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Aquatic training in MS: neurotherapeutic impact upon quality of life

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Abstract

Three fundamental principals associated with aquatic therapy differentiate it with respect to exercise on land, and in air. These are buoyancy (reduction in weight of the body within the buoyant medium of water), viscosity (a "drag force" is generated when moving within water, when compared with the same movement in air), and the thermodynamic aspect of water exercise, during which the heat capacity of water is about 1000 times greater than that of an equivalent amount of air; equating to a heat transfer from the body into water at a rate 25 times faster than that of air. Aquatic conditioning, can improve neurologic functioning, with dividends favorably impacting activities of daily living, health maintenance, safety, and ultimately quality of life. Here, we review the application of aquatic exercise training in MS patients.

Introduction

Demyelination leads to a compromise of axonal conduction, resulting in the incorporation of new sodium channels on the axonal surface to restore electrical transmission of frequency-coded messages. This can lead to excessive influx of sodium, which prompts reversal of the sodium-calcium exchanger. The eventual accumulation of

intra-axonal calcium can lead to the activation of calcium-dependent proteases; release of excitatory amino acids; and the eventual demise and destruction of the axon (transaction with consequent dying back and wallerian degeneration).

An unintended consequence of the ion channel adaptation, is that the newly assembled sodium channels exhibit altered safety factor characteristics in response to temperature changes, such that core body temperature elevation can provoke closure of the sodium channel pore at a lower temperature than normal (Fig. 1).[1] In such a circumstance, activities such as exercise, fever, infection, exposure to increased ambient temperatures, ingestion of hot liquids or food, and even psychological stressors may precipitate sodium channel pore closure, and abrupt cessation of the action potential (which can correspond to functional abnormalities affecting a diversity of activities of daily living (ADLs) such as walking, vision, bladder control, cognitive processes, among others).

Neurophysiologic investigations have revealed that multiple sclerosis (MS) patients exhibit a reduced capacity, or long latency for onset, of sweating in response to a heat stress, such that a rise in core temperature can occur quite quickly without an appropriate autonomic response to maintain core-body thermoregulation.[2–4] Further, greater predisposition to delayed responses in sympathetic responses to positional-induced reductions in blood pressure (i.e., orthostatic effects upon upright posture) leads to inadequate venous return, and a corresponding requirement for heart rate elevation (chronotropic adaptation that also appears to be diminished in MS), in order to maintain cardiac output and normal perfusion dynamics across the various tissue organ beds of the body; most critically to the heart and brain.

A consequence of the increased density of sodium channels (channels that exhibit altered thermal characteristics; with their pores capable of closing at only modest temperature elevation, thereby terminating the depolarization phase of the action potential) along demyelinated segments, is that the normal fast saltatory conduction properties of axons, that involve electrical propagation from the node and paranode of Ranvier, is transformed to slow membrane conduction mechanisms, with a greater likelihood of temporal dispersion, conduction slowing and even failure; especially under those circumstances where core body temperature elevation occurs (Fig. 1).[1]

With the greater density of sodium channels along the demyelinated axon, the excessive entry of sodium can lead to substantial energetic consequences, when greater amounts of intra-axonal ATP must be utilized in order to reverse the sodium-calcium pump, where sodium efflux is coupled to excessive entry of calcium (the latter of which can in and of itself trigger axonal damage by activation of calcium-dependent proteases and release of intra-axonal excitatory amino acids such as glutamate).

In addition to the pathophysiologic consequences of demyelination upon axonal depolarization, the reduction or loss of myelin internodes along the axon serves to unmask an increased density of potassium channels, thereby exacerbating potassium efflux (often referred to as "current leak"), and lowering the threshold for transmembrane hyperpolarization; leading to abrupt cessation of the action potential (Fig. 1).[1]

The reversible, and often stereotyped development of MS symptoms in response to a heat stress, prolonged exercise, fever and infection, and psychological stress is referred to as *Uhthoff's phenomenon*, and mechanistically occurs when two fundamental changes occur in ion channel physiology; closure of the sodium channel pore, thereby aborting depolarization and action potential propagation, while concomitantly there is excessive potassium efflux across an increased unmasked density of potassium channels; thereby promoting hyperpolarization and premature cessation of the action potential (Fig. 1).[1]

Interventions that promote body cooling (application of cooling devices, use of antipyrexic agents during fever/infection, ingestion of ice-cold liquids, and precooling before exercise) have been shown to improve the fidelity and duration of action potentials across demyelinated axons. Pharmacologic agents, such as 4-aminopyridine (4-AP), serve to block potassium channels (thereby attenuating potassium efflux), prolong action potential duration, and produce evidence-based dividends upon walking, with the application of the sustained-release formulation of 4-AP; dalfampridine (Ampyra®Acorda Therapeutics, Ardsley, NY, USA), and upon vision with the application of the compounded formulation (Fig. 1).[5,6] Alternately, conditioning and training can serve to both accelerate information processing and task completion, while also demonstrating an attenuation in the size of the recruited neural network required for task completion (akin to plasticity, while potentially improving supply and demand intra-axonal energetics).[7]

Landmark human investigations, objectively and precisely characterizing Uhthoff's phenomenon, were published in 2008, and involved the application of a novel paradigm with passive heat exposure (whole-body heating with a water perfused suit), and its reversibility with the subsequent application of active cooling.[8] For these studies, we investigated the horizontal eye movements of MS patients with internuclear ophthalmoparesis (INO); an eye movement abnormality secondary to demyelination of the medial longitudinal fasciculus (MLF), the brainstem tegmental tract system responsible for the coordination of all classes of eye movements. We observed significant

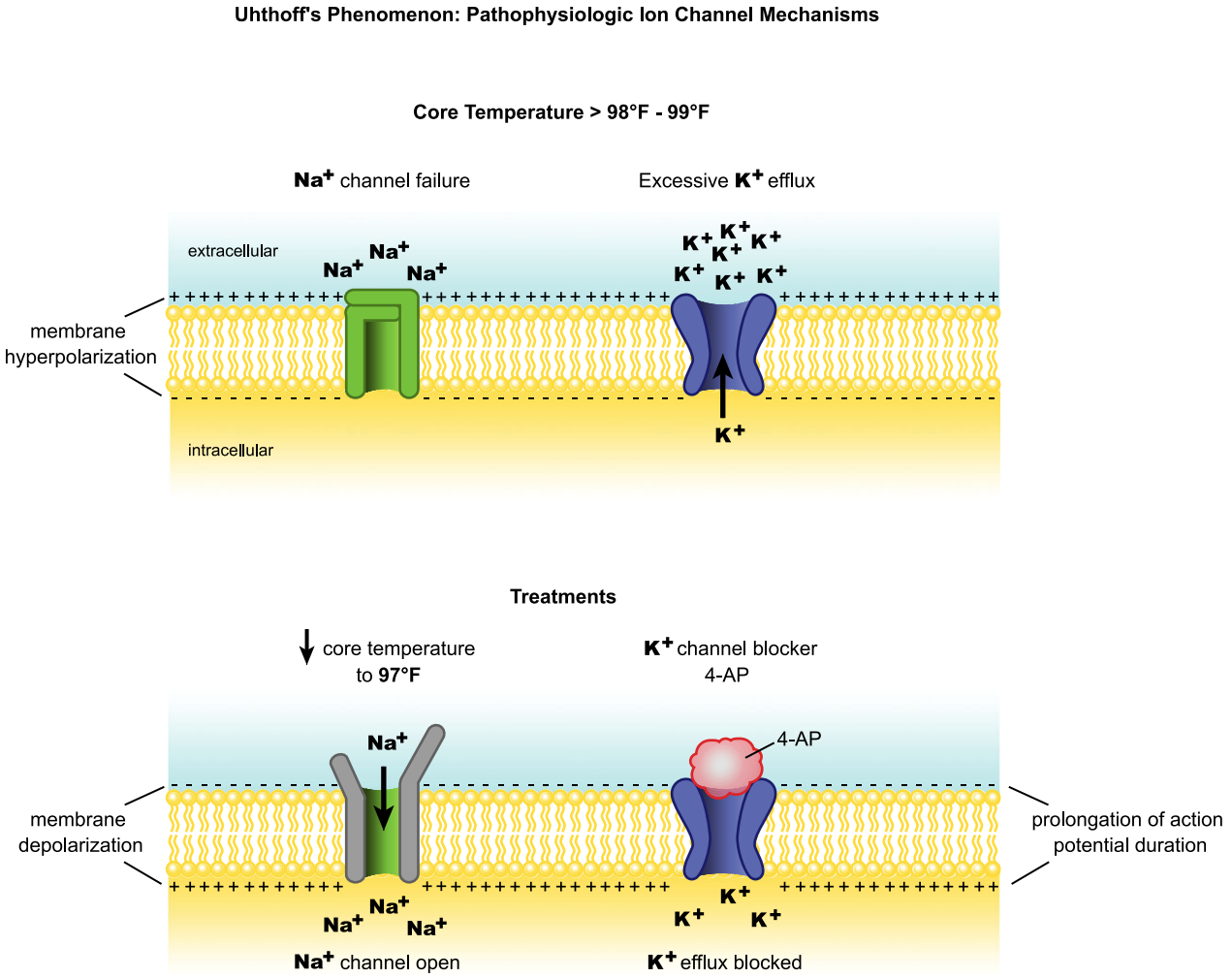

Figure 1. Ion channel pathophysiology in MS. pathophysiological mechanisms of Uhthoff's phenomena and potential treatment interventions. Elevation in core body temperature in the context of axonal demyelination results in pore closure of voltage-gated sodium channels, thereby compromising action potential depolarization. Alternatively, segmental demyelination unmasks an increased density of membrane-localized potassium channels with a high predilection for current leak via potassium efflux. Two mitigating factors that have therapeutic effects on action potential fidelity and duration: active cooling facilitates sodium channel pore patency, whereas 4-aminopyridine (4-AP) is a broad-spectrum potassium channel blocker that prolongs action potential duration (reduces current leak). From Frohman et al.[1]

adduction slowing during the systematic escalation of core body temperature (from 0.2 to 0.8°C), whereas their conjugacy returned to baseline during whole body cooling (Fig. 2).

Deconditioning and reconditioning

While reduced conditioning has important ramifications upon health and wellness in otherwise normal subjects, the impact upon patients with MS can be devastating (Table 1). For instance, with reduced conditioning and exercise tolerance over protracted periods of time, there can be impairment in the MS patient's ability to execute their ADLs. Alternately, overwhelming evidence now indicates that exercise is beneficial to individuals with MS, with improvements seen both physiologically and psychologically, and should be incorporated into their overall disease management plan (Tables 2, 3).[9]

Strategies for Limiting Heat Sensitivity

Despite the "general" proscriptions of many health care providers, instructing MS patients to avoid exercise because of the risk associated with Uhthoff's phenomenon, we instead strongly support regular exercise for our patients, while also emphasizing the necessity to avoid overheating, and to use preexertion cooling strat-

egies, as well as cooling techniques during exercise. Studies have reported discreet benefits when using simple, inexpensive, and widely available cooling strategies.[10]

Mechanistically, precooling allows the lower limbs to effectively serve as heat "sinks" in order to blunt internal temperature increases and decrease reliance on heat dissipation mechanisms, such as eccrine sweating, which may be compromised in MS patients (Fig. 3).[2] This cooling (or temperature blunting effect) can last for several hours, depending on the intensity of the activities performed by the individual with MS.

Why promote aquatic therapy for MS patients?

Of the most conspicuous benefits associated with aquatic therapy, buoyancy, and hydrostatic pressure in water decrease the apparent body weight and make it easier and safer for patients to move their extremities without any assistive devices; activities that when performed on land would be considerably more difficult or untenable, energy consuming, and with compromised safety (Table 3). Indeed, patients with spinal cord damage who are unable to ambulate independently on land, are able, with some

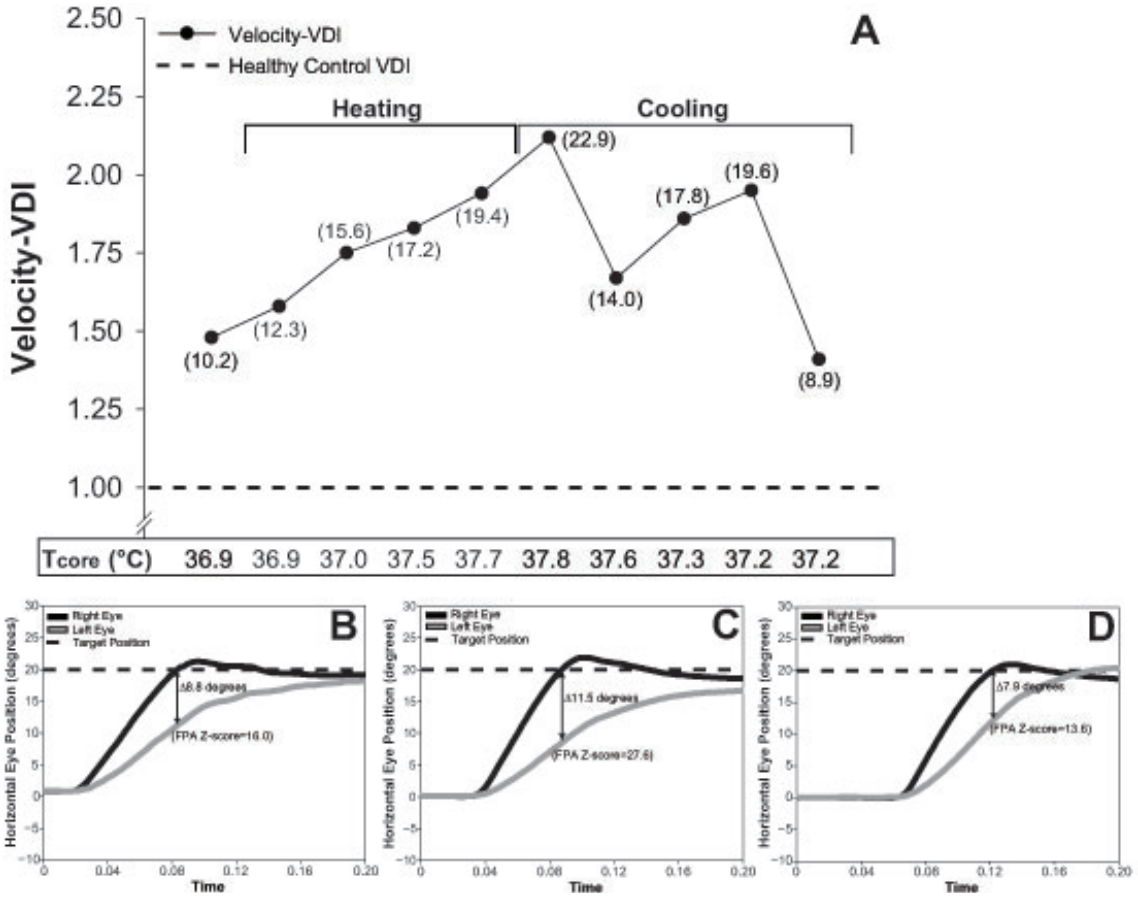

Figure 2. Dynamic and reversible changes in INO during heating and cooling. Here we show information on the velocity ratio of the abducting/adducting eye, known as the VDI during horizontal saccades, triggered by random LED illumination at 20° to the right or left. Normally the VDI ratio for velocity, acceleration, and amplitude will approximate unity, as synchronized eye movements are important to achieve retinal foveation, binocular fusion, and stereopsis. The data shown are derived from our MS patient with INO. Note that as core body temperature increases, there is a corresponding increase (worsening of dysconjugacy) in the VDI-velocity (as well as an increase in the VDI-velocity *Z*-scores; in parentheses at each 10-min eye movement recording epoch). Note that after the transition from heating to cooling, that the VDI-velocity improves (reduced toward baseline values). In fact, the panels below depict binocular eye movement waveforms for baseline (left), with peak heating (center), and upon core body cooling (right). Note that following cooling, the level of interocular dysconjugacy is actually improved compared to baseline, preheating levels. Preemptive cooling may therefore provide some period of mitigation in the dysconjugacy associated with INO. This effect would have ramifications on driving, walking, reading, and other activities of daily living that are contingent upon the coordination of eye movement synchrony. In C we show the effects of heating and cooling on a population of normal subjects, MS patients without INO, and MS patients with INO. From Davis et al.[8] INO, internuclear ophthalmoparesis; VDI, versional dysconjugacy index.

Table 1. Consequences of deconditioning.

Psychological	Cognition	Physical
Psychological stress	Reduced cognitive vigilence	Reduced exercise tolerance
Anxiety disorder	Depression and its effect on cognition	Reduced heat tolerance
Panic	Slowing in information processing speed	Reduced strength with impact upon safety and ADLs
Fulfillment of self fulfilling prophesies		Altered balance mechanisms and compromised "righting" reflexes
Psychosocial impact upon family and relationships		Agonist Antagonist mismatching with tendon shortening leading to pain and energy inefficiency
Social isolation		Reduced bone density with increased risk of fracture
Depression and hopelessness		Chronic fatigue
Demoralization		
Lowered self esteem		
Loss of gainful employment		
Lowered self control and independence		
Suicidal ideation		

Suggested readings: references.[20-26]

adjustments, to walk quite effortlessly in water.[11] The magnitude of ground reaction and impact forces are smaller in water compared to dry land.[12–14] Although the range of motion in the lower extremity joints is similar to that on dry land, aquatic locomotion allows more hip and knee flexion, stability of stance, as well as ankle neutrality, enabling foot clearance during the swing phase.[11,13,15]

In MS, aquatic exercises have been shown to improve muscle strength.[16] Pain, decreased joint mobility, and osteoarthritis are frequently encountered problems in MS patients. Buoyancy in water decreases the loading on joints, and aquatic exercises are effective forms of activity in patients with these symptoms.

It is important to remember that since swimming is a non-weight-bearing aerobic exercise, it is associated with an increase in lean body mass, but without positive effects on bone density. Both prospective and cross-sectional studies in athletes show no benefit in bone density among swimmers.[17] This is unsurprising since Wolff's rule of bone density states that in healthy subjects, bone will respond over time to the stress that it is placed under.

Strength training exercises may also be used in aquatic therapy, taking advantage of the viscosity (i.e., viscous drag) of the water as a resistance medium. Limbs moving through water are subject to such "drag" forces that provide a resistance against the intended movement; making aquatic exercise routines a bona fide form of resistance training.

In addition to the beneficial effects of buoyancy and viscosity of water, the *thermal properties of water may be the most important factor for aquatic exercise in MS patients*. Water can conduct heat 25 times faster than air. While the potential benefits of several cooling strategies prior to and following exercise in MS patients have been previously discussed, aquatic exercise in a cool pool is a cooling strategy to limit heat sensitivity that can be employed *during* exercise with the added benefits of buoyancy and viscosity as discussed above.

Most community pools control temperature between 80 and 88°F, which is ideal for heat transfer during aquatic exercise in MS, however, each individual patient with MS, must identify their own particular "comfort zone" with respect to water temperature.

Benefits of Aquatic Exercises for Multiple Sclerosis

As mentioned above, there are three cardinal principles that support the benefits of aquatic therapy (Table 3) for patients with MS:

1 Buoyancy
   a Feeling lighter
      i Immersion to the pubic symphysis offloads ~40% of a person's body weight; immersion to the xiphoid offloads ~60% of the person's body weight. With neck deep immersion, about 15 lb of compressive force (the approximate weight of your head) is applied to the spine, hips, and knees.
      ii Allows for muscle relaxation due to less force being generated
      iii More movement with less energy exertion due to weight reduction of the body within the buoyant environment.

2 Viscosity – refers to the amount of internal friction that is specific to a fluid in motion
   a Water resistance can be used to build strength
   b Reduced speed of movement in water allows emphasis of proprioceptive and spatial awareness with reduced risk of injury
   c The resistive movement in water against the velocity of the body or body part in motion is called "drag force"

Table 2. Aquatic therapy studies in MS.

Study	Type of study	No. of subjects	Type and duration of exercise	Results
Gehlsen et al.[16]	Uncontrolled nonrandomized	10 relapsing remitting MS pts	10-week exercise program consisting of freestyle swimming and shallow water calisthenics	The results of this investigation indicated that individuals with MS who participated in a program of aquatic exercise were able to overcome some of the neuromuscular deficits characteristic of the disease process
Roehrs and Karst[18]	Uncontrolled nonrandomized	31 progressive MS patients	12 weeks for a 1-h session 2 times per week	Significant improvements in the QoL domains of social functioning and fatigue were found for the exercise participants
Salem et al.[19]	Uncontrolled nonrandomized	11 MS pts	5-week community-based aquatic exercise program. Aquatic exercises were held twice weekly for 60 min and included aerobic exercises, strength training, flexibility exercises, balance training and walking activities	Analysis of the scores demonstrated improved gait speed, BBS, TUG test and grip strength
Kargarfard et al.[20]	Randomized controlled trial	32 Women diagnosed with relapsing-remitting MS	8 weeks supervised aquatic exercise in a swimming pool (3 times a week, each session lasting 60 min)	Patients in the aquatic exercise group showed significant improvements in fatigue and subscores of HRQOL after 4 and 8 weeks compared with the control group
Bansi et al.[22]	Randomized controlled clinical trial	60 MS patients	3 week endurance training conducted on a cycle ergometer or an aquatic bike	This study indicates that aquatic training activates brain-derived neurotrophic factor (BDNF) regulation and can be an effective training method during rehabilitation in MS patients

3 Thermodynamics – the heat capacity of water is 1000 greater than the equivalent amount of air.

   a Water transfers heat 25 times faster than air. Therefore, water retains heat or cold quickly when the body part(s) is/are immersed

Evidence-Based Support for Aquatic Therapy in Multiple Sclerosis

Gehlsen and colleagues in 1984 demonstrated positive increases in muscular strength, reduced fatigue, in conjunction with improved work performance and power following 10 weeks of aquatic exercise that included freestyle swimming and calisthenics (Table 2).[16] Exercises were performed three times per week for 1 h at ~60% of maximum effort in water at a temperature range of 25–27.5°C. Roehrs and Karst showed positive improvements in fatigue in progressive MS patients (both primary and secondary) following 12 weeks of aquatic exercise performed twice a week for 1 h.[18] Another study observed improved motor function (balance and gait speed) following 5 weeks of a community-based aquatic exercise program.[19]

A randomized, controlled trial of aquatic therapy performed over 8 weeks compared two groups of MS patients; a control not assigned to therapy, and an aquatic exercise group. Exercises were performed three times per week for 60 min per session, at 50–75% of maximum effort, in water at a temperature of 28–30°C under supervised and controlled conditions. The group performing aquatic exercise demonstrated improvement in quality of life and reduction in fatigue.[20] More recently, Marandi and colleagues showed increases in dynamic balance following 12 weeks of aquatic exercise three times per week for 60 min per session.[21]

Molecular Immunology of Physical Fitness

Physical fitness has demonstrated up-regulation of TH2 (i.e., immunoregulatory) cytokines and brain-derived neurotropic factors (BDNF). An increased amount of BDNF is associated with improved neuroplasticity; an observation potentially germane to the optimization of neurorehabilitation strategies. A recent paper compared two groups of patients with MS in a 3-week endurance program. One group performed land-based exercises, while the other engaged in an aquatic exercise program. Both groups exercised 30 min daily with a target of ~70% of their individually ascertained maximum heart rate. Training programs were consistent and similar in both groups. The group that exercised in the water demonstrated a significant increase in the levels of BDNF in

Table 3. Benefits of aquatic therapy for patients with MS.

Benefits	Risks	Special considerations
Buoyancy helps patients avoid the ballistic pounding of training on land A lower to upper body shift in venous blood distribution, promotes improved efficiency to modify cardiac output in response to a heat, exercise, or infectious stress, when rapid modifications are necessary in order to ensure physiologic response characteristics that are commensurate with the body's escalated metabolic requirements (i.e., demand) Training in water provides surface cooling that is immediate and is an important adaptation for MS patients who have compromised sweating responses to a heat stress (including exercise) Cardiovascular conditioning Improved oxygen utilization and improved supply:demand matching Improved stretching and thereby musculo-tendon lengthening Postural/Core stability Resistance training of most important muscle groups Promotes independence and self control	Beware of Uhthoff's Falls while getting into or out of the pool	Inquire about "open" swim pool access such that the MS Patient has access to a working area adjacent to the pool wall If heat intolerant, identify local pools where the local school swim teams train, as these aquatic facilities maintain cooler water temperatures (80–84°F) Particularly at the start of a new exercise routine, being accompanied by a friend or family member is an important safety factor

response to the cardiopulmonary exercise test. Alternately, there was an absence of a significant increase of BDNF in the land-based exercise group.[22]

Coupling these findings with evidence that improvements in conditioning fitness are comparable to those achieved with land-based exercise regimens, aquatic therapy training may serve to enhance ADLs, promote general conditioning and improved exercise tolerance, facilitate strength and righting reflexes, all conducted within a highly safe, buoyant, and efficient thermal transfer medium, while reducing, or even eliminating, the risk of Uhthoff's phenomenon.

Conclusions

There are innumerable exercise programs capable of promoting a wide variety of benefits in our MS patients, which range from routines focused upon stretching and range of motion, cardiovascular regimens aimed at enhancing exercise tolerance and endurance, efficient oxygen consumption (a dividend of cardio-pulmonary training which has ramifications on the utilization of energy stores, and more efficient energy consumption), resistance training to promote muscle strength (associated with the intended or unintended effect of augmenting muscle bulk).[23–29]

In contrast to training on land, aquatic therapy provides for an ideal medium within which our MS patients can exercise, while simultaneously providing near instantaneous and diffuse body surface cooling (Table 3). This particular attribute of the aquatic environment, at least partially replaces sweating (which we now know is reduced in most MS patients) as a thermoregulatory strategy, aimed at reducing the risk of core body temperature escalation, which in the context of demyelination, can quickly achieve threshold for closing the axonally distributed sodium channel pores, thereby abolishing the action potential. Further, the properties of buoyancy produce additional benefits such as a reduced fall and fracture risk, while promoting more efficient venous return (in buoyancy there is a lower to upper body shift in the venous compartment distribution, along with reduced hydrostatic leg and pedal edema), with an associated reduction in orthostasis; a common problem in MS; and one which is at least partly explained by the recently characterized deficits in the sympathetic nervous system reflexes; those that serve to promote venous return through the portal circulation to the right heart, in order to maintain cardiac output.

A number of training exercises can be performed easily, and without any equipment whatsoever. Access to a pool of any size, where the MS patient can safely enter is the first precondition for any aquatic therapy program. Once within the water environment, all the proposed routines can be performed in a very small area (as little as 8 ft x 8 ft), in close proximity to the sidewall (which will be used both for safety and stabilization purposes, when executing specific routines that isolate the use of specific body parts). [See Videos 1–14 and still photographs on line in the Supporting Information materials, which

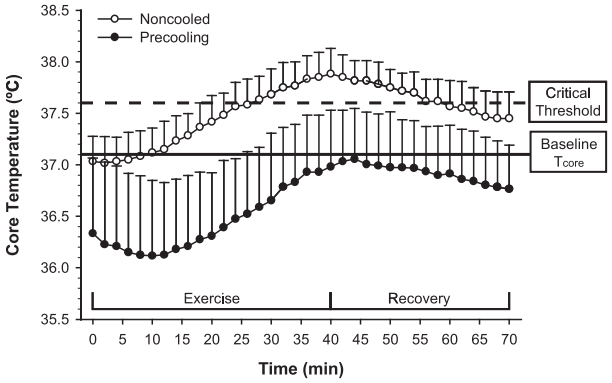

Figure 3. Autonomic failure in MS. In this figure we present objective data supporting the contention that precooling before exercise provides a significant benefit in reducing the rate of rise in core body temperature; thereby attenuating the emergence of Uhthoff's phenomenon. The graph depicts the core temperature rise at baseline, during exercise, and subsequently during the recovery period. Note that with precooling, the baseline temperature is lower than that condition where no precooling was employed. During the exercise phase of the study, note the highly conspicuous divergence in the core temperature elevation plots across the two conditions. This divergence is maintained throughout both the exercise and recovery periods of the two experimental condition from the same patient. The condition without precooling, exhibits a greater baseline, peak, and recovery core temperature, making the MS patient under these circumstances more likely to experience Uhthoff's phenomenon, with conduction slowing or even block along central nervous system (CNS) tract systems that harbor demyelination. From Davis et al.[2]

demonstrate a broad diversity of aquatic exercises that were prepared for this manuscript].

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Author Contributions

Ashley Frohman, BS was involved in the formulation, design, and execution of the photography, video production, narration, and drafting of the manuscript. Darin Okuda, MD was involved in the execution of the photography, video production, and drafting and revision of the manuscript. Shin Beh, MD was involved in the drafting, editing, and revision of the manuscript. Katherine Treadaway, LSW was involved in the execution of the photography, video production, and drafting and revision of the manuscript. Caroline Mooi, LSW was involved in the execution of the photography, video production, and drafting and revision of the manuscript. Scott Davis, PhD was involved in the drafting, editing, and revision of the manuscript. Anjali Shah, MD was involved in the drafting, editing, and revision of the manuscript. Teresa Frohman, PA-C was involved in the formulation, design, and execution of the photography, video production, narration, drafting of the manuscript, and is co-senior author on the manuscript. Elliot Frohman, MD, PhD was involved in the formulation, design, and execution of the photography, video production, narration, drafting of the manuscript, and is co-senior and corresponding author on the manuscript. All co-authors contributed to the preparation, editing, and revision of the manuscript.

Conflict of Interest

Darin Okuda, MD received personal compensation for consulting, advisory board, and speaking activities from Biogen and Genzyme/Sanofi-Aventis. He has received speaker fees from Acorda Therapeutics and has been compensated for advisory board and speaking activities for TEVA. Katherine Treadaway, LCSW has received speaker fees from Genzyme. Caroline Mooi, LMSW has received speaker fees from Genzyme. Elliot Frohman, MD, PhD has received speaker and consulting fees from Genzyme, Novartis, Acorda, and TEVA. Teresa Frohman, PA-C has received speaker and consulting fees from Genzyme, Novartis, Acorda, and TEVA. The following authors have nothing to disclose: Ashley Frohman, BS, Scott Davis, PhD, Shin Beh, MD, Anjali Shah, MD.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Video S1. Groin adductor stretching.
Video S2. Hip abductor/adductor resistance training.
Video S3. Hamstring stretch.
Video S4. Dynamic and fixed quadriceps (Quads) stretching.
Video S5. Core-muscle-complex training.
Video S6. Hand-finger-intrinsic muscle-complex training.
Video S7. Shoulder-chest side swiping.
Video S8. Shoulder-chest bilateral swiping.
Video S9. Arm flexion-extension.
Video S10. Arm extensor "push-downs".
Video S11. Bicep curls.
Video S12. Prone kicking.
Video S13. Hip flexor cycling.
Video S14. Jogging in place.

