A randomized controlled study of the acute and chronic effects of cooling therapy for MS

NASA/MS Cooling Study Group*

Abstract—*Background:* Cooling demyelinated nerves can reduce conduction block, potentially improving symptoms of MS. The therapeutic effects of cooling in patients with MS have not been convincingly demonstrated because prior studies were limited by uncontrolled designs, unblinded evaluations, reliance on subjective outcome measures, and small sample sizes. *Objective:* To determine the effects of a single acute dose of cooling therapy using objective measures of neurologic function in a controlled, double-blinded setting, and to determine whether effects are sustained during daily cooling garment use. *Methods:* Patients (n = 84) with definite MS, mild to moderate disability (Expanded Disability Status Scale score < 6.0), and self-reported heat sensitivity were randomized into a multicenter, sham-treatment controlled, double-blind crossover study. Patients had the MS Functional Composite (MSFC) and measures of visual acuity/contrast sensitivity assessed before and after high-dose or low-dose cooling for 1 hour with a liquid cooling garment. One week later, patients had identical assessments before and after the alternate treatment. Patients were then re-randomized to use the cooling garment 1 hour each day for a month or to have observation only. They completed self-rated assessments of fatigue, strength, and cognition during this time, and underwent another acute cooling session at the end of the period. After 1 week of rest, they had identical assessments during the alternate treatment. *Results:* Body temperature declined during both high-dose and low-dose cooling, but high-dose produced a greater reduction ($p < 0.0001$). High-dose cooling produced a small improvement in the MSFC (0.076 ± 0.66, $p = 0.007$), whereas low-dose cooling produced only a trend toward improvement (0.053 ± 0.031, $p = 0.09$), but the difference between conditions was not significant. Timed gait testing and visual acuity/contrast sensitivity improved in both conditions as well. When patients underwent acute cooling following a month of daily cooling, treatment effects were similar. Patients reported less fatigue during the month of daily cooling, concurrently on the Rochester Fatigue Diary and retrospectively on the Modified Fatigue Impact Scale. *Conclusions:* Cooling therapy was associated with objectively measurable but modest improvements in motor and visual function as well as persistent subjective benefits.

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MS is an inflammatory demyelinating disorder of the CNS, with symptoms resulting from impaired conduction through demyelinated and transected axons.[1] The ability of elevated body temperature to increase MS symptoms and signs has long been appreciated.[2,3] Experimental nerve preparations demonstrate that conduction block through partially demyelinated nerves increases steadily as temperature increases through the physiologic range.[4,5] Conversely, reducing body temperature enhances conduction in vitro,[6] improves evoked potentials,[7] and improves symptoms in patients with MS.[8] These effects are commonly assumed to be mediated directly by changes in temperature adjacent to demyelinated axons, but it is also possible that cooling-induced changes in nitric oxide[9] or other inflammatory mediators[10] may be involved.

Despite these observations, the therapeutic impact of cooling in patients with MS remains uncertain because prior studies have been limited by uncontrolled designs, unblinded evaluations, reliance on subjective outcome measures, and small sample sizes.[11] Prior studies have also focused primarily on the acute effects of a single cooling session. Even if these studies demonstrated an effect, they did not address the long-term benefits of treatment. To overcome these limitations, we performed a multicenter, randomized, double-blinded, controlled trial of the acute and chronic effects of active cooling using liquid cooling garments (LCG) in patients with MS. The hypotheses to be tested were that 1) a single, acute dose of cooling therapy (1-hour cooling session) will produce objectively measurable improvements in performance on tests of neurologic function (acute phase) and 2) measurable improvements will be sustained (i.e., the cooling therapy will not lose effectiveness) when therapy is repeated daily for 4 weeks (chronic phase).

Methods. *Organization.* This multicenter trial was designed and performed by the NASA/MS Cooling Study Group, a collabo-

*See the Appendix on page 1960 for a list of members of the NASA/MS Cooling Study Group.

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Address correspondence and reprint requests to Dr. Steven R. Schwid, University of Rochester, Department of Neurology, 601 Elmwood Avenue, Box 605, Rochester, NY 14642; e-mail: steven_schwid@urmc.rochester.edu

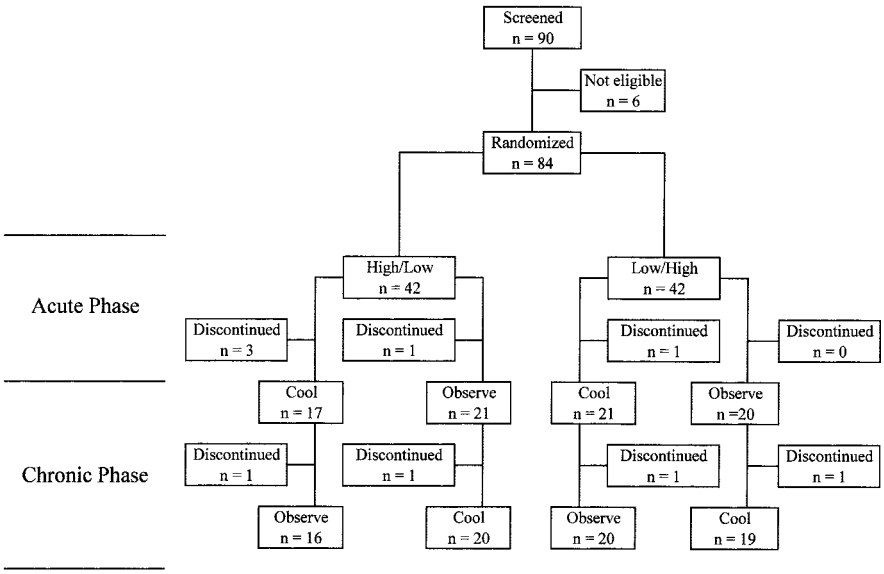

Figure 1. Patient disposition through screening, randomization, and the acute and chronic phases of the study.

rative group of investigators organized and sponsored by the Commercial Technology Office of the NASA Ames Research Center, Moffett Field, CA. The NASA Commercial Technology Program is responsible for transferring applicable NASA technology, such as the cooling garments based on space-suit technology, to the commercial sector for the public benefit. The protocol was approved by the institutional review boards at the five participating centers, and all patients provided written consent to participate in this research study. All data were collected and managed by the NASA Coordination Center, and analyses were performed by a statistician (G.C.) unaffiliated with NASA or any of the study sites.

Patients. Each of the participating MS research centers recruited a minimum of 10 patients (ages 18 to 70) with clinically definite MS and Expanded Disability Status Scale (EDSS) score 0 to 5.5 (ambulatory without a cane for at least 100 meters). All patients had a history of heat sensitivity (as reported by the patient or physician) and had not used cooling therapy for at least 90 days before this study. Patients were excluded if they had used antihypertensive or vasoactive medications, diuretics, or corticosteroids within the previous month, or if they had other significant medical diagnoses, including thyroid or cardiovascular disease. Patients were also excluded if their size or weight was outside of the range necessary to fit the cooling garment.

Procedures. The study design (figure 1) consisted of two consecutive crossover phases to examine the acute and chronic effects of cooling separately. After a screening visit in which patients were introduced to testing procedures, patients entered the acute phase with random assignment to a single session of high-dose or low-dose cooling and neurologic evaluation before and after treatment. One week later, patients returned for an identical visit employing the alternate treatment. The employment of low-dose cooling during this phase was an attempt to provide a sham control, so that the acute effects of cooling could be assessed in a double-blind fashion. We used active LCG (Lifetime Enhancement Technologies, Santa Clara, CA) because previous studies indicated that these were most effective in reducing core body temperature and they allowed adjustment of cooling intensity.[12] Cooling levels were set by a separate investigator who did not participate in any of the evaluations. Units were set to maintain the coolant circulating through a vest and cap at 55 °F during high-dose cooling and 70 °F during low-dose cooling. These settings were based on prior studies suggesting that high-dose cooling would lower core body temperature by approximately 1.0 °F, that low dose cooling would lower body temperature by less than 0.5 °F, that shivering would not be provoked by either condition, and that patients would be unable to distinguish the settings.[10]

During each cooling session in the acute phase, patients underwent standardized neurologic evaluation, and then probes were applied for continuous recoding of skin (sternum, forearm, calf) and rectal temperatures, electrocardiogram, and respiration rate using Biolog monitors. Oral temperature was also monitored every 10 minutes. Patients sat quietly for a 20-minute precooling baseline period, and then donned the cooling garment with the cooling system inactive. The cooling system was turned on and adjusted as needed to achieve the desired coolant temperature. The patient continued to sit quietly for 60 minutes. The cooling garment was removed at the end of the cooling period, and patients remained seated with temperature monitoring for an additional 30 minutes. Body temperature continued to decline during this period because the cooled skin serves as a heat sink. The instrumentation was then removed and the neurologic evaluation was repeated.

One week after completing the second acute cooling session, patients entered the chronic phase of the study, which included a second randomization. Half were assigned to home cooling for 4 weeks balancing those initially and subsequently exposed to high cooling in the first phase, and half to observation only. Patients were instructed in the independent use of the cooling garments, and those assigned to home cooling were provided with garments to wear for 1 hour each morning during the cooling month and to return at the end of the period. Cooling levels were individually preset and locked to provide high-dose cooling for each patient as determined during the acute phase. Patients assigned to observation completed all of the same assessments, but did not have cooling therapy or garments. Neurologic evaluation was performed at the start of this period, and patients completed self-reported measures of fatigue and neurologic function daily. At the end of the 4-week period, patients returned for an observed high-dose cooling session identical to those performed during the acute phase. Following 1-week washout when cooling was not performed, patients crossed over to the alternate treatment for 4 more weeks. To minimize test-retest variability, all tests for a given patient were performed at the same time of day. Medications and daily activities remained stable during the entire study period.

Outcome measures. Neurologic evaluations performed before and after cooling sessions during the acute and chronic phases of the study included the MS Functional Composite (MSFC)[13] and the Sloan letters test.[14] The MSFC combines results from quantitative functional tests of lower extremity impairment (time to walk 25 feet [T25FW], average of two trials), upper extremity impairment (the 9-hole peg test [9HPT], average of two trials in each hand), and cognitive impairment (the Paced Auditory Serial Addition Test–3-second version [PASAT]). The Sloan letters test assesses visual acuity at four levels of optical contrast—100%, 5%, 1.25%, and 0.625%—averaged for both eyes. To minimize practice effects, which can be particularly prominent on the PASAT, patients performed all of these tests twice at the screening visit, so that the first performance used for efficacy analysis was the third exposure to the tests. Alternate forms were used for the PASAT and Sloan letters test. The acute phase of the study was double-blinded, with neither the patients nor the examiners aware of the order of high-dose and low-dose cooling.

During the chronic phase of the study, patients also completed self-reported assessments of fatigue and neurologic function. Fatigue was assessed with the Modified Fatigue Impact Scale (MFIS), a 21-item questionnaire assessing the self-reported impact of fatigue on motor, cognitive, and psychosocial function, completed at the end of the 4-week cooling and observation periods.[15] Fatigue was also assessed with the Rochester Fatigue Diary (RFD), in which patients rated their energy level on a visual analog scale every hour for 24 hours.[16] This was completed on days 3, 4, 10, 11, 17, 18, 24, and 25 of each of the 4-week cooling and observation periods. On all other days patients rated their energy level, muscle strength, and cognitive ability on a nine-point Likert scale ranging from −5 for extremely reduced function to 0 for not affected to +5 for extremely increased function. Neither patients nor examiners were blinded to treatment assignments during the chronic phase of the study.

Sample size. Although there were no data when this study was planned to indicate what would be a clinically significant change in the MSFC, the investigators determined a priori that changes of one third of a SD unit would be relatively large. To detect a difference between the two cooling conditions of this magnitude, approximately 75 patients were estimated to be necessary to provide 80% power with a two-sided $\alpha = 0.05$. To account for potential dropouts, we planned to recruit at least 80 patients. For the chronic phase, this sample size provided greater than 90% power to detect a five-point difference in the MFIS assuming a SD of the change of 10 points.

Statistical analyses. SAS statistical software system was utilized for data entry and analysis. The design of this crossover trial provided repeated measures on the same patients under four different conditions: acute high-dose cooling, acute low-dose cooling, chronic high-dose cooling, and chronic observation. Generalized linear models were used to assess the within-patient correlations among the measurements and to test the changes before and after cooling as well as between the two cooling protocols using PROC Mixed in SAS.

The MSFC was created as described previously, standardizing each component (arm, leg, and cognitive components) to the mean of the two baseline values for each person from the before cooling measures at each visit (two and three). The standardized mean (SD) results were as follows: PASAT = 48.95 (9.56), 1/9HPT = 0.0461694 (0.0101174), T25FW = 6.40 (3.66).

Results. A total of 90 patients were invited to the screening visits and six were determined to be ineligible. Table 1 shows the baseline characteristics of the 84 patients randomized. Where the numbers do not sum to 84, the data were not obtained. There were no significant differences among the four randomized groups (low/high/observe/cool, low/high/cool/observe, high/low/observe/cool, high/low/cool/observe) or between the high and low groups during the acute phase. Figure 1 shows the numbers of patients at each point in the study process. All 84 patients completed the initial two visits. Five patients withdrew between the acute and chronic phases. Four additional patients failed to complete the final month of the study, one from each treatment combination. Thus, 75 patients (89.3%) completed all evaluations. There were no differences between the dropouts and completers in demographic or baseline variables. *Acute effects of cooling.* Body temperature reductions during cooling varied slightly at different body surfaces, but appeared to be adequately represented by oral temperatures (data not shown). At the time of neurologic testing, the mean reduction in temperature from baseline was -0.81 ± 0.07 °F (mean ± standard error) during high-dose cooling and -0.52 ± 0.06 °F during low-dose cooling (table 2). Thus, both cooling conditions reduced oral temperature, but the high-dose cooling condition produced a greater reduction ($p < 0.0001$).

High-dose cooling produced a small improvement in the MSFC of 0.076 ± 0.066 ($p = 0.0073$, see table 2). Low-dose cooling, on the other hand, was only associated with a trend toward improvement in the MSFC (0.053 ± 0.031, $p = 0.087$). There was no difference between groups in MSFC changes ($p = 0.56$). Both cooling conditions were associated with improvements in T25FW (0.423 ± 0.126 seconds, $p = 0.0012$, for high-dose cooling, and 0.328 ± 0.106 seconds, $p = 0.0026$, for low-dose cooling). There was no difference between T25FW improvements for the high-dose and low-dose cooling conditions ($p = 0.47$). Cooling did not produce a significant change in the 9HPT or the PASAT under either condition.

Table 1 *Patient characteristics at baseline*

Variable	Mean (SE) or n (%)
Age, y	48.1 (0.92)
Female sex	52 (61.9%)
Race	
Black	2 (2.4%)
Hispanic	1 (1.2%)
White non-Hispanic	79 (95.2%)
Other	1 (1.2%)
Mean EDSS score	3.3 (0.16)
0–2.5	34 (39.8%)
3.0–3.5	16 (19.0%)
4.0–5.5	34 (40.5%)
Disease pattern	
Stable or relapsing	74 (92.7%)
Progressive	6 (7.3%)
Relapses in prior year	
0	41 (48.8%)
1	27 (32.1%)
2 or more	16 (19.0%)
Prior history of cooling	9 (11.0%)

EDSS = Expanded Disability Status Scale.

There were four levels of visual acuity/contrast sensitivity tested. At the 100% level of contrast, equivalent to a Snellen chart, there were trends toward improvement during cooling in the number of letters correctly identified ($p = 0.068$ for high-dose cooling and $p = 0.153$ for low-dose cooling). At all lower levels of contrast, there was significant improvement in the number of letters correctly identified in both cooling conditions (see table 2). There were no differences between the effects of high-dose and low-dose cooling on contrast sensitivity (see table 2).

Chronic effects of cooling. When patients underwent acute cooling following a month of daily cooling, they experienced a slightly greater reduction ($p = 0.02$) in temperature following the month of cooling (-0.76 ± 0.08 °F) compared to the observation month (-0.60 ± 0.07 °F). Following a month of daily cooling, MSFC improved during the acute cooling session (MSFC change = 0.051 ± 0.024, $p = 0.041$). Following a month of observation, MSFC improvements were not significant during acute cooling (change = 0.039 ± 0.031, $p = 0.21$). MSFC changes after acute cooling were not different following the month of home cooling compared to the month of observation ($p = 0.77$). MSFC components and visual contrast sensitivity tests showed similar effects to acute cooling sessions performed earlier in the study (table 3).

Patients reported less fatigue ($p < 0.0001$, table 4) on the MFIS after a month of daily cooling (35.89 ± 1.85) compared to after a month of observation (43.61 ± 1.67). RFD scores also demonstrated less fatigue during the month of cooling compared to the month of observation ($p < 0.0001$). RFD ratings demonstrate that the benefits of cooling began midmorning and persisted into the evening (figure 2). Using the daily Likert scale ratings, 75.3% of the patients reported increased energy during the month of cooling compared to 39.4% of the patients during the observation month. The mean score on this scale was 1.35 ± 0.03 (indicating 1.35 unit improvement compared to not affected) for the cooling month compared to 0.32 ± 0.04 for the patients during the observation month ($p < 0.0001$). For strength, 57.8% reported increased strength during the cooling month compared to 30.9% during the observation month. The mean scores were 0.94 ± 0.03 for the cooling month and 0.19 ± 0.04 for the observation month ($p < 0.0001$). Similarly, for cognition, 55.0% of the patients re-

Table 2 *Acute effects of high-dose and low-dose cooling*

Outcome measure	High-dose cooling		Low-dose cooling		Difference between sessions, p†
	Mean change (SE)*	p	Mean change (SE)*	p	
Oral temperature, °F	−0.81 (0.07)	<0.0001	−0.52 (0.06)	<0.0001	<0.0001
MSFC, z-score units	0.08 (0.03)	0.007	0.05 (0.03)	0.087	0.56
T25FW, s	−0.42 (0.13)	0.001	−0.33 (0.11)	0.0026	0.47
9HPT, s	−0.10 (0.29)	0.74	−0.46 (0.48)	0.34	0.49
PASAT, number correct	0.18 (0.59)	0.76	0.56 (0.63)	0.38	0.61
Visual acuity, 100% contrast, number correct	1.4 (0.7)	0.068	0.25 (0.17)	0.15	0.14
Visual acuity, 5% contrast, number correct	2.2 (0.7)	0.004	0.93 (0.43)	0.034	0.13
Visual acuity, 1.25% contrast, number correct	2.2 (0.6)	0.0002	1.6 (0.4)	0.0001	0.40
Visual acuity, 0.625% contrast, number correct	2.5 (0.6)	<0.0001	2.2 (0.7)	0.0014	0.54

* Postcooling value minus precooling value. Positive values for tests of impairment/disability represent improvements, except for T25FW.

† p Values derived from repeated measures longitudinal models taking correlation within patients into account.

MSFC = MS Functional Composite; T25FW = timed 25-foot walk; 9HPT = 9-hole peg test; PASAT = Paced Auditory Serial Addition Test, 3-second version.

ported improvement during the cooling month compared to 30.7% during the observation month. The mean scores were 0.90 ± 0.03 for the cooling month and 0.31 ± 0.04 for the month of observation ($p < 0.0001$). Neither the RFD nor the Likert scales showed any evidence that treatment benefits were progressively increasing or decreasing during the month of daily cooling. No treatment-related adverse effects were reported during the acute or chronic phases of the study.

Discussion. This study was designed to overcome some of the limitations present in previous studies of cooling effects in patients with MS. First, we assessed the acute effects of cooling by providing both active and sham cooling with rigorous quantitative assessment of neurologic function while both patients and examiners were blinded. Unfortunately, the sham cooling condition, which did not produce significant changes in body temperature in smaller studies,[10] caused a mild reduction in temperature in our study, complicating interpretation of the results.

Table 3 *Acute effects of high-dose cooling after a month of home cooling or observation*

Outcome measure	After home cooling		After observation		Difference between sessions, p†
	Mean change (SE)*	p	Mean change (SE)*	p	
Oral temperature, °F	−0.76 (0.07)	<0.0001	−0.60 (0.07)	<0.0001	0.02
MSFC, z-score units	0.05 (0.02)	0.04	0.04 (0.03)	0.21	0.77
T25FW, s	−0.26 (0.10)	0.01	−0.39 (0.24)	0.11	0.58
9HPT, s	0.08 (1.58)	0.95	−0.37 (0.40)	0.35	0.57
PASAT, number correct	0.08 (0.06)	0.19	−0.19 (0.51)	0.35	0.18
Visual acuity, 100% contrast, number correct	0.77 (0.59)	0.55	0.66 (0.22)	0.003	0.05
Visual acuity, 5% contrast, number correct	1.5 (0.4)	0.0001	1.6 (0.4)	<0.0001	0.89
Visual acuity, 1.25% contrast, number correct	1.5 (0.5)	0.002	2.3 (0.4)	0.0001	0.24
Visual acuity, 0.625% contrast, number correct	1.9 (0.6)	0.004	1.4 (0.5)	0.003	0.55

* Postcooling value minus precooling value. Positive values for tests of impairment/disability represent improvements, except for T25FW.

† p Values derived from repeated measures longitudinal models taking correlation within patients into account.

MSFC = MS Functional Composite; T25FW = timed 25-foot walk; 9HPT = 9-hole peg test; PASAT = Paced Auditory Serial Addition Test, 3-second version.

Table 4 *Effects of cooling on self-reported fatigue, strength, and cognition during the month of home cooling and observation*

Outcome measure	During cooling month, mean (SE)	During observation month, mean (SE)	p*
MFIS†	35.9 (1.9)	43.6 (1.7)	<0.0001
RFD‡	35.6 (0.6)	33.8 (0.6)	<0.0001
Energy‡	1.4 (0.03)	0.3 (0.04)	<0.0001
% Reporting improvement§	75	39	
Strength‡	0.9 (0.03)	0.2 (0.04)	<0.0001
% Reporting improvement§	58	31	
Fatigue‡	0.9 (0.03)	0.3 (0.04)	<0.0001
% Reporting improvement§	55	31	

* p Values derived from repeated measures longitudinal models taking correlation within patients into account.
† Mean values obtained at the end of the month of home cooling and observation. Higher scores on the MFIS indicate more fatigue.
‡ Mean values obtained on multiple days during the month of home cooling and observation. Higher scores on the RFD and daily Likert scales indicate lower fatigue.
§ Percentage of patients rating energy, strength, and cognition as improved (mean of all days of recording within the relevant period).

MFIS = Modified Fatigue Impact Scale; RFD = Rochester fatigue Diary.

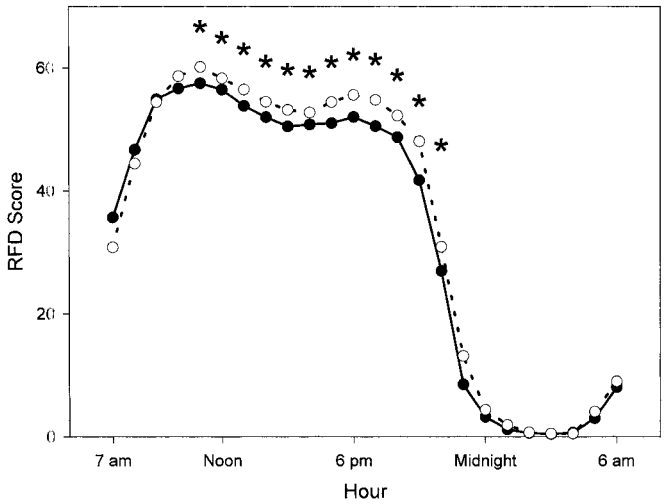

Figure 2. Self-reported energy level as measured by the Rochester Fatigue Diary (RFD), which allows patients to rate their current energy level on a visual analog every hour of the day. Each point is the average of 8 days of recording, converted to a 0 to 100 scale, for all patients (n = 76) during the month of daily cooling (dotted line) compared to the month of observation (solid line). Ratings follow the typical diurnal pattern, with significantly higher scores (less fatigue, marked by asterisks) from 11 AM to 10 PM during the month of home cooling compared to the month of observation.

Thus, rather than providing a true control condition, patients had one session with high-dose cooling and another with low-dose cooling. High-dose cooling produced a small but significant improvement in the neurologic function as summarized by the MSFC, whereas low-dose cooling produced only a trend toward improvement. Differences between the high-dose and low-dose groups were not significant, however, and timed walking and visual acuity/contrast sensitivity improved significantly in both conditions. Although similar effects of high-dose cooling were demonstrated during high-dose cooling sessions performed in the chronic phase of the study, results must be interpreted cautiously because observed treatment effects were very modest.

Similar improvements have been detected in several previous studies of cooling therapy, but conclusions were tempered by uncontrolled designs,[8,17-22] unblinded evaluations,[8,9,17-22] total reliance on subjective outcome measures,[8,17] and small sample sizes.[8-10,17-22] A few studies have also failed to detect significant benefits of cooling, but these had small sample sizes, raising the likelihood of type II statistical errors.[23-25]

Although the MSFC was designed to monitor long-term changes in patients' functional abilities, it was also sensitive to short-term symptomatic effects in this study. The MSFC is well suited to this purpose compared to traditional measures such as the EDSS because its quantitative nature provides superior reliability and responsiveness for relatively small changes in neurologic function. In its present form, the MSFC includes quantitative functional measures for the lower extremities, upper extremities, and sustained attention/concentration. In this study of symptomatic therapy in patients with EDSS < 6 and a predominance of relapsing MS, the T25FW test appeared to be the most sensitive to change. In contrast, studies of disease-modifying therapies performed in patients with more advanced disease and progressive MS have found the 9HPT to be more sensitive to change.[26,27] These observations suggest that components of the MSFC have different levels of responsiveness, depending on the study population and treatment goals. Our study suggests that the Sloan letters test may have appropriate reliability and responsiveness to be incorporated into future iterations of the MSFC as a sensitive measure of visual acuity/contrast sensitivity.

During the chronic phase of the study we relied on self-reported measures of fatigue, strength, and cognition to demonstrate treatment-related improvements during the month of cooling compared to the month of observation. These results must be interpreted cautiously because patients were not blinded and assessments were subjective. Nevertheless, the consistency and persistence of these effects collected using different assessment tools clearly demonstrates patients' impressions that cooling was beneficial, improving these important determinants of

quality of life. The RFD provided especially useful information, allowing patients to report concurrently improvements in fatigue that persisted throughout the day, rather than relying on retrospective assessments as most questionnaires do.

Although other studies have demonstrated that continuous cooling can promote improvement in neurologic signs over several days,[17] no other study has systematically assessed the long-term benefits of daily cooling, as patients would typically use it. We found no evidence that cooling effects changed over time. Given the lack of side effects observed in this study, modest improvements demonstrated using objective measures of motor and visual function, and persistent subjective benefits, cooling therapy could be considered as a potential adjunct to other symptomatic and disease-modifying treatments for patients with MS.

Appendix

The following investigators participated in this study and authored this report: *Site investigators:* Steven R. Schwid, MD, Mary D. Petrie, RN (University of Rochester, Rochester, NY); Ronald Murray, MD, Jennifer Leitch, RN (Rocky Mountain MS Center, Englewood, CO); James Bowen, MD, Alan Alquist, PhD (University of Washington, Seattle, WA); Richard Pelligrino, MD, PhD, Adam Roberts, Judith Harper-Bennie, Maria Dawn Milan, RN (MS Association of America, Hot Springs, AR); Raul Guisado, MD (Center for Neurodiagnostic Research, San Jose, CA); Bernadette Luna, MS, Leslie Montgomery, PhD, Richard Lamparter, MS, Yu-Tsuan Ku, MS, Hank Lee, BS, Danielle Goldwater, MD (NASA Ames Research Center, Moffett Field, CA). *Coordinating personnel:* Gary Cutter, PhD (AMC Cancer Research Center, Denver, CO, independent biostatistician); Bruce Webbon, PhD (NASA Program Manager and Principal Investigator).

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