Clinical Interventions in Aging

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PERSPECTIVES

# Reversal of Soleus Muscle Atrophy in Older Adults: A Non-Volitional Exercise Intervention for a Changing Climate

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**Abstract:** The World Health Organization recommends that older adults undertake at least 150 minutes of moderate intensity physical activity over the course of each week in order to maintain physical, mental, and social health. This goal turns out to be very difficult for most community dwelling older adults to achieve, due to both actual and perceived barriers. These barriers include personal health limitations, confinement issues, and self-imposed restrictions such as fear of injury. Climate change exacerbates the confinement issues and injury fears among the elderly. To assist older adults in obtaining the benefits of increased physical activity under increasingly challenging climate conditions, we propose a targeted non-volitional intervention which could serve as a complement to volitional physical activity. Exogenous neuro-muscular stimulation of the soleus muscles is a non-invasive intervention capable of significantly increasing cardiac output in sedentary individuals. Long-term daily use has been shown to improve sleep, reduce bone loss, and reverse age-related cognitive decline, all of which are significant health concerns for older adults. These outcomes support the potential benefit of exogenous neuro-muscular stimulation as a complementary form of physical activity which older adults may find convenient to incorporate into their daily life when traditional forms of exercise are difficult to achieve due to barriers to completing traditional physical activities as a result of in-home or in-bed confinement, perceptual risks, or real environmental risks such as those arising from climate change.

**Keywords:** cardiac output, neuro-muscular stimulation, resting metabolic rate, osteoporosis, cognitive aging

## Introduction

Reduced level of daily physical activity is a defining characteristic of modern life. This reduced demand for physical labor has significantly reduced risks of acute injuries among both young and old, but at the same time, reduced physical activity has increased the risk of acquiring a wide range of physical and mental health complications, including cardiovascular disease,[1] diabetes,[2] fall injury,[3] all-cause mortality,[4] and age related cognitive decline.[5] Lack of physical activity is of particular concern for the elderly due to the presence of co-morbidities. In the absence of close supervision, older adults do not generally follow through on recommendations to increase their physical activity levels above that required to complete activities of daily living.[6] In fact, one-half of older Americans engage in no leisure time aerobic activity at all, and only about one-quarter meet recommended weekly physical activity levels.[7]

Though cognizant of the long-term health issues associated with lack of regular exercise, real and perceived barriers to physical activities in daily life play a critical role in implementation. For example, while exercising in the home would seem a simple approach for increasing physical activity, numerous complications limit compliance. Exercise equipment can be expensive, difficult to use, and tends to occupy a large space within the residence, a significant issue for older adults who often live in relatively small homes or apartments. Further, in-home exercise equipment can be dangerous. Annually, over 20,000 emergency room visits result from in-home exercise equipment use, and older adults (over age 65) have a greater than 2.5-fold increased risk of hospitalization following an exercise injury, compared to younger adults.[8]

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Exercising outdoors does not reduce the activity risk profile. Undertaking a brisk walk outdoors during the winter months in the northern latitudes significantly increases risk of a serious injury. Similarly, in moderate climates, fall risk has been shown to increase as outdoor temperatures increase above 10°C.[9] Exercise in subtropical climates is particularly challenging due to the introduction of the increased risk of dehydration, cardiovascular events, heat stroke, and increased exposure to both UV and air pollutants. Consistent with these increased risks, outdoor exercise participation rates decline significantly as ambient temperatures rise in warm climates.[10] Exercising in a public facility reduces both environmental risk and equipment injury risk, but introduces the increased risk of exposure to an infectious disease.

Climate change is exacerbating many of these challenges which face older adults who are trying to obtain sufficient physical activity to maintain or improve their long-term health. The most obvious result of climate change is environmental warming, which has both indirect and direct effects on health. The main indirect effect is increased prevalence of infectious diseases resulting in greater self-isolation due to concerns over exposure.[11] Increased warming directly influences thermoregulation during exercise,[12] increasing the risk of organ failure. But it is the increase in extreme weather events which likely has the greater impact on the older population by creating environments where regular exercise becomes more difficult, while at the same time creating additional mental stress by making almost every aspect of daily living (transportation, shopping, meeting medical needs) more difficult. So, at a time when increased activity levels are becoming ever more important to maintain the physical and mental health of the older population, completing planned exercise activities is becoming ever more difficult to achieve.

The impact of climate change on physical activity raises the question of whether alternative activities could be safely, and conveniently, implemented by older adults in the home environment, and which provide the recommended daily energy expenditures. This is a challenge which has been partially addressed in the context of promoting physical activity among individuals restricted to bed rest, are home-restricted, or have limited mobility. Two approaches proposed for the immobile elderly include "full-body in-bed" exercise regimen[13] and neuro-muscular stimulation.[14] A "full-body in-bed" regimen is based on established post-hospitalization physical therapies, and involves a series of short-duration exercises which can be completed by an individual while lying or sitting on a bed. Both self-perceived psychophysical status and pain levels in older adults have been shown to be improved using this approach.[15]

In-bed exercises are limited in their ability to exercise the lower limb voluntary muscles, as well as the deep postural muscles of the body. Exogenous muscle stimulation can potentially address this limitation. Neuro-muscular electrical stimulation (NMES) is a muscle activation technique used to treat lower limb muscle atrophy. This approach requires the attachment of electrodes to the skin above the targeted muscles, with electrical current injected at intensity levels sufficient to activate those muscles. NMES has been applied to the retraining of leg muscles both in clinical and home settings. In a recent short-term study on hospitalized, post-surgery patients, vastus lateralis muscle size and strength were shown to be significantly increased following 90 minutes per day of NMES applied for four days.[16] However, three quarters of the subjects in the study found the stimulation to be uncomfortable. In an eight-week trial in the home setting, NMES was utilized to activate the quadriceps and calf muscles in middle-aged individuals with early heart failure. A one-hour per day stimulation protocol led to small increases in 6-minute walk distances but resulted in no significant improvements in whole-body metabolic activity.[17] Little research, to date, has addressed issues related to extended use of NMES on older adults in the home environment, so widespread application of this technology for community dwelling elderly has been limited.

## Intervention Concept

Building on these previously studied approaches, we propose that a convenient and readily accessible in-home exogenous stimulation intervention, which complements traditional exercise regimen, may be capable of significantly improving the health of older adults who face barriers in achieving recommended daily physical activity levels. Recent research has identified sedentary activity time (behavior requiring <1.5 METS of energy expenditure), as a significant predictor of metabolic risk (glycemic control, cardiovascular disease, all-cause mortality), independent of physical activity levels.[18] This observation leads to the concept of promoting behavior which significantly reduces sedentary activity time, that is, providing a non-volitional activity for the older individual which increases metabolic energy expenditure up to, or above, 1.5 METS during otherwise sedentary activity.

Metabolic energy expenditure is dependent on cardiac output, and while exercise benefits all physiologic systems, the cardiovascular (CV) system is widely considered a primary target of exercise training. More specifically, the principal benefits of physical activity on the CV system is the increase in cardiac output, with aerobic activities, ie, those which can be maintained for long durations, being most effective for improving cardiac function.[19] This leads to the suggestion that an optimal strategy for developing a complementary behavior to traditional physical activity for the older individual would be to focus on creating a significant and sustained increase in cardiac output while the individual is sedentary.

This strategy should be particularly useful for older adults as it has long been known that cardiac output peaks in young adulthood, and then declines through to the elderly years. Katori,[20] in a now classic study, showed that upright resting cardiac output in adults declines by more than one-third during adulthood, from an average of over 7.5 L/min at age 20, to less than 5 L/min by age 80 (Figure 1). This decline is primarily the result of decreasing stroke volume rather than changes in average heart rate, with stroke volume index declining from an average of 65mL/m$^2$ to 48mL/m$^2$ over this age range. Consistent with this inability to maintain cardiac output, older adults are unable to maintain a normal resting metabolic rate.[21]

Young and middle-age adults do not typically suffer from heart failure and so this age-related decline in stroke volume must arise through an alternative mechanism. Specifically, age-related decline in cardiac output is commonly the result of reduced cardiac return. During locomotion, the musculature throughout the lower body serves to pump blood back to the heart, against the force of gravity, through the process of skeletal muscle pumping. However, during upright sedentary activity (sitting or standing), the soleus muscles in the lower leg play the predominant role in returning both blood and interstitial fluid back up to the heart.[22]

The soleus muscles are deep postural muscles, which, along with the gastrocnemius, are used to maintain balance during standing. When squatting, the gastrocnemius is inactive and the soleus muscles play an exclusive role in maintaining balance. Squatting is the natural resting position of humans, and certain cultures continue to rely on squatting when resting. While children commonly squat while playing, with increasing age, modern adults rarely squat. As a result, the fatigue resistant Type I and IIa muscle fibers, which should make up the vast majority of fibers in the soleus muscles, convert to fast-twitch (Type IIb) fibers and the muscles lose their fatigue resistance. This is reflected in the normative standards which have been established for one-legged heel raises, an assessment of soleus fatigue resistance. Healthy (average physical activity level of 4 on a 6-point scale) 20-year-old men and women can be expected to complete 30 or more one-legged heel raises before fatiguing.[23] Healthy 70-year-olds, in contrast, are typically able to achieve only about 16 repetitions, reflecting an approximate 50% decline in fatigue resistance over five decades.

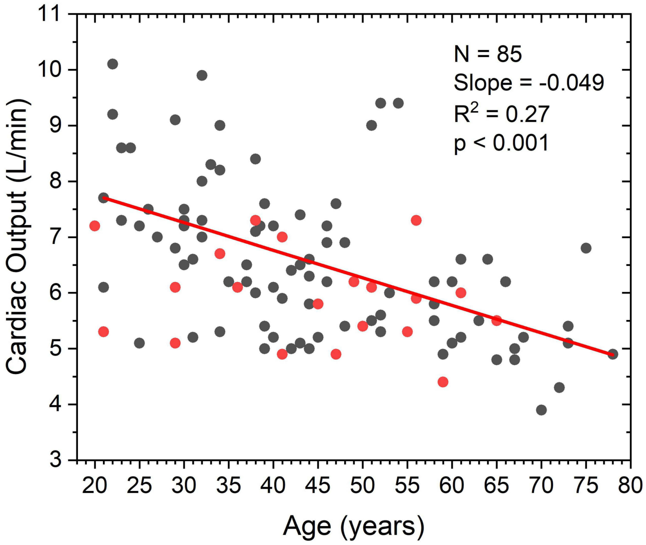

**Figure 1** Decline in resting cardiac output as a function of age in men (black) and women (red). Measurements obtained 5–10 minutes after subjects assumed a semi-reclined position using an earpiece dye-dilution method. In this cohort study, cardiac output peaks near age 20, then declines continuously with increasing age at an approximate rate of 50mL per year. (After Katori, 1978).[20]

Given that only a quarter of older adults undertake the minimal level of daily physical exercise recommended by public health services, it can be expected that soleus fatigue resistance among older adults is often below normative levels for the healthy elderly, and this appears to be the case. In a group of older (61–81 years) adults who participated in less than 3 hours per week of moderate or greater intensity physical activity, soleus fatigue testing demonstrated that only 2 of 29 subjects (7%) had maintained their soleus fatigue resistance at or above normative levels (Figure 2).

Loss of fatigue resistance means the soleus muscles have lost their ability to maintain the sustained periodic contractions necessary to support the cardiac return levels required to support normal cardiac output throughout the day. If cardiac output declines, resting blood pressure cannot be maintained in the upright individual during sedentary activity. In a pilot study evaluating the association between resting blood pressure (obtained after 10 minutes of quiet sitting) and fatigue resistance of the soleus muscles we observed DBP to be strongly (p=0.001) dependent on soleus muscle fatigue resistance (Figure 3). Remarkably, up to two-thirds of individuals over age 60 years were unable to maintain a normal level of resting diastolic blood pressure, that is, a level above 80mmHg as per current clinical recommendations.[24]

These blood pressure values, obtained after a brief sedentary period of time, do not fully capture the cardiac return challenge facing the older adult. Blood pressure is not commonly followed over extended durations of upright, sedentary posture, yet, extended duration upright sedentary behavior is more the rule than the exception among older adults. Raichlen et al[25] recently reported that in a population of 49,000 older adults (average age of 67.2 years) median sedentary activity time (not including sleeping) exceeds 9 hours per day.

Tracking of cardiac output (CO) in a study of older adults during quiet sitting illustrates the effect of extended sedentary behavior on cardiac output (Figure 4). Quiet standing, in healthy individuals, involves metabolic activity rates of approximately 1.6 METS, while quiet sitting requires only about 1.3 METS. Consistent with these differential energy requirements, an initial 20% decline in cardiac output is observed when study subjects transition from standing to sitting with cardiac index declining from an average of 3.3 L/min/m$^2$ to about 2.8 L/min/m$^2$ over the first 10 minutes of measurement. However, with continued quiet sitting, cardiac output continues to decline for over two hours, resulting in a final average cardiac index level of 2.2 L/min/m$^2$. This level of cardiac output is sufficient to support a metabolic activity rate of only about 0.9 METS, well below that necessary to support normal resting metabolic activity.

Given that older individuals are, on average, sedentary for over 9 hours each day (not including sleeping time), these observations indicate that cardiac output is well below RMR in a large fraction of older adults for much of the day. Reduced circulation and metabolic activity can lead to a drop in core body temperature, fatigue, reduced wound healing rates, increased risks of peripheral neuropathy, and numerous other health complications commonly reported by older

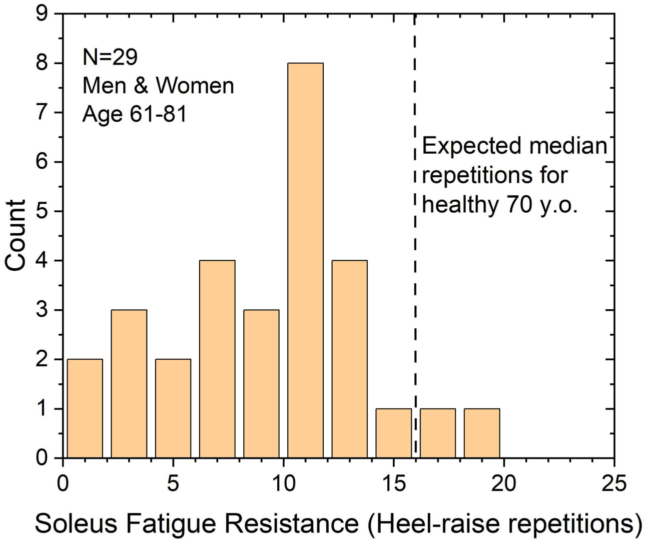

**Figure 2** Distribution of soleus muscle fatigue resistance in older (age 61–81 years) non-athletic men and women. Fatigue resistance was assessed through slow (60°/second) one-legged heel raises (IRB exempt pilot study). While normative data indicates that healthy adults in this age range should be able to complete about 16 such heel raises before fatiguing, only 2 of 29 individuals in this convenience sample achieved this level of soleus fatigue resistance.

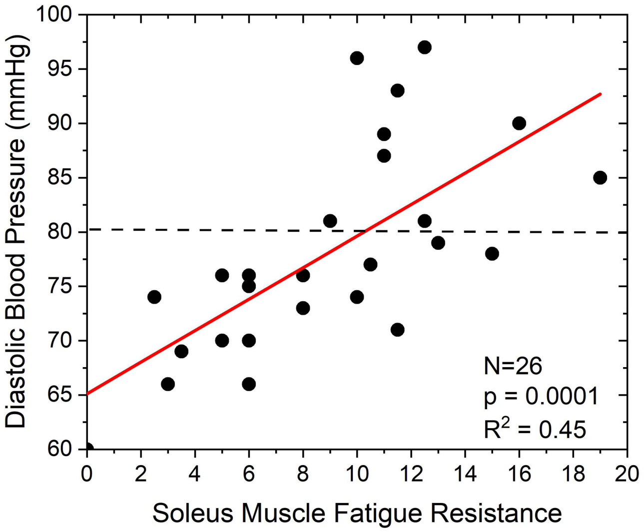

**Figure 3** Resting diastolic blood pressure (DBP) as a function of soleus fatigue resistance. In a group of non-athletic (those undertaking less than 3 hours per week of intense physical activity) older adult (61–81 years) men and women, DBP was obtained following 10 minutes of quiet sitting (IRB exempt pilot study). Soleus fatigue resistance obtained by one-legged heel raises. DBP is significantly correlated to soleus fatigue strength (p=0.0001). Two-thirds of subjects were found to be unable to maintain a normal level of DBP (>80mmHg).

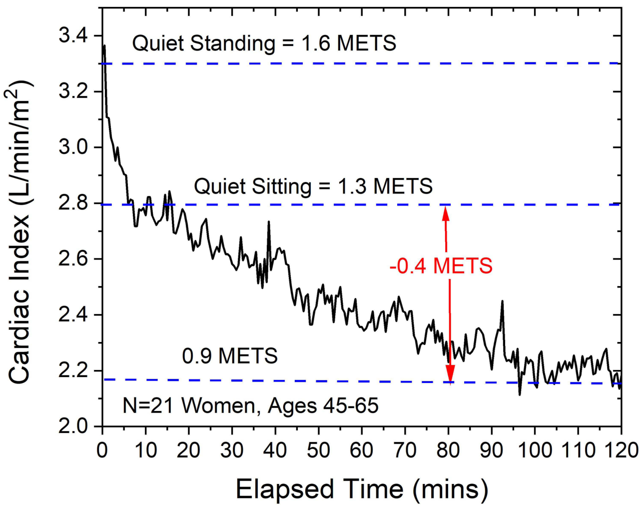

**Figure 4** Cardiac Index tracked over two hours during quiet sitting. Cardiac index (CI) in 21 women aged 45–65 years was obtained using continuous cardiac output monitoring (NICOM, Cheetah, Inc.) as they transitioned from quiet standing to quiet sitting. Within 10 minutes, CI falls from 3.3 L/min/m$^2$ to 2.8 L/min/m$^2$, or about 15%, consistent with the difference in metabolic rate required for quiet standing vs quiet sitting. CI is then observed to continue to decline for two hours, reaching 2.2 L/min/m$^2$, a level capable of supporting only about 1.0 METs of metabolic activity. Data obtained in IRB approved study undertaken at Binghamton University, Binghamton, NY.

adults. Reduced cardiac output and the corresponding drop in blood pressure is a particular challenge for brain tissue. Recent work has shown that each 1mmHg decrease in diastolic blood pressure leads to a 1% decline in cerebral perfusion.[26] Low cerebral perfusion is associated with cognitive impairment,[27] and chronic cognitive impairment is strongly associated with increased risk of developing dementia.[28]

## Intervention Strategy

Sarcopenia occurs in all skeletal muscles, with muscle mass and strength typically peaking in individuals around 30–35 years of age and then declining. Correspondingly, retraining of voluntary skeletal muscles generally focuses on increasing muscle mass and strength. Soleus muscles are involuntary, deep postural muscles. Age-related atrophy in these muscles does not involve the loss of muscle mass and strength per se, but rather the conversion of fatigue-resistant slow twitch fibers

(Type I and IIa) to fast-twitch Type IIb fibers. Correspondingly, rejuvenation requires fiber reconversion. To convert Type IIb fibers back to slow twitch fibers involves imposition of muscle activation patterns which mimic normal soleus function, that is, sustained stimulation (hours per day) composed of individual episodes lasting one minute or more.[29]

The sustained postural activity of soleus muscles is mediated by reflex action. During squatting or standing, pressure on the plantar surface of the foot is detected by mechano-receptive nerve endings of the plantar nerve. These include Merkel disk receptors (sensitive to 5–15Hz mechanical stimuli), Meissner's Corpuscles (10–50 Hz) and Pacinian Corpuscles (60–400Hz).[30] Activation of receptors on the frontal plantar surface results in initiation of the postural reflex leading to contraction of the soleus muscles. Conversely, pressure on the heel region of the plantar surface results in relaxation of the soleus muscles. This postural reflex provides a convenient pathway for exogenously initiating soleus activity.

Incorporation of the soleus reflex arc into a type of non-volitional activity involves identification of the plantar surface stimulation characteristics which optimizes the responsiveness of the soleus, specifically, stimulation frequency, intensity, and duration. An initial characterization of the frequency sensitivity of the reflex arc provides insight into the type of mechanoreceptors involved in the soleus reflex, and consequently, the required stimulus intensity. To obtain this information, we studied the response of older adult women (average age of 56 years) with orthostatic intolerance to plantar mechanical stimulation. Plantar stimulation in the region of 45 Hz was found to be optimal for reversing the observed drop in orthostatic blood pressure in these subjects.[31] As Meissner's Corpuscles respond to mechanical stimuli in the 10–50Hz range, these results implicate Meissner's Corpuscles as the dominant initiating mechanoreceptor in the soleus reflex arc. The minimal skin displacement necessary to activate Meissner's Corpuscles has been shown to be about 10 micrometers, an observation which provides a reference point for establishing an appropriate stimulus intensity.[32]

The remaining stimulus characteristic requiring definition is stimulus duration. Gross electromyographic recordings from soleus muscles during non-locomotory activity show that in the mature soleus muscle, motor neuron firing episodes can extend for up to two minutes. Following such a sustained contraction, motor neuron activity pauses. This pause provides a period of time during which blood and interstitial fluid can refill the venous sinuses in the soleus prior to the next contraction. These pauses/refilling periods are typically 2–3 minutes in duration.

Physiologic studies using prototype neuro-muscular stimulation devices with the above characteristics demonstrate that activation of the soleus muscles through plantar micro-mechanical stimulation produces significant physiologic responses in sedentary older adults. Soleus muscle stimulation in seated older adults not only prevents lower limb fluid pooling but also reverses fluid pooling.[33] Consistent with this reduction of lower limb pooling, cardiac output during quiet sitting is significantly enhanced. This can be seen for a group of older adults who experienced an average 40% reduction in stroke volume index (SVI) during 60 minutes of sitting after transitioning from a quiet standing posture (Figure 5). This includes an initial 25% drop to 28mL/m$^2$ within the first 10 minutes, which is expected to occur as a result of the stand to sit transition, and then a further 5mL/m$^2$ drop as the subjects continued to sit. Assuming quiet standing is associated with an energy expenditure rate of about 1.6 METS, these results indicate that the metabolic rate in these subjects has fallen to approximately 1.0 MET over just 60 minutes of quiet sitting. Repeating the seated exposure with concurrent micro-mechanical plantar stimulation results in a very different cardiac response in these individuals. While the initial drop in SVI is still observed over the first 5–10 minutes of recording, SVI then starts to rise as the subjects continue to sit. After 60 minutes of sitting, SVI is at 29 mL/m$^2$, indicating a 0.4 MET enhancement in metabolic activity relative to sedentary control levels.

This enhanced cardiac output during rest results in enhanced blood flow throughout the body.[34] Impedance plethysmographic recordings of individuals in the upright position show that micromechanical stimulation of the plantar surface at 45Hz results in an average 47% increase in blood flow in the lower legs as compared to no stimulation, 35% in the pelvic region, and 17% in the thoracic region.

In addition, the increase in cardiac output arising from soleus muscle stimulation serves to normalize blood pressure in individuals who cannot maintain their resting blood pressure when in upright sedentary posture. Delayed orthostatic hypotension (DOH) is a common complication in individuals whose soleus muscles have lost their fatigue resistance. DOH is a critical health marker as the ten-year mortality rate for those with DOH is 50%.[35] In a group of older adult women identified with DOH, average diastolic blood pressure (DBP) after sitting for 30 minutes was below 55mmHg.[36] Thirty minutes of soleus activation through plantar stimulation was observed to raise the average DBP to above 75 mmHg.

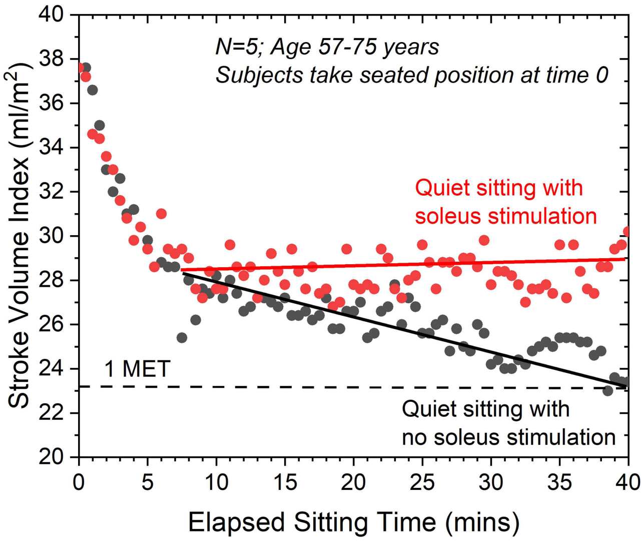

**Figure 5** Stroke volume index (SVI) in five older adults (aged 57–68 years) following transition from a quiet standing to a quiet seated position, with (red) and without (black) soleus muscle stimulation. In the absence of muscle stimulation, SVI rapidly falls from 38 mL/m$^2$ to 28 mL/m$^2$, consistent with the reduced metabolic requirement of quiet sitting versus quiet standing. SVI then continues to fall for up to an hour, reaching an SVI of 23 mL/m2. Repeated with concurrent soleus muscle stimulation, SVI again demonstrates a rapid decline over the first 5–10 minutes, but then SVI slowly increases over the following 50 minutes. At the one-hour time point, SVI has risen to 29 mL/m$^2$, a level sufficient to support an estimated 1.4 METs of metabolic activity. (Data from IRB approved clinical study executed at Binghamton University, Binghamton, NY).

## Clinical Effectiveness

Physiologic studies have shown that soleus muscle activation in sedentary older adults can significantly enhance fluid return from the lower body back to the heart, resulting in increased cardiac output, normalization of blood pressure, and improved blood flow throughout the body. While these are encouraging outcomes, the goal of identifying a useful complementary intervention to physical exercise for older adults is to improve health outcomes, which requires longer-term clinical studies. To that end, the influence of long-term daily soleus muscle stimulation on health conditions of importance to older adults, including sleep impairment, lower limb edema in heart failure, bone loss, and cognitive aging, has been investigated.

Sleep complaints are a common concern for older adults with over 30% reporting sleep impairment and over half of those with sleep impairment reporting sleep apnea episodes.[37] Numerous sleep investigations have linked daytime lower body fluid pooling with impaired sleep quality.[38] The proposed mechanism of action is that fluid which accumulates during the day shifts rostrally during supine sleep, expanding the veins and interstitial spaces in the neck. Increased fluid pressure in the neck can collapse the upper airway leading to disordered breathing. Reduction of daytime lower limb fluid pooling therefore has the potential to improve night time sleep quality. This possibility has been tested in a group of older adults (average age of 60 years) who undertook soleus muscle stimulation for at least one hour per day over four weeks.[39] Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and Functional Outcomes of Sleep questionnaire (FOSQ) in a pre/post test experimental design. Following four weeks of daily soleus stimulation, sleep quality, per the PSQI, was observed to improve significantly (p=0.003). FOSQ scores showed that the group mean score increased from an abnormal sleep level (16.8) to a normal level of sleep function (17.9) for 9 of the 11 subjects showing improvement.

Congestive heart failure (CHF) has a prevalence of only 1% at age 50, but this rate doubles each decade, such that CHF becomes a significant health complication for the elderly. The lower limb edema associated with CHF is a major cause of medical complications and reduced quality of life. Standard treatments for edema have significant side effects including electrolyte imbalances, hyperuricemia, hypovolemia, and renal failure.[40] To evaluate whether daily soleus muscle stimulation could help alleviate lower limb edema in CHF patients, a one-month intervention study with six diagnosed CHF patients with preserved ejection fraction was undertaken.[41] Subjects were asked to utilize soleus neuromuscular stimulation for at least 30 minutes per day, with compliance monitored by an internal timer in the stimulator. Lower limb body fluid volume was assessed by Dual Energy X-Ray Absorptiometry (DXA). Subject compliance ranged from an average of 0.4 hours per day, to 1.8 hours per day. Increasing compliance was associated with greater reductions in lower limb fluid volume. The minimally compliant subject (0.4 hours/day) lost a total of 200mL of fluid in the lower limbs over the four-week study period, while the most compliant user (1.8 hours/day) lost a liter of fluid from the lower limbs at the four-week time point.

A major objective of muscle strength building in older adults is reduction in fall risk. Falls are a major concern due to the increased risk of fracture in this population. While fall prevention is an important factor in fracture risk, low bone mineral density plays an equally important role. Similar to muscle mass, bone mineral density peaks in the fourth decade of life, and then declines slowly, although women often experience a more rapid decline in the peri-menopausal years. Exercise interventions have not been shown to be particularly helpful in slowing or reversing age-related bone loss,[42,43] so osteopenia and osteoporosis remain a major concern for healthcare providers caring for older adults.

Like all tissues, bone requires adequate nutrient flow to support metabolic activity, and in bone, this nutrient flow is carried by fluid flow from the endosteal to periosteal surfaces. This transcortical fluid flow is driven by the pressure differential between blood pressure in the marrow cavity and tissue fluid pressure outside of the bone. When blood pools in the lower body, blood pressure falls and interstitial fluid pooling leads to tissue pressure rises, with the net result being a decrease in the fluid pressure gradient driving transcortical flow. Consistent with the important role interstitial fluid pooling plays in this process, osteopenia and osteoporosis are much more significant problems in the lower body as compared to the upper body.

Soleus muscle stimulation, which leads to a reduction of lower limb fluid pooling as well as increased cardiac output, would be expected to normalize the transcortical fluid pressure gradient resulting in the slowing, or reversal, of lower body bone loss. This premise has been tested in a one-year study incorporating micromechanical plantar stimulation to activate the soleus muscles.[44] Twenty-eight older adult women office workers (aged 42–68 years) were asked to utilize a soleus muscle stimulator daily for a period of one year. Recommended daily treatment duration was one hour, but subjects were encouraged to use the stimulation ad-lib. Bone mineral density (BMD) of the lumbar spine, proximal femur, and proximal tibia was monitored by DXA at enrollment and at one year. Compliance with device usage was monitored by an electronic clock internal to the neuro-muscular stimulation device.

Average soleus stimulation usage among the subjects ranged from 0.4 Hours/day to 5 Hours/day. Change in BMD was significantly associated with device usage time. The largest effects of intervention were observed in the tibia, where the least compliant subjects lost as much as 4% of the proximal tibia bone mass over one year, while those who, on average, undertook soleus muscle stimulation for five hours/day gained over 3% in bone density ($p=0.004$). In the proximal femur, a similar, but less strong relationship was observed with change in BMD ranging from −1.5% to 1.5% ($p=0.05$). As hypothesized, BMD change in the lumbar spine showed the least benefit, with the least compliant subjects losing 1.5% of BMD, and the most compliant showing no bone loss. On average, for the three sites, 2.5 hours/day of soleus stimulation was sufficient to prevent any net bone loss over the course of the year (Figure 6).

A health condition which raises substantial concern among older adults is age-related cognitive decline. Brain function is exquisitely dependent on high levels of blood perfusion. While representing only 2% of body mass, brain blood flow consumes 20% of cardiac output. When cardiac output falls during sedentary activity, resting blood pressure falls, and cerebral perfusion falls. For each 1mmHg drop in diastolic blood pressure below normal (80mmHg) cerebral perfusion has been shown to decline by 1%.[26] As diastolic blood pressure in older adults commonly drops 20–30 mmHg during extended sedentary activity and the impact on cerebral perfusion and cognitive function can be substantial. Enhancing cardiac return such that cardiac output remains at near normal levels during sedentary activity would be expected to result in improved cerebral perfusion and improved cognitive function.

This hypothesis is supported by the results of two pilot clinical studies where changes in cognitive performance in older individuals who utilized soleus muscle stimulation daily were monitored over several months. In an initial study,[45] older adults (average age 82 years) with chronically low blood pressure (resting DBP < 65mmHg) were asked to use a soleus neuromuscular stimulation device for at least one hour per day. A similar aged group with normal resting blood pressure (DBP average of 77mmHg) served as control. Cognitive performance was assessed weekly using classic pencil and paper tests (Congruent and Incongruent Stroop, Trailmaking A&B). Over a period of 14 weeks, the DBP in the intervention group rose to match that of the control group. As well, test times to complete the Trailmaking and Stroop tests also improved to the point of matching that of the control group ($p=0.0001$).

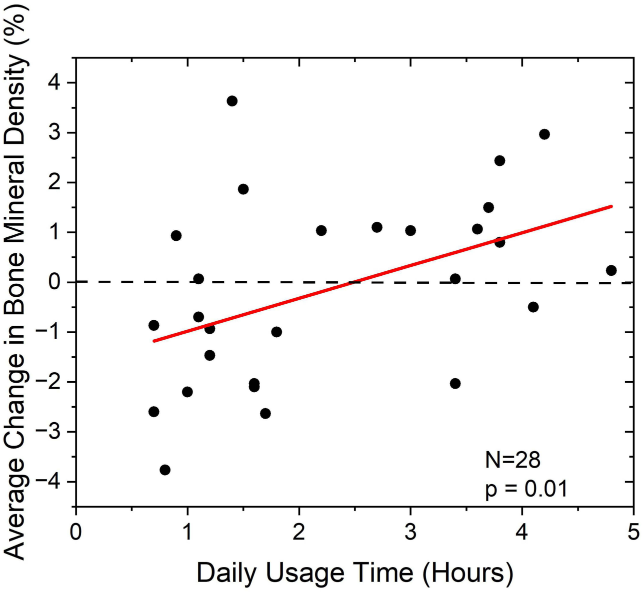

**Figure 6** Change in bone mineral density (BMD) over one year in a peri-menopause study population (age 42–68) undergoing daily soleus muscle stimulation. Change in BMD obtained by dual energy x-ray densitometry for the lumbar spine, proximal femur and proximal tibia. BMD change at the three sites are averaged. Change in BMD is significantly correlated to duration of daily soleus muscle stimulation. Less than 1 hour/day usage is associated with an average 1.5% decline in BMD. Average daily usage of over 4 hours/day is associated with a 1.5% increase in BMD. Daily use of soleus stimulation for 2.5 hours/day, or less than 1/3 of typical daily sedentary activity time appears to be sufficient to prevent net bone loss in this population. (After McLeod and Pierce, 2018).

In a second study utilizing a quantitative computer aided cognitive performance evaluation (Cognivue, Inc., Victor, NY), a similar temporal cognitive improvement pattern has been observed. Cognitive performance was assessed monthly in a group of 10 older adults (average age of 78 years) who utilized soleus muscle stimulation daily. Average initial cognitive scores were 52 on a scale of 0–100, with a score below 50 representing severe cognitive impairment and a score over 75 representing normal cognitive function. Within three months, average cognitive performance scores crossed the threshold into the normal range, and by the end of the six-month study period, average cognitive performance scores exceeded 80 (Figure 7).

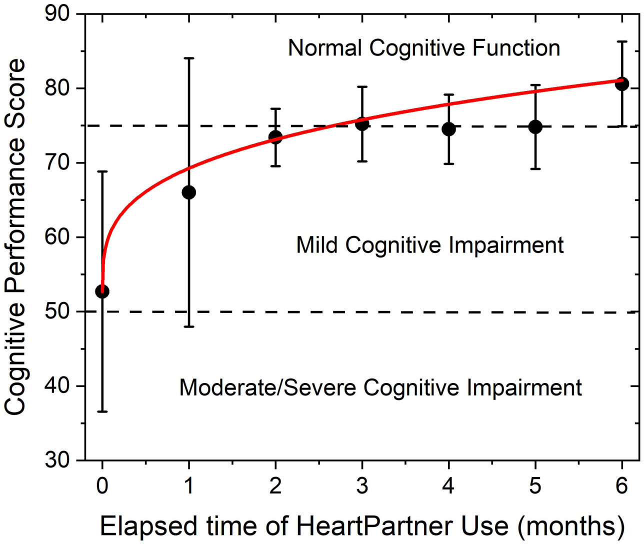

**Figure 7** Change in cognitive performance in an older adult (aged 71–81 years) population identified by their primary care physician as demonstrating cognitive challenges. Cognitive performance measured using the Cognivue, Inc. (Victor, NY) computer aided cognitive assessment tool. Average initial assessment for this group place their performance near the border of significant cognitive impairment. Daily soleus stimulation use resulted in significant improvement in cognitive performance, with performance attaining a level associated with normal cognitive function after 3 months. Continued daily soleus muscle stimulation resulted in a continued slow improvement in cognitive performance. (Data from IRB approved pilot study).

## Discussion

Physical activity increases cardiac output, and as a direct result, blood flow throughout the body. This increased blood flow permits the increase in metabolic activity required to support the physical activity through enhanced delivery of both oxygen and nutrients. Metabolic activity in the human is measured in terms of "metabolic equivalents" (METS) with 1 MET being roughly equal to 1 Kcal/Kg/Hr, a level referred to as our basal metabolic rate (BMR). BMR is the energy requirement for a person to maintain the basic metabolic functions necessary to support tissue growth, maintenance, and repair processes when in a supine position at neutral temperature.

Physical activity involves increased skeletal muscle activity, which places increased demands on the cardiovascular and respiratory systems. As a result, physical activity leads to substantial increases in metabolic rate relative to BMR. Quiet sitting, for an adult, is associated with a whole-body metabolic rate of about 1.3–1.4 METS, an energy expenditure level referred to as resting metabolic rate (RMR). Standing requires 1.6–1.8 METs of energy expenditure, a slow walk about 3 METS, and a brisk walk (moderate physical activity) 4–6 METS.[46] While moderate and intense physical activities can involve relatively high levels of metabolic activity compared to RMR, for most older adults, such activities are performed for relatively short time periods during the course of the day. RMR, therefore, typically represents 50%–70% of the total daily energy consumption in older adults.[47] For older adults, the National Institutes of Health recommends a minimum weekly physical activity level of 150 minutes of moderate activity (4–6 METS), spread over at least three days of the week, in order to maintain physical and mental health. This is a relatively small addition to daily metabolic demands. 4–6 METS of additional activity for 2.5 hours per week represents just 10–15 MET-Hours per week of metabolic demand, or approximately 1.4–2.1 MET-Hours per day.

Here, we have considered the potential for assisting older adults in achieving this daily metabolic activity goal by enhancing non-volitional muscle activity while sedentary. When older adults are sedentary, fluid pooling in the lower body leads to reduced cardiac output, to an extent that the individual cannot support normal resting metabolic activity levels, thus limiting growth, maintenance, and repair of the body tissues. This decline in cardiac output is commonly a direct result of insufficient cardiac return, arising from atrophy of the soleus muscles. These muscles are essential for maintaining adequate venous and interstitial fluid return to the heart during upright posture. Like all muscles, the soleus muscles can be rejuvenated with appropriate stimulation, which, in the case of the soleus muscles, involves low level, long duration stimulation.

We have observed that neuro-muscular stimulation of the soleus is capable of increasing metabolic activity by at least 0.4 METS during sedentary activity. This observation indicates that 3–4 hours per day of soleus muscle stimulation, while an individual is sedentary, could provide the minimal additional weekly metabolic activity recommended by the NIH. As the elderly are sedentary, on average, for over 9 hours each day, this extended intervention time does not seem unreasonable. When coupled with in-bed or other at-home exercise modalities which are directed more towards muscle strength and balance improvements, even the higher end of the NIH weekly activity recommendations could potentially be achieved.

## Conclusions

Muscle quality begins to decline in the fourth decade of life, and so most older adults are living with reduced muscle strength, reduced balance control, and reduced endurance, all of which increase health risks and decrease quality of life. This muscle decline is due, in part, to reduction in physical activity, but also to the increase in sedentary activity time resulting from changes in type of work, home life, and entertainment. While an increase in aerobic and anaerobic physical activities can slow or reverse this progression, compliance with voluntary exercise programs (ie physical activity undertaken beyond that necessary to complete activities of daily living) is generally poor among older adults. Ongoing climate change and extreme weather events are increasing the challenge even for those older adults who would like to increase their daily physical activity levels.

Physiologic and clinical studies have demonstrated that exogenous soleus stimulation is capable of significantly reducing lower limb fluid pooling in older adults, resulting in up to a 40% enhancement in cardiac output during sedentary activity. This increase in CO is able to support a sustained 0.4 METS of additional energy expenditure. Three to four hours per day utilization of such exogenous soleus muscle stimulation is sufficient to provide the additional 1.4 MET-Hours of daily energy consumption recommended by the public health organizations for older adults. Importantly, this level of daily, non-volitional exercise appears to be sufficient to normalize resting blood pressure, reduce sleep disturbances, prevent bone loss, and slow/reverse cognitive aging in older adults.

As older adults are sedentary for over 9 hours of their waking day, developing a soleus neuro-muscular stimulation apparatus which becomes active whenever an individual is sedentary could potentially raise additional daily energy expenditure to over 3 MET-Hours. We propose that exogenous stimulation of the soleus muscles could be a highly beneficial complement to voluntary physical activity for older adults who, in this era of climate change, are struggling to find the time and opportunity to safely increase their physical activity levels.

## Disclosure

Dr Kenneth McLeod holds an equity interest in Sonostics, Inc. a manufacturer of neuro-muscular stimulation devices. Dr Kenneth McLeod also reports a patent application #63/628,007 pending to Sonostics, Inc.

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