Brief review

Premature skeletal muscle fatigue in multiple sclerosis and its implications for exercise therapy

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Abstract:
This paper reviews work on skeletal muscle fatigue as it relates to multiple sclerosis. Accumulation of products of metabolism contribute significantly to the onset of fatigue in normal healthy muscles whereas the primary cause of muscle fatigue in multiple sclerosis is due to impairment of central nervous system activation of motor units followed by changes in muscle metabolism due to progressive disuse. As performing repetitive gross
motor activity of the limbs becomes increasingly difficult, the MS individual becomes vulnerable to a host of secondary health concerns including weak respiratory muscles. Pranayam is a type of yogic exercise that focuses one’s attention on regulation of the breath. Many of the benefits of practicing pranayam are similar to the physiological and psychological benefits attributed to performing repetitive gross motor exercises of the limbs. Pranayam should be explored as a potential adjunctive therapeutic exercise modality in individuals with multiple sclerosis.

**List of abbreviations:**
- ADP: adenosine diphosphate
- ATP: adenosine triphosphate
- CMAP: compound muscle action potential
- CNS: central nervous system
- EMG: electromyography
- e-stim: electrical stimulation
- $\text{H}^+$: hydrogen ion
- $\text{H}_2\text{PO}_4^-$: monovalent phosphate
- iEMG: integrated electromyogram
- MRS: magnetic resonance spectroscopy
- MS: multiple sclerosis
- MVC: maximal voluntary contraction
- PCr: phosphocreatine
- Pi: inorganic phosphate

**1. Introduction:**

Multiple sclerosis (MS) is an autoimmune disease characterized by progressive demyelination of the central nervous system (CNS). In the course of the disease, demyelination occurs sporadically throughout the CNS leaving areas of non-functional scar tissue in place of the myelin sheath. Eventually neural transmission is severely compromised and symptoms of MS can be traced to areas of damage in the spinal cord, brain stem, cerebellum, optic nerve, and cerebral cortex [1]. As the disease advances, obvious symptoms of the disease include loss of muscle tone and strength, gait and postural disturbances, and difficulties with speech and visual tracking. Less obvious symptoms include sensory abnormalities, mood disturbances, fatigue and cognitive impairment [2]. Progressive inactivity becomes a typical feature of MS individuals. This results in progressive deconditioning of skeletal and cardiac muscle [3] – which, eventually, may affect respiration, blood and lymphatic flow, and digestive and elimination processes, as well as mood and sleep [4-10].

The general loss of control of musculoskeletal and body functions experienced by those with MS can be attributed, in part, to premature muscle fatigue [11, 12]. Research into this phenomenon was quite active in the last decade. Traditionally, muscle fatigue is defined as the reduction in the ability of the neuromuscular system to generate a required force during sustained or repeated contractions [13]. Essentially, it refers to the immediate sensation of fatigue in a localized group of muscles while performing repetitive contractions, such as in sprinting, weightlifting, or playing a musical instrument. It is a temporary and reversible phenomenon.

Much of the early research on muscle fatigue revolved around developing the best methods to measure the various possible components involved in the onset of this phenomenon. Eventually, with appropriate technology, a pattern of fatigue in normal healthy muscle was worked out [14 -17]. With this established, the logical progression of events was to move toward the investigation of the phenomenon of muscle fatigue in individuals with neuromuscular disorders.
The purpose of this paper is to review literature on muscular fatigue as it relates to MS. The review will begin with a general description of common, non-invasive methods of testing for skeletal muscle fatigue as well as a discussion of the findings in normal muscle. Following this will be a presentation of some of the most significant research findings in the area of muscle fatigue in individuals with MS. The implications of these results will then be discussed in light of the current research in exercise. Finally, pranayam, a type of yogic breathing exercise, will be introduced as a potential therapeutic exercise modality.

1.1 Noninvasive muscle testing techniques:

Force generation by skeletal muscle requires an intact sequence of events initiated in the CNS progressing to the depolarization of the muscle fiber and subsequent interaction of contractile proteins [16], and terminating in force production. Fatigue may result from impaired activation of neurons, impaired neuromuscular transmission, and or metabolic inhibition of the contractile process, or altered calcium kinetics [18, 19]. There are a variety of non-invasive techniques to determine to what degree each one of these steps is involved in the onset of skeletal muscle fatigue. Though invasive techniques have been used, non-invasive measures are preferred because data often need to be recorded continuously throughout the fatigue protocol.

The use of electromyography (EMG) in combination with measurements of force has been popular for many years. EMG can be combined with electrostimulation (e-stim) to determine if the onset of fatigue is due to central or peripheral mechanisms [13, 15]. Fatigue protocols have also included the use of magnetic resonance spectroscopy (MRS) to monitor energy metabolism in muscle [20]. This non-invasive technique has contributed significantly to our understanding of metabolic concomitants of muscle fatigue. Thus, it has become common to employ a combination of EMG, e-stim, and MRS in investigations of muscular fatigue.

Though other muscles have been used, many of the recent studies of muscle fatigue employ the tibialis anterior muscle – a dorsiflexor of the foot. This muscle is easily accessible, contains a relatively consistent mixture of fiber types [1, 16], and the limb is relatively easy to stabilize. The leg is usually placed in an apparatus that stabilizes the lower leg, so that movement in the synergistic and antagonistic muscles is restricted throughout the exercise protocol. The foot is tightly strapped to a foot plate which is attached to a force transducer.

Fatigue protocols may vary between studies. Some may employ a series of intermittent isometric contractions using incremental increases in force, and others may use a single sustained contraction at maximal voluntary force. Contractions are produced either voluntarily or through electrical stimulation of the muscle, depending on the needs of the researchers. In general, isometric contractions are the most useful because little to no movement occurs at the joint, thus minimizing the amount of noise picked up by the electrodes. EMG electrodes and the MRS surface coil are placed on the belly of the muscle, and stimulating electrodes are placed on the peroneal nerve [13, 18].

1.1A Electromyography (EMG):

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EMG is the study of the electrical activity of muscle. The technique is based on the transference of bioelectrical charges in the motor unit to an electrical current on electrodes placed either on the surface of the muscle, or inserted directly into the muscle. EMG activity is displayed and saved on a personal computer. Once recorded, the activity can be analyzed in a variety of ways according to the needs and interest of researchers. A common data reduction technique is the integration of the raw EMG signal (iEMG). This procedure involves the calculation of the area under the raw or rectified EMG signal. This can either be done continuously during the total time of muscular activity, or during specific intervals of time to represent the EMG amplitude in that time period [13, 15, 21].

An initial increase in iEMG activity will be seen as the force of the muscle contraction intensifies. At this time new motor units are recruited and/or the frequency of firing of the active motor units will increase to maintain the required force output [22]. Eventually, as maximal voluntary contraction (MVC) force is approached, there will be no more motor units available for recruitment, and the frequency of firing will have reached a peak. This may be followed by a substantial decrease in recruitment of motor units and / or decreased rates of neural firing. If either or both were to occur, the force generated would decline substantially. This event would be classified as failure of central activation [15, 18].

A supramaximal train of stimuli superimposed during a 3-4 second MVC, at the time of onset of fatigue, can be administered to test if failure of central activation contributes to the decline in force. If force production during MVC increases with superimposition of electrical stimuli, it suggests failure of CNS activation is the cause of fatigue. Comparing the reduction of MVC during fatigue protocols using both voluntary and electrically stimulated contractions can also reveal whether fatigue is due to central or peripheral mechanisms. If the reduction in force produced during electrically stimulated and voluntary contractions is similar, then, it suggests fatigue is due to a mechanism distal to the point of electrical stimulation (‘peripheral fatigue’). Yet, if MVC drops significantly below force elicited by electrical stimulation, failure of CNS activation is likely. Monitoring differences in the rate of force development between voluntary contractions and those produced by electrical stimulation can also help determine the site of origin of fatigue [15, 18].

Peripheral mechanisms implicated in fatigue include efficacy of neuromuscular transmission, excitability of skeletal muscle membrane, and excitation-contraction coupling (ECC). A single stimulus is often given to obtain measures of the compound muscle action potential (CMAP) and twitch force prior to performing the fatigue protocol. The CMAP is a measure of both the transmission of the electrical signal sent from the CNS across the neuromuscular junction and the excitability of the muscle fiber membrane [15]. This same protocol is often repeated at the termination of the exercise protocol. If the amplitude of CMAP decreases significantly, it suggests a decline in transmission across the neuromuscular junction and excitability of the muscle membrane. A reduction in twitch force with no change in CMAP suggests a decline in the efficacy of ECC. Failure in ECC mechanisms would also be indicated by the combination of a slowing of electrically-stimulated force production and slow or incomplete recovery of force production following exercise [18, 19]. Reduction in iEMG and MVC with little change in the amplitude of CMAP reflects failure of central activation [15, 18]. In contrast, when a
reduction in MVC is accompanied by little change in iEMG and amplitude of CMAP, fatigue is likely due to a
decrease in the efficacy of excitation-contraction coupling and metabolic events occurring within the muscle cell
[15, 21].

1.1B Magnetic resonance spectroscopy (MRS):
This technique allows relative concentrations of metabolites to be estimated through the use of radiofrequency
waves transmitted through a nonmagnetic coil placed on the belly of the test muscle, while simultaneously
recording EMG. It requires that the limb be placed within a superconducting magnet with the belly of the muscle
and the coil in the isocenter of the magnet. Radiofrequency waves are then transmitted to the spectrometer
where they appear as a series of peaks. Each compound studied can be identified by its unique location on the x-
axis, and its relative concentration can be determined by measuring the area under its peak. Each spectrum is
usually an average over time, and the time over which data is acquired may vary between protocols. Spectra
obtained during a prolonged exercise protocol can then be stacked to observe changes in concentration of
metabolites over time [17, 20].

Muscle contraction requires the hydrolysis of ATP and subsequently rapid rephosphorylation of ADP to ATP
by phosphocreatine (PCr). During contraction of a normal healthy muscle, as ATP is hydrolyzed, there will be an
increase in the peak of inorganic phosphate (Pi), and the concentration of PCr will decrease as ADP is
rephosphorylated. ATP concentrations remain relatively constant except during intense exercise. Normally, ADP
levels are too low to be visible in the spectra. Therefore, it is common to express the metabolites as a ratio of Pi
to PCr (Pi/PCr). Often, during repeated contractions, intracellular pH will decrease because of accumulation of
acid products of metabolism. This can be evaluated by measuring the distance between the Pi and PCr peaks.
Concurrent with the decrease in pH is an increase of hydrogen ions (H+), which have been shown to combine
with the free Pi forming monovalent phosphate (H₂PO₄⁻), levels of which can be determined from Pi and pH [20].

2. Fatigue in healthy muscle:
Numerous studies of muscle fatigue in healthy individuals have been performed throughout the second half of
the 20th century and into this decade. Results of these studies are variable largely because of the variation in
exercise protocols, the muscle tested, and choice of data gathering and analysis techniques [13, 16, 20, 21].
A series of elegant studies from the University of California, San Francisco, using EMG, e-stim, and MRS were
able to sketch out a general sequence of events that result in muscle fatigue. An initial concern revolved around
the issue of the muscle tested and exercise protocol. Weiner, Moussavi, Baker et al. [17] set out to determine if
the relationship between the muscle metabolite response to fatigue protocols differed between types of muscles
studied or fatigue exercise. They compared results of both aerobic and anaerobic fatigue protocols of the
somewhat fatigue resistant tibialis anterior muscle to similar data from the easily fatigable adductor pollicis
brevis muscle. Though, as suspected, there was a significant difference in the time to fatigue in both muscles,
there was a consistent relationship between MVC, changes in metabolites, and fatigue – regardless of exercise
conditions. Accumulation of both H\(^+\) and H\(_2\)PO\(_4\) were implicated in the development of muscle fatigue. However, more recent work that combined EMG and MRS suggests that fatigue due to high-intensity short term (anaerobic) exercise is likely precipitated by accumulation of metabolites in muscle, whereas central mechanisms may contribute to fatigue experienced during prolonged submaximal activation of muscle (i.e., aerobic conditions) [20].

Kent-Braun, Miller, and Weiner [14] were able to map out the sequence of metabolic events that occur during the transition from rest to fatigue in an isometrically exercised muscle. Data from this study suggests that there are three phases of metabolism that occur during progressive exercise to fatigue. The first phase, when exercise remained submaximal, showed a steady increase in the Pi/PCr ratio with little to no change in H\(^+\) concentration in muscle. This suggests that during this early phase, oxidative metabolic processes predominate, and stores of ATP are readily replenished. As exercise became more intense, a sharp increase in the Pi/PCr ratio and loss of the steady-state condition was observed (this is the second phase). Yet, no increase in H\(^+\) concentration or significant fatigue was found during this phase. The authors suspected that the need for greater force production, at this time, triggered a shift from type I muscle fiber activity toward greater recruitment of type II muscle fibers. The third phase started soon after the onset of the second phase with a sharp rise in H\(^+\) concentrations. A significant decline in MVC seems to have occurred at about the same time, suggesting that the primary source of energy was from glycolytic metabolic activity and that the resultant accumulation of intracellular metabolites was the primary cause of fatigue.

Taking this another step further, Kent-Braun [18] proposed that metabolites such as Pi, H\(^+\) and the subsequently produced H\(_2\)PO\(_4\) which accumulate during this third phase interfere with the contractile process. Of these metabolites, they found that H\(^+\) accumulation was most closely related to the decline in force typical of fatigue particularly when force production dropped below 60% of maximal force. This was illustrated by a strong linear association between and iEMG and pH \((r = 0.95)\), yet Pi and H\(_2\)PO\(_4\) plateaus as force continued to fall. A strong, yet non-linear, association between the iEMG activity and change in force production \((r = 0.92)\) was also seen in this study. This coupled with no reduction in CMAP suggests a role of central indices in fatigue as well. These results were consistent with previous data that linked excessive H\(^+\) accumulation to altered central motor drive during a fatigue protocol. The authors conclude that though peripheral factors contribute greatly to fatigue, there is a strong possibility that feedback loops between metabolites in muscle and central activation exist.

**Summary:**
In summary, it appears that regardless of the muscle and the exercise protocol used, the accumulation of intracellular metabolites contributes significantly to the onset of fatigue. Yet, there may also be feedback loops from the periphery to the CNS that could result in reduced central activation. Perhaps, in short, intense exercise protocols where anaerobic conditions predominate, rapid accumulation of metabolites results in failure of the contractile mechanisms before these feedback loops are utilized. Whereas, during sustained exercise protocols
where aerobic conditions predominate, progressive changes in central factors such as firing rates and recruitment of motor units may contribute to fatigue. Subsequent metabolic accumulation may also be slow enough to activate feedback loops that further affect central activation factors, eventually causing complete failure of the contractile mechanism.

3. Fatigue in MS:
A common problem in individuals with MS is the rapid onset of muscle fatigue during sustained or repeated muscle contraction. Ultimately, this phenomenon is a result of progressive demyelination of neurons in the CNS. Initially, fatigue can be just an irritating annoyance to the individual; yet, as the disease progresses physical activity can become severely restricted, so much so, that even performing normal everyday activities can become difficult. Inactivity can lead to a host of secondary phenomena, both physical and psychological, and eventually further deterioration in quality of life [3, 8, 11, 23, 24]

3.1. Origin of fatigue in MS:
Early investigation into the phenomenon of fatigue in MS assumed that the primary cause of fatigue was due to central defects [12]. Yet, the question remained as to whether secondary changes in muscle might be contributing significantly to the fatigue experienced by these individuals. In order to bypass central mechanisms, the effects of nine minutes of intermittent supramaximal tetanic stimulation of the peroneal nerve on intermittent isometric contractions of the tibialis anterior muscle were studied. Fatigue occurred earlier in individuals with MS compared to healthy controls. Also, decreases in muscle PCr and pH were greater in subjects than controls at the time of fatigue. Both muscle fiber relaxation after tetanic stimulation, and recovery of maximum force after the protocol took significantly longer in individuals with MS than in controls. No decrement in CMAP amplitude was found from pre-exercise values or between the first and last evoked potential of each train of stimuli, indicating that there was no impairment of neuromuscular transmission. Taken together, these results suggest that the origin of fatigue in this experimental situation may be due to decreased efficacy of excitation-contraction coupling, contractility, or metabolic changes in muscle secondary to disuse.

Results of these earlier investigations using tetanic stimulation raised the question as to the cause of fatigue during voluntary exercise. Using similar measures, Kent-Braun, Sharma, Miller et al. [11] had subjects mildly impaired with MS and controls perform intermittent, incremental, isometric contractions of the tibialis anterior to fatigue. The overall change in Pi/PCr was less pronounced in those with MS compared to controls, and pH was unchanged. Yet, they found that fatigue occurred sooner in individuals with MS, but the extent of fatigue was not greater in individuals with MS compared to controls. This suggests that accumulation of metabolites was not a significant contributor to fatigue in this group.

The authors ruled out the possibility that two fiber pools (one active, the other inactive) might be responsible for the minimal change in the metabolites as a result of the exercise protocol through further analysis of the Pi peaks. ‘Splitting” of the Pi peaks, which would indicate the possibility of two fiber pools, was not present. This
was further supported by the fact that pH remained stable throughout the protocol. Results of previous studies using fatigue protocols on this population also ruled out the possibility that individuals with MS had a greater capacity for oxidative metabolism than controls. Together this information led the authors to conclude that all fibers participated in the protocol, yet their activation was attenuated, and that the development of fatigue in voluntary exercise is largely due to central activation failure.

It was suggested that as a result of this attenuation, maximal voluntary firing frequencies of motor units are reduced. This may require an unaccustomedly high tetanic stimulus frequency during fatiguing protocols, which might result in greater fatigue and metabolic responses. If so, this might explain the discrepancy in results seen in this study using voluntary contraction, as compared to those using tetanic stimulation.

### 3.2 Central motor drive in MS:

Impaired activation of motor units was still suspected in individuals with MS [26]. In either case, reduced firing rates or poor activation of motor units might require an increase in central motor drive to elicit a desired force. Chronic increases in central motor drive, even for low-intensity activities, may result in symptoms of perceived fatigue. If so, this might explain the persistent feeling of fatigue experienced by so many with MS. Ng, Miller, and Kent-Braun [27] compared the iEMG / force relationship in patients with MS and control subjects performing a series of non-fatiguing contractions of the tibialis anterior. They found that individuals with MS had significantly increased iEMG activity, at all relative force levels, compared to controls. This suggests that the components of motor drive are necessarily reorganized in MS in order to achieve the same desired force, as controls. It is difficult to discern the exact nature of this reorganization because iEMG reflects both motor unit recruitment and firing rates. The authors speculate that the increase in central motor drive, seen in this study, may reflect compensations in motor unit recruitment for reduction in voluntary firing rates, as increased motor unit recruitment has been shown to result in increased iEMG /force relationship [28].

There was no significant difference in motor drive between spastic and non-spastic individuals, yet for both MS groups severity of the disease as measured by the Expanded Disability Status Scale (EDSS) was highly correlated with the iEMG/force slope (r = -0.87), suggesting that central motor drive, at a given force, becomes more excessive as the disease becomes more severe. No measures of symptomatic fatigue were taken in this study.

### 3.3 Deconditioning in MS:

As research progressed, it appeared that the primary cause of muscle fatigue in individuals with MS is due to defects in central activation which results in secondary changes in the muscle that aggravate the situation. One way to assess the condition of a muscle is to measure its oxidative capacity, which reflects the muscle fibers' ability to resynthesize PCr. The rapid resynthesis of PCr is an important rate limiting factor in the generation of ATP and, hence, the ability to recover after exercise. It is well known that detraining results in a rapid decline in the activity of oxidative enzymes as well as a decrease in the pool of type I (oxidative) fibers [29]. In order to
determine the degree of impairment of oxidative capacity in individuals with mild to moderate MS, Kent-Braun, Sharma, Miller, et al. [11] measured PCr resynthesis in muscle during and after fatiguing exercise. The exercise protocol consisted of nine minutes of intermittent isometric tetanic contractions of the tibialis anterior. Though the level of fatigue and metabolic changes during exercise were similar in both individuals with MS and controls, PCr resynthesis was significantly slower in patients with MS, confirming reduced oxidative capacity in these individuals. In addition to metabolic measures, they observed a trend toward a moderate correlation of frequency of rapid foot taps performed in 10 seconds (a measure of CNS impairment) to PCr recovery rates. Pre-testing evaluation also confirmed that average daily physical activity was less in those with MS than controls. Together these data suggest that impaired muscle metabolism in MS is at least in part due to disuse.

Subsequently, skeletal muscle function, biochemistry, and morphology were assessed through biopsies of the tibialis anterior muscle of individuals with moderate MS [24]. Results confirm that muscle atrophy is prevalent in individuals with MS. Muscle fiber size was markedly smaller, resulting in reduced whole muscle volume and weight. Fewer type I (oxidative) fibers were found, compared to controls, explaining the reduced ability to sustain force; the activity of oxidative enzymes was found to be reduced to levels close to those found in individuals with complete spinal cord transection. Yet, activity of glycolytic enzymes was not changed. This suggests that anaerobic metabolism may be the principal source of energy during muscular exercise in individuals with MS. Coupled with significant atrophy of muscle fibers, this could only perpetuate fatigue conditions. The authors observed, however, that these changes in muscle were similar to those found in detraining protocols, and therefore may be improved with exercise therapy.

### 3.4 Skeletal muscle fatigue vs. perceived fatigue:

In 1997, Kent-Braun et al. [24] reported a relationship between activity of oxidative enzymes in muscle and perceived symptomatic fatigue. Yet, previous measures of muscle fatigue and symptomatic fatigue did not correlate well [26]. Together, these results suggest that skeletal muscle detraining, due to progressive disuse, is not alone responsible for the overwhelming sensation of fatigue in individuals with MS, though it might contribute to it. It is likely that other CNS factors and factors secondary to progressive disuse of skeletal muscles are involved in symptomatic fatigue.

### Summary:

It appears that the primary cause of skeletal muscle fatigue during voluntary activity in individuals with MS is due to impairment of central activation. It is not easy to discern the exact nature of this impairment but it is possible that motor unit firing frequencies are reduced in MS, compensation for which results in increased motor unit recruitment at a given force. If this is the case, the rapid onset of muscle fatigue during sustained or repeated muscle contraction may be due, in part, to the unavailability of new motor units for recruitment. This alone may contribute significantly to decreased force production and should be explored further. Yet,
progressive disuse results in secondary changes to the metabolic milieu in muscle, which also contributes significantly to premature skeletal muscle fatigue experienced by those with MS.

It is possible that appropriate exercise therapy may alleviate some of the secondary changes seen in muscles in individuals with MS. Yet, studies of voluntary activity showed that the onset of fatigue preceded any metabolic changes. A conundrum persists. In order for training to occur, the individual must be able to put muscles to task [29]. How then can this be done as the disease progresses? Short of e-stim protocols, a somewhat invasive technique, the challenge is finding effective exercise therapy that can be consistently performed by individuals with MS, particularly as the disease advances.

3.5 Exercise in the management of multiple sclerosis:

Exercise is often recommended for the management of MS and exercise programming for those with MS has begun to flourish [30-33]. Yet, as the disease progresses, repetitive gross motor activity of the limbs becomes a problem for most [3]. The individual becomes vulnerable to a host of secondary health concerns as performing aerobic activities becomes progressively difficult [4, 5, 9]. Many pursue yoga and tai chi because these techniques emphasize gentle movement, stretch and balance [34-38]. These techniques, however, may not task the cardiovascular and respiratory systems enough to enhance the integrity of these systems [5, 33, 39].

Weak and ineffectual respiratory muscles often result in chronic respiratory infection and sometimes death [40]. Yet, in one study, respiratory muscles of individuals with MS responded positively to resistance training [41] and in another, to three months of individualized music/singing therapy [42]. Results of these studies are interesting in light of some recent investigations into the muscle structure and training effects of the diaphragm muscle that show rapid improvement in oxidative and antioxidant capacity as a result of exercise training [43]. Improved oxidative capacity results in enhanced muscle strength and overall muscle function which reduces peripheral fatigue [29].

This suggests that exercise that targets muscles of inspiration and expiration may be beneficial to individuals with MS. The physiological benefits of stronger respiratory functions may also include reduced feelings of fatigue and improved mood [5, 44, 45]. Regulated breathing has been found to enhance immune processes [46] and mood [47-51], in addition to improving respiratory and cardiovascular function [47, 51, 52].

3.6 Potential role of Pranayam as adjunctive therapeutic exercise:

One therapeutic modality that should be explored more seriously is pranayam (often spelled “pranayama” in English). Pranayam is a type of yoga training that focuses one’s attention on regulation of the breath. It is routed in yoga tradition and is an integral component of more advanced yoga practices. Derivation of ancient theory suggests that regular practice of pranayam can impart to the individual a plethora of physiological and psychological benefits because one consciously unites his or her breath with a universal life force [50, 53-55]. Modern science has found that regulation of the breath may actually contribute significantly to improving lung volumes, respiratory muscle strength, and cardiorespiratory autonomic control. This may benefit respiratory
Morbidity in MS is often the result of complications due to inactivity. Despite their best efforts, individuals with MS find that exercise becomes more difficult as the disease progresses, in part, because of the phenomenon known as premature muscle fatigue. All types of exercise should be encouraged [30-33]; yet, there may be activities that do not require gross motor movements of the limbs that provide benefits similar to those of exercise. Finding these activities poses a creative challenge to those in therapeutic recreation and research.

One modality that should be explored further is pranayam. The premise of pranayam is regulation of the breath. Various breathing techniques are sequenced for specific therapeutic effects. A host of research supports the link between regulation of the breath as a way to regulate physiologic and psychological health. Yet, it is not clear how this may play out in the MS population. Weak respiratory muscles are a known outcome of the disease; performing pranayam exercises would directly target this muscle group. Fatigue, depression, anxiety, cognitive deficits, and isolation are also characteristics of the disease, all of which affect overall quality of life. The right sequence of pranayam exercises may also alleviate some of these symptoms.

Pranayam literature is dense and should be looked at carefully before designing research protocols for those with MS. Research that does move forward in this area should start with well established pranayam sequences, and appropriate physiological and subjective measures that target specific symptoms of MS. Results of these
studies may lend to science a deeper understanding of the health benefits of pranayam, and also provide an additional therapeutic exercise option for those with MS and others with limited mobility.

**Conflict of interest:** none declared

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