disability and Rehabilitation: Assistive Technology*, vol. 1, no. 4, pp. 225–233, 2006.

[28] A. Gossmann, P. Eling, A. Kastrup, and H. Hildebrandt, *No Effect of Cooling on Cognitive Fatigue, Vigilance and Autonomic Functioning in Multiple Sclerosis*, 2013.

[29] B. Gonzales, G. Chopard, B. Charry et al., “Effects of a training program involving body cooling on physical and cognitive capacities and quality of life in multiple sclerosis patients: a pilot study,” *European Neurology*, vol. 78, no. 1-2, pp. 71–77, 2017.

[30] J. H. Petajan and A. T. White, “Recommendations for physical activity in patients with multiple sclerosis,” *Sports Medicine*, vol. 27, no. 3, pp. 179–191, 1999.

[31] D. Kay, D. Taaffe, and F. Marino, “Whole-body pre-cooling and heat storage during self-paced cycling performance in warm humid conditions,” *Journal of Sports Sciences*, vol. 17, no. 12, pp. 937–944, 1999.

[32] E. Miller, J. Kostka, T. Wlodarczyk, and B. Dugué, “Whole-body cryostimulation (cryotherapy) provides benefits for fatigue and functional status in multiple sclerosis patients. A case–control study,” *Acta Neurologica Scandinavica*, vol. 134, no. 6, pp. 420–426, 2016.

[33] A. Campbell, B. Killen, S. Cialone, M. Scruggs, and M. Lauderdale, “Cryotherapy and self-reported fatigue in individuals with multiple sclerosis: a systematic review,” *Physical Therapy Reviews*, vol. 24, no. 5, pp. 259–267, 2019.

[34] E. Beenakker, T. I. Oparina, A. Hartgring, A. Teelken, A. V. Arutjunyan, and J. De Keyser, “Cooling garment treatment in MS: clinical improvement and decrease in leukocyte NO production,” *Neurology*, vol. 57, no. 5, pp. 892–894, 2001.

[35] D. A. Grahn and H. C. Heller, “Cooling via one hand improves physical performance in heat-sensitive individuals with multiple sclerosis: a preliminary study,” *BMC Neurology*, vol. 8, no. 1, pp. 1–8, 2008.