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Effects of Cooling During Exercise on Thermoregulatory Responses of Men With Paraplegia.

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Effects of Cooling During Exercise on Thermoregulatory Responses of Men With Paraplegia


Background. People with spinal cord injury (SCI) have an altered afferent input to the thermoregulatory center, resulting in a reduced efferent response (vasomotor control and sweating capacity) below the level of the lesion. Consequently, core body temperature rises more rapidly during exercise in individuals with SCI compared with people who are able-bodied. Cooling strategies may reduce the thermophysiological strain in SCI.

Objective. The aim of this study was to examine the effects of a cooling vest on the core body temperature response of people with a thoracic SCI during submaximal exercise.

Methods. Ten men (mean age = 44 years, SD = 11) with a thoracic lesion (T4–T5 or below) participated in this randomized crossover study. Participants performed two 45-minute exercise bouts at 50% maximal workload (ambient temperature 25°C), with participants randomized to a group wearing a cooling vest or a group wearing no vest (separate days). Core body temperature and skin temperature were continuously measured, and thermal sensation was assessed every 3 minutes.

Results. Exercise resulted in an increased core body temperature, skin temperature, and thermal sensation, whereas cooling did not affect core body temperature. The cooling vest effectively decreased skin temperature, increased the core-to-trunk skin temperature gradient, and tended to lower thermal sensation compared with the control condition.

Limitations. The lack of differences in core body temperature among conditions may be a result of the relative moderate ambient temperature in which the exercise was performed.

Conclusions. Despite effectively lowering skin temperature and increasing the core-to-trunk skin temperature gradient, there was no impact of the cooling vest on the exercise-induced increase in core body temperature in men with low thoracic SCI.
Effect of Cooling in Paraplegia

People with spinal cord injury (SCI) have an impaired sensory and motor function, which often is associated with damage to the autonomic nervous system, causing reduced afferent input to the thermoregulatory center and impairment of the efferent system, leading to attenuated sweating response and vasomotor control below the level of the lesion. These characteristics result in impaired thermoregulation in people with SCI, especially in highly demanding conditions. Thermoregulatory strain typically occurs during prolonged exercise in challenging ambient conditions, which leads to an increased core body temperature.

A recent meta-analysis showed that cooling strategies prior to (ie, precooling) or during (ie, percooling) exercise effectively attenuate the increase in core body temperature during a bout of prolonged exercise of 60 minutes in able-bodied athletes. Accordingly, cooling strategies prior to or during exercise also may be effective in individuals with SCI. A previous meta-analysis demonstrated conflicting results of percooling (using ice vest foot, head, and neck cooling) on the thermoregulation of individuals with SCI. Some studies demonstrated a lower core body temperature using percooling techniques during intermittent sprint or continuous exercise and other studies showed no effects.

The conflicting results of percooling interventions during intermittent sprint and continuous exercise may relate to the weight of the vest or comfort level. Taking these limitations into consideration, a new lightweight evaporative cooling vest was developed (HyperKewl, TechNiche Int'l, Vista, California), which is designed for use during exercise. In able-bodied athletes, this cooling vest effectively decreased skin temperature and improved thermal sensation during exercise. To date, no previous study has explored the effectiveness of this cooling vest on thermoregulatory responses during exercise in individuals with SCI. Therefore, we examined the effects of wearing a cooling vest during 45 minutes of moderate-intensity exercise on the core temperature, skin temperature, core-to-trunk skin temperature gradient, and thermal sensation in individuals with SCI. We hypothesized that the cooling vest is effective in attenuating the exercise-induced increase in core body temperature through markedly increasing the core-to-trunk skin temperature gradient.

Method

Participants

Ten men with paraplegia volunteered to participate in this study (Tab. 1). The level of the thoracic lesions ranged between T4 and T12, with American Spinal Injury Association (ASIA) Impairment Scale (AIS) scores of A and B (AIS score = A for 8 participants, AIS score = B for 2 participants). Furthermore, all participants were >1 year postinjury and were able to perform an arm crank exercise for at least 45 minutes (maximum oxygen consumption [VO2max] = 24.0 ml/min/kg; SD = 6.5; Tab. 1). Exclusion criteria were based on the use of the temperature pill and included: (1) body weight <36.5 kg, (2) implanted medical device, (3) gastrointestinal disease, and (4) a scheduled magnetic resonance imaging scan. All participants gave written informed consent prior to participation in the study, and the study was approved by the Medical Ethical Committee of the Radboud University Medical Center. All procedures were in accordance with the guidelines of the Declaration of Helsinki.

Study Design

In this randomized crossover study, participants were invited to participate in 3 study visits. The first visit consisted of obtaining the signed informed consent form, performing a medical screening to check whether the volunteers were eligible for participation, and performing a maximal arm crank exercise test to assess VO2max and peak power output (peak PO). During the randomized second and third visits, participants performed a 45-minute submaximal arm crank exercise test at 50% of peak PO with or without the cooling vest. Prior to exercise, the participants were allowed to drink and eat ad libitum. However, they were instructed to follow the same diet prior to both testing days to minimize the effects of nutrition. Furthermore, participants registered their fluid intake 24 hours prior to the test, and they were instructed to wear the same clothes during both tests. All participants had at least 5 days of recovery between visits. To minimize the effects of the circadian rhythm on core body temperature and heart rate (HR), we scheduled both submaximal exercise tests consistently at the same time of day for each participant. Finally, participants were not allowed to perform strenuous exercise or consume alcohol or caffeine 24 hours before all study visits; these activities may affect the exercise test.

Day 1: maximal exercise test. Physical fitness (VO2max) and peak PO were determined using a maximal exercise test on an arm ergometer (Angio Cycle Ergometer, Lode, Groningen, the Netherlands) at an ambient temperature of 19°C. During the maximal exercise test, participants started cycling at 10 W with an arm crank cycle frequency of 60 to 80 repetitions per minute. The workload was increased 10 W every minute until voluntary exhaustion. Continuous measurement of oxygen uptake and carbon dioxide output was performed using an automatic gas analyzer (Quark CPET, version 9.1b, COSMED, Rome, Italy). Peak oxygen uptake was calculated as the average oxygen uptake during the last 30 seconds of the test. Peak PO was defined as the workload at the highest intensity that the participant could maintain for at least 30 seconds. Heart rate was measured continuously using a 12-lead electrocardiograph.

Days 2–3: submaximal exercise test. During the second and third visits, participants performed a 45-minute submaximal arm crank exercise test at 50% of their individual peak PO. Both tests were performed in a temperature-controlled chamber with an ambient temperature of 25.4°C (SD = 0.4°C) and a relative humidity of 41.0% (SD = 8.4%). Ambient temperature during both submaximal exercise tests was higher compared with the maximal exercise test to induce a higher thermal stress. Ambient temperature was similar between both testing days to ensure valid assessment of the potential cooling effect of the vest. Upon arrival, body mass was measured in
the sitting position, and recorders were applied to assess core body temperature, skin temperature, and HR. Prior to exercise, a baseline measurement of 10 minutes in the sitting position was taken to obtain baseline values of core body temperature, skin temperature, and HR. Thereafter, participants performed a standardized warm-up, with workload being increased from 30 to 50 W (10 W per 2 minutes), followed by 2 minutes at 40 W. Subsequently, a fan was turned on, and participants had 2 minutes for stretching and resting before the start of the submaximal exercise test. The fan was placed 140 cm in front of the participants, and the speed of the fan was 1.44 m/s. Air circulation was created by turning on the fan to mimic real-life conditions and facilitate the cooling capacity of the evaporative cooling vest. After the warm-up, the cooling vest was applied (for the intervention visit). Then, the exercise test was started, and participants were instructed to exercise at a frequency of 60 to 80 repetitions per minute.

In the second submaximal exercise test, the same protocol was used to ensure that thermal load was comparable between the tests. After completing the submaximal exercise, the workload was, depending on the peak PO, decreased to 20 to 40 W, and participants performed a cool-down for 5 minutes. Finally, participants rested for 10 minutes, during which the cooling vest was removed and the fan was turned off. Throughout the test, core body temperature, skin temperature, and HR data were obtained every 5 minutes, and rate of perceived exertion (RPE) and thermal sensation were scored every 3 minutes (during exercise) or every 2 minutes (during warm-up, cool-down, and recovery). After completing the protocol, post-exercise body mass was determined to assess exercise-induced fluid loss.

### Intervention: Cooling Vest

In this study, a lightweight evaporative cooling vest was used as a cooling intervention. The cooling vest covered the major part of the participants’ trunk. The cooling vest contains a water management system, which consists of 3 layers that stimulate water absorption and storage. Subsequently, the evaporation process of the water contributes to cooling of the skin. The cooling surface area of the evaporative cooling vest was approximately 2,294 cm² (SD=134). The day before each timed trial, the cooling vest was applied according to manufacturer instructions: (1) soak in water for 2 minutes, (2) squeeze to remove excess water, (3) leave the vest at room temperature for 2 hours to dry the outside of the vest, and (4) place the vest in a refrigerator (5.8°C ± 0.2°C) for at least 10 hours. The weight of the activated cooling vest was 388 g (SD=67).

### Measurements

#### Core body temperature. Core body temperature was measured using an ingestible temperature pill (CoreTemp System, HQ Inc, Palmetto, Florida), which is a safe and reliable technique. Participants were instructed to ingest the individually calibrated telemetric temperature pill at least 5 hours preceding the measurement to avoid any interaction with fluid ingestion. During the protocol, core body temperature was measured every 20 seconds using an external recorder, and data were presented every 5 minutes. For safety reasons, the submaximal exercise test was terminated when the core body temperature exceeded 40°C.

#### Skin temperature. Skin temperature was examined using wireless temperature sensors (iButton DS1922L, Dallas Semiconductor Corp, Dallas, Texas).
configuration of the sensors was set to collect data at 20-second intervals with a resolution of 0.0625°C. Furthermore, all skin temperature data were presented every 5 minutes during the exercise test. The sensors were placed on the skin using Tegaderm Film (Tegaderm, Neuss, Germany), and skin temperature was measured at 8 different locations according to the ISO-9886 standard (Fig. 1). An index of mean skin temperature was calculated as the weighted average of the 8 sensors for each participant, which was based on the relative surface of the body area that each measuring point represents.

Trunk skin temperature. To assess the effects of the cooling vest more precisely, we added 2 additional thermal sensors to the chest. The average value of the 4 sensors (2 from the standard 8-point placement and the 2 additional sensors) placed on the trunk was considered as trunk skin temperature (Fig. 1). Differences between core body temperature and trunk skin temperature were expressed as the core-to-trunk skin temperature gradient, which was calculated by subtracting these values.

Cooling vest temperature. Four additional sensors were placed on the inside and outside fabric layers of the cooling vest (Fig. 1) to obtain the cooling vest temperature, which was calculated as the average of these 4 measurement locations. The vest-to-trunk temperature gradient was calculated by subtracting these values.

HR. Heart rate was continuously monitored during exercise at 15-second intervals using a Polar RS400 system (Polar Electro Oy, Kempele, Finland). Data were presented every 5 minutes, and the highest HR value was presented as the maximum HR. The exercise-induced increase in HR (ΔHR) was calculated by subtracting the HR value recorded during exercise by the baseline HR value.

Fluid balance. The relative change in body mass (percentage) between the pre-exercise and post-exercise measurements was calculated. Dehydration was defined as a body mass loss of 2% or more.

RPE and thermal comfort. The RPE was scored using a 10-point Borg scale, in which 0 corresponded to rest and 10 corresponded to maximal exertion. Thermal sensation was scored using a 7-point category scale in which -3 represents very cold and +3 is very hot. Both subjective parameters were scored and presented every 3 minutes during the submaximal exercise and every 2 minutes during warm-up, cool-down, and recovery.

Differences between core body temperature, skin temperature, trunk skin temperature, HR, RPE, and thermal sensation) over time between the cooling and control conditions, in which time and intervention were used as within-participant factors.

Role of the Funding Source
This work was supported by the Dutch Heart Foundation (E. Dekker stipend 2009T064, D.H.J.T) and the Technical Science Foundation (STW) (12864, C.C.W.G.B).

Results

Participant and Exercise Characteristics
Participant characteristics and the results of the maximal exercise test are shown in Table 1. Average exercise intensity, ambient temperature, and relative humidity were 81.3% (SD=10.1%), 25.4°C (SD=0.4°C), and 41.0% (SD=8.4%), respectively, and did not differ between testing days (Tab. 2). None of the participants exceeded the core
body temperature safety limit of 40°C during exercise, and none met the criteria for being dehydrated after completing the test (>2% loss in body weight). During exercise, HR increased in both conditions (*P* < .001). Interestingly, throughout the exercise protocol, HR was significantly higher in the cooling condition (*P* = .012), and the workload was exactly the same in both protocols. Peak heart rate was significantly higher in the cooling condition (X̄ = 148 beats per minute [bpm], SD = 26) compared with the control condition (X̄ = 142 bpm, SD = 27) (*P* = .013), with an MD of 6 bpm (95% CI = 2, 12). In contrast, ΔHR throughout exercise did not differ between conditions (MD = 3 bpm; 95% CI = −5, 10) (*P* = .46).

### Thermoregulation

#### Core body temperature

At baseline, core body temperature was comparable between the cooling condition (X̄ = 37.1°C, SD = 0.3°C) and the control condition (X̄ = 37.0°C, SD = 0.3°C) (MD = 0.1°C; 95% CI = −0.2°C, 0.4°C) (*P* = .45). Core body temperature increased significantly during both submaximal exercise tests (*P* < .001), and the increase was comparable between conditions (Fig. 2A). We found no differences between the cooling vest and control intervention for maximum core body temperature (X̄ = 37.8°C, SD = 0.1°C, versus X̄ = 37.9°C, SD = 0.1°C) (MD = 0.1°C; 95% CI = −0.2°C, 0.3°C) or for the increase in core body temperature (X̄ = 0.9°C, SD = 0.1°C, versus X̄ = 0.8°C, SD = 0.1°C) (MD = −0.02°C; 95% CI = −0.3°C, 0.3°C).

#### Skin temperature

Baseline skin temperature was comparable between the cooling condition (X̄ = 32.5°C, SD = 0.9°C) and the control condition (X̄ = 32.8°C, SD = 1.0°C) (MD = −0.3°C; 95% CI = −1.0°C, 0.4°C). We demonstrated a significant increase in skin temperature over time during exercise, with significantly lower values in the cooling condition compared with the control condition (Fig. 2B). In addition, maximum skin temperature was lower during the cooling condition compared with the control condition (X̄ = 33.1°C, SD = 0.4, versus X̄ = 32.5°C, SD = 0.3°C) (MD = −0.6°C; 95% CI = −1.2°C, −0.05°C).

#### Trunk skin temperature

Trunk skin temperature significantly increased over time (*P* = .008), with a lower increase in the cooling vest condition compared with the control condition (*P* = .010, Fig. 3A). Furthermore, the core-to-trunk temperature gradient was higher in the

### Table 2. Exercise Characteristics During Submaximal Exercise Test

<table>
<thead>
<tr>
<th>Outcome Parameter</th>
<th>Control</th>
<th>Cooling</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise intensity (%)</td>
<td>79.3 (6.2)</td>
<td>83.4 (6.5)</td>
<td>.40</td>
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<td>Ambient temperature (°C)</td>
<td>25.5 (0.4)</td>
<td>25.4 (0.5)</td>
<td>.75</td>
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<td>Relative humidity (%)</td>
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<tr>
<td>Baseline core body temperature (°C)</td>
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<td>37.1 (0.3)</td>
<td>.45</td>
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<tr>
<td>Peak core body temperature (°C)</td>
<td>37.8 (0.4)</td>
<td>37.9 (0.3)</td>
<td>.47</td>
</tr>
<tr>
<td>Baseline HR (bpm)</td>
<td>76 (13)</td>
<td>80 (14)</td>
<td>.11</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>142 (27)</td>
<td>148 (27)</td>
<td>.013</td>
</tr>
<tr>
<td>ΔHR (bpm)</td>
<td>66 (25)</td>
<td>68 (26)</td>
<td>.41</td>
</tr>
<tr>
<td>Body mass loss (kg)</td>
<td>−0.33 (0.08)</td>
<td>−0.29 (0.09)</td>
<td>.11</td>
</tr>
<tr>
<td>Body mass loss (%)</td>
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<td>−0.4 (0.1)</td>
<td>.15</td>
</tr>
<tr>
<td>Dehydration, &gt;2% body mass loss, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*a* Data are presented as mean (SD), except as otherwise indicated. HR = heart rate.

---

**Figure 2.**

Core body temperature and skin temperature responses during the submaximal exercise test for the cooling condition (solid line) and the control condition (dashed line). (A) A significant increase in core body temperature was observed (*P* < .001), with a comparable change over time across both conditions (*P* = .81). (B) The skin temperature was significantly lower in the cooling condition compared with the control condition (*P* = .003). The data are presented as mean (SD) (N = 10).
cooling condition compared with the control condition ($P=.003$, Fig. 3B).

**Cooling vest temperature.** Directly after applying the cooling vest, the mean cooling vest temperature was 12.2°C (SD=6.1°C), and the cooling vest temperature increased during exercise ($P<.001$, Fig. 3C). Mean vest-to-trunk skin temperature gradient decreased during exercise from 17.1°C (SD=2.8°C) to 6.5°C (SD=1.1°C) ($P<.001$) (Fig. 3C).

**Subjective Parameters**

Submaximal exercise caused an increase in RPE and perceived thermal sensation during exercise for both groups (Fig. 4). However, the increase in thermal sensation score was different between conditions ($P<.001$), with participants reporting a trend for a lower thermal sensation in the cooling condition ($P=.07$). Additionally, the RPE did not differ between conditions ($P=.11$).

**Discussion**

In this study, we aimed to examine the impact of wearing a cooling vest during prolonged exercise on the thermoregulatory responses of individuals who have had a low thoracic SCI. We demonstrated that wearing a cooling vest during exercise did not affect the exercise-induced increase in core body temperature or the maximum core body temperature in individuals with a low thoracic SCI. Nonetheless, we found that the cooling vest during exercise resulted in a lower skin temperature and an increased core-to-trunk temperature gradient and tended to improve thermal sensation in individuals with SCI. Despite these effects of the cooling vest on skin temperature and subjective parameters of thermal comfort, our results suggest that percooling using a lightweight evaporative cooling vest is not effective in attenuating the increase in core body temperature in individuals with SCI.

The cooling vest did affect the exercise-induced increase of core body temperature. A possible explanation for the absence of an effect of cooling on core body temperature could be the relatively moderate ambient conditions in which the exercise tests were performed. Previous studies showed beneficial effects of wearing a cooling vest in ambient temperatures of 30°C and higher, but not at temperatures ≤25°C.15,16,20 Although an ambient temperature of 25°C is on the lower end of the spectrum, the maximum core body temperature in our study was comparable to those observed in previous studies that were performed under higher ambient temperatures.15–17,19 Furthermore, in a study by Armstrong and colleagues,19 a comparable increase in aural temperature during exercise was shown after ice vest cooling under challenging conditions (32.9°C). These findings may suggest that the relatively moderate ambient temperature, as adopted in our study, is unlikely to fully explain the lack of an effect of the cooling vest on the exercise-induced increase in core body temperature in individuals with a low thoracic SCI.
Studies that demonstrated differences in thermoregulatory response between cooling and control conditions have typically included individuals with SCI with lesions between C1 and T5.15–17 In these individuals, a large area of sensate skin, including both afferent information on thermal state and efferent responses to dissipate heat, is being affected.3 This thermoregulatory impairment provides room for cooling strategies to affect core body temperature.30,31 Indeed, the rise in core body temperature during exercise is proportional to the level of the lesion,6,32–34 which makes individuals with SCI with a cervical or high thoracic lesion more susceptible to developing a large increment in core body temperature during exercise. This finding is in line with the findings of a study by Griggs et al,35 in which a higher increase in core body temperature was found in individuals with tetraplegia (C4–C7) compared with individuals with paraplegia (T4–S1). Nine of our participants reported a lesion level <T6, suggesting the presence of a relatively normal thermoregulatory and sweating response. The relatively low lesion level in our study may be an explanation for the absence of an effect of cooling. However, in studies with participants who were able-bodied, the effects of wearing a cooling vest during exercise also were absent.21,36

An alternative explanation for the comparable core body temperature during exercise in both conditions could be the cooling capacity of the evaporative cooling vest. Directly after applying the cooling vest, the mean cooling vest temperature was 12.2°C (SD = 6.1°C), and the mean vest-to-trunk skin temperature gradient was 21.6°C (SD = 6.1°C). However, after 10 minutes of exercise, the mean cooling vest temperature increased to 23.9°C (SD = 2.0°C), and the mean vest-to-trunk skin temperature gradient was decreased to 7.6°C (SD = 1.6°C) (Fig. 4C). Although the cooling vest temperature was still lower than skin temperature, heat exchange and cooling capacity of the vest were markedly lower compared with the start of the exercise bout. A higher cooling capacity may contribute to a larger impact on the vest-to-trunk temperature gradient and, consequently, be able to affect core body temperature during exercise.

The lack of an effect of the cooling vest on core temperature also may be explained by the location of cooling. Previous work demonstrated that arteriovenous anastomoses, which are mainly located in the distal part of the extremities, have an important role in the heat exchange with the environment.37 Under warm conditions, arteriovenous anastomoses stimulate heat loss by supplying blood to the upper parts of the skin. As a result, heat conduction to the environment will be enhanced, and cooled blood will be returned to the core.17,38 Active manipulation of the arteriovenous anastomoses using cooling techniques may be highly effective in heat removal in rest and during exercise.39 Therefore, the lack of an effect of the cooling vest may relate to the focus of cooling central regions, while not changing the (possibly more important) distal areas rich in arteriovenous anastomoses.

In addition to core body temperature responses, we explored whether the cooling vest intervention had an impact on skin temperature. As a result of the damaged autonomic nervous system in people with SCI, the ability to vasconstrict and vasodilate the peripheral vasculature is diminished.7,9,31 Hence, while wearing a cooling vest, there will be no vasoconstriction of the cutaneous blood vessels below the level of the lesion, allowing for a greater thermoregulatory effect of the cooling vest. Indeed, we found a lower skin temperature in the cooling condition and a higher core-to-trunk skin temperature gradient. These findings demonstrate that the cooling intervention effectively affects the thermoregulation in people with a low thoracic SCI. However, the reduction in skin temperature was insufficient to attenuate the exercise-induced increase in core body temperature.

An unexpected finding of the present study is the higher HR in the cooling
Effect of Cooling in Paraplegia

condition compared with the control condition. Workload, ambient conditions, and time of the day were comparable between conditions and, therefore, unlikely to contribute to this difference in HR. Interestingly, when correcting for individual differences in resting HR by presenting the change in HR from baseline (ΔHR), we found a comparable increase in HR during exercise between both conditions. Therefore, differences in HR during exercise may be explained by potential differences in baseline HR. Furthermore, we found no difference between the exercise tests for RPE, and the cooling vest condition was associated with a lower perceived thermal sensation. Therefore, it may be suggested that individuals with SCI felt more comfortable while wearing a cooling vest during submaximal exercise in moderate ambient conditions.

Strengths and Limitations

The strengths of this study are the randomized crossover design and novel approach to using a lightweight cooling vest during exercise in participants with a low thoracic lesion. A limitation of the study is that we did not measure sweat rate using sweat sensors. However, measuring changes in body mass may represent a good alternative for sweat loss, especially as participants were not allowed to drink anything or go to the toilet. Interestingly, we found no difference in weight loss between conditions (−0.4%±0.1% in both conditions), suggesting that sweat loss was not different between trials. Furthermore, we were not able to blind the participants for the type of intervention (with or without cooling vest), which may result in a placebo effect. However, we tried to minimize the placebo effect by keeping the participants naïve about the potential positive or negative effects of cooling.

In conclusion, in this study, we demonstrated that wearing an evaporative cooling vest during a 45-minute submaximal arm crank exercise is not effective in limiting or delaying the increase in core body temperature in individuals with SCI with a low thoracic lesion. Nonetheless, the cooling vest improved the perception of thermal sensation and decreased the skin temperature. These findings may suggest that wearing a cooling vest may be comfortable for individuals with SCI during exercise in moderate ambient conditions, despite the fact that it does not affect core body temperature. Whether the cooling vest has any potential impact on exercise performance warrants further research.

All authors provided concept/idea/research design and writing. Mr Bongers provided data collection. Mr Bongers and Dr Eijsvogels provided data analysis and project management. Mr Bongers, Dr van Nes, and Dr Thijssen provided participants. Mr Bongers and Dr Thijssen provided facilities/equipment. Professor Hopman provided consultation (including review of manuscript before submission). The authors acknowledge the help of Nathalie Benda, Matthijs Veltmeijer, Piet Vis, Bregina Hijmans-Kersten, Rebecca Verheggen, Pauline Maassen, Roel Elbers, and Hai Ngo for medical back-up and assistance during the exercise tests.

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