

## **Author's response to reviews**

**Title:** Cooling via one hand improves physical performance in heat-sensitive individuals with Multiple Sclerosis: a preliminary study.

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**Author's response to reviews:** see over



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Managing editor  
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Dear Sir,

We are pleased that the reviewers of our Research Article our manuscript titled “Cooling via one hand improves physical performance in heat-sensitive individuals with Multiple Sclerosis: a preliminary study” have recommended that the manuscript be accepted for publication after minor essential revision. To the extent possible we have incorporated the reviewers’ suggestions and comments into the revised manuscript. We appreciate the reviewer diligent and thorough evaluation of the manuscript and their insightful comments. Below is a point by point response to the reviewers’ comments.

Reviewer 1:

Major compulsory revisions:

Overall: Could the authors detail the degree of impairment/disability of participants using standardised scales.

The following text has been added to the Subjects sub-section of the Methods section:

“The subjects had mid-range Kurtzke Expanded Disability Status Scale (EDSS) scores ranging from 3.5 (fully ambulatory but with moderate disability in 1 functional system and mild disability in 1 or 2 functional systems) to 6.0 [intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters with or without resting].”

The limitations placed on the findings due to the lack of placebo control, measure of temperature or perceived heat should be more clearly discussed and clarified.

This issue is addressed in the first and second paragraphs of the revised discussion section. The details of the specific revision are listed below.

Method:Testing: Was the tester blinded to the training conditions? This needs stating and if the tester was not blind this needs discussing as a limitation in the discussion - see later. Peak exercise test data is in particular influenced by the tester and how hard they push individuals and as such is vulnerable to effects of both the confidence of the individual being tested to work into discomfort and of the tester’s confidence to push the individual. It appears that the tester was aware of the condition which could have affected performance, can the authors clarify.

The following text has been added to as paragraph 1 and 2 of the discussion section:

“Under the experimental conditions described in this report, the use of a device that facilitates

removal of heat from the circulating blood provided a performance benefit to individuals with MS who had a history of transient worsening of symptoms associated with elevations in body temperatures. In this study, the dependant variable was physical performance while the independent variable was the application of a cooling technique. Methodological limitations in the study design may have weakened the association between the independent and dependent variables and should be considered when evaluating the merit of the data presented in this report. We are aware of three methodological limitations in the study design that needed to be addressed: 1) the lack of a placebo control, 2) the researchers were not blinded to the treatments, and 3) the absence of a temperature measure or a subjective assessment of thermal comfort.

To facilitate heat transfer into or out of a body, it is necessary to apply a heat source or sink to a surface of the body. The sensations of temperature result from the differential activation of warm and cold cutaneous temperature sensors that respond to changes in local skin temperature and, thus, individuals can perceive the presence of a thermal source or sink when it is applied to the body surface [23]. Blocking the afferent input from the cutaneous thermosensors in local skin regions would be a way to eliminate the sensory input, but use of a nerve block to control for a placebo effect seemed excessive for this preliminary study. We are unaware of a practical means to blind subjects to treatment when a treatment entails applying a thermal stimulus to the skin surface. In these studies the researchers as well as the subjects were aware of the treatments being applied during a given trial. A common confound in exercise performance trials is researcher bias. In trials with subjective stop criteria on healthy subjects, peak performance can be influenced by external motivational factors such as differences in the researcher's confidence to push the subject. Researcher bias, while always a potential confound, likely had little influence on exercise duration in these trials on individuals with MS because the primary stop criterion for exercise was an exacerbation of physical symptoms rather than being related to motivational factors. One way to have totally eliminated researcher bias from these trials would have been to physically isolate the subjects from the researcher. However, since these subjects were physically compromised and exercising on a treadmill often to near the point of physical collapse, we deemed it prudent to have the researchers directly observe the subjects during the trials and be immediately available to assist the subjects at the termination of exercise."

#### Discussion:

The discussion could be shorter, more focused and better structured.

The addition of the text regarding study limitations expanded the discussion section. We have attempted to shorten the discussion by revising the remainder of the existing text without substantially changing the information contained in the original text.

Could the first pp state the main findings of this study?

Done. See above.

Could the limitations of the design then be stated in pp 2?

Done. See above.

The lack of a measure of core temperature in relation to the design used in this study is discussed as a weakness. However a further weakness would appear to be that the tester was aware when the individuals were being cooled. Can the authors discuss this limitation particularly when considering the hear rate data that shows an unexpected response that is not in line with the cooling theory.

Done. See above.

PP 3 could be more focused.

The following text has been removed from that paragraph:

"Presumably, the heightened temperature sensitivity of MS patients is CNS-mediated."

#### Minor essential revisions:

Table 1. would benefit from time since diagnosis and the use of a standardised impairment scale, in order for readers to better understand the degree of

ability of participants.

Those individual subject data were Protected Health Information (PHI) only to be used for establishing eligibility and unlinked from the individual subjects immediately after the screening process. However, the range of impairments of the subject population has been added to the methods section.

#### Methods

Inclusion/exclusion criteria need explicitly stating.

The following text has been added to the paragraph:

“Inclusion/exclusion criteria for this study were a diagnosis of MS, a history of heat sensitivity, engagement in a regular exercise physical fitness program, and the ability to ambulate independently.”

Analysis: The section would benefit from more explicit description of how the regression analysis was performed on the exercise duration v exercise duration data. How was the exponential curve determined &## what curve fits were examined what was the criteria. Did the data meet the requirements for this analysis, ie residual analysis etc .

The following text has been added to the data analysis sub-section of the Methods section:

“Trendlines (based on linear, log, polynomial, power and exponential equations) were calculated for the graphed data and the variance in the data accounted for by each function calculated. The variances were then compared to determine best fit curves.”

#### Discretionary comments

#### Methods

How was the randomisation managed?

The following text has been added to the protocol sub-section of the Methods section:

“A flip of a coin before the first of two paired trials determined treatment order.”

Can the authors explain why they chose 23degrees . The device was operating from 18-220, it would not appear to be a great gradient. Can the authors explain their reasoning?

Such an explanation belongs in the discussion section. The following text has been added to paragraph 7 of the discussion section:

“In the present study the temperature of the water perfusing through the cooling device was maintained at 23°C to avoid triggering a local vasoconstriction response which would, in addition to increasing vascular resistance, reduce blood flow through the heat exchange vascular structures and, thereby, decrease heat transfer.”

#### Results

Can mean and SD for HR be reported under both conditions at test termination.

The following text has been added to the Results section:

“There was no significant difference between treatment groups in initial heart rates [ $87 \pm 7$  vs.  $88 \pm 10$  beats per minute (bpm), cooling group vs, control group, mean  $\pm$  standard deviation,  $n = 10$ ,  $p \leq 0.56$ , paired t-test] or maximum heart rates ( $123 \pm 18$  bpm with cooling compared to  $118 \pm 20$  bpm without cooling, mean  $\pm$  standard deviation,  $n = 10$ ,  $p \leq 0.03$ , paired t-test). The higher maximum heart rates observed during the cooling treatment trials were likely related to increased exercise durations with the cooling treatment.”

Can temperature data and impairment data be added if possible; see below.

It is not clear what is being requested here.

Table 1. would benefit from time since diagnosis and the use of a standardised impairment scale &## in order for readers to better understand the degree of ability of participants.

The impairment levels of the individual subjects is PHI and was discarded after screening for inclusion/exclusion criteria. The following text has been added to the subjects sub-section of the methods section:

“The subjects had mid-range Kurtzke Expanded Disability Status Scale (EDSS) scores ranging from 3.5 (fully ambulatory but with moderate disability in 1 functional system and mild disability in 1 or 2 functional systems) to 6.0 [intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters with or without resting].”

## Table 2. # undefined

“#” has been replaced with the text “number of”.

## Discussion

PP5 discusses the effect of increased peripheral resistance lowering heart rate.

Could the authors back this statement up with their data; it would be surprising if cooling in one hand by 1 degree were to affect blood pressure etc, can this be referenced and clarified.

Reference #35 has been added to paragraph 7 of the discussion section:

“Mourot L, Bouhaddi M, Gandelin E, Cappelle S, Dumoulin G, Wolf JP, Rouillon JD, Regnard J:

**Cardiovascular autonomic control during short-term thermoneutral and cool head-out immersion.** *Aviat Space Environ Med* 2008, **79**(1):14-20.”

Could the authors discuss why the temperature was held at 23degrees in relation to optimising the design for this test.

The following text has been added to paragraph 7 of the discussion section:

“In the present study the temperature of the water perfusing through the cooling device was maintained at 18-22°C to avoid triggering a local vasoconstriction response which would, in addition to increasing vascular resistance, reduce blood flow through the heat exchange vascular structures and, thereby, decrease heat transfer.”

## Reviewer 2

### Minor Essential Revisions

- Could it be specified what “heat-related MS symptom exacerbations” contain?

The first paragraph describes heat related symptom exacerbations. The following text has been added:

“MS symptoms vary between individuals and often include deficits associated with coordinated movement such as: muscle weakness, muscle spasms, ataxia, and visual problems. Heat- or exercise-induced symptom exacerbations are a transient expression of new symptoms, or a worsening of existing symptoms. ”

“regular exercise programs”? Could training-intensity and training-volume be specified as well as the duration of the program?

Those specific subject history data were not recorded and, thus, are not available.

- Legend to figure 2 states that 5 subjects is presented? The figure contains subject 1, 7, 3 and 2.

The figure legend has been changed to: “Examples of heart rates during paired control and experimental trials from 4 subjects.”

About reference no 4: The second author is missing (JM, name?)

The last name of the second author has been added.

Sincerely,

*Demi A. Sal*