Chapter

Reversal of Cognitive Aging through Enhancement of Cardiac Output

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Abstract

Cognitive aging is a progressive condition leading to dementia, a condition which is now the sixth leading cause of death in the U.S., as well as being among the most expensive healthcare conditions to manage. With over 5 million affected in the U.S. alone, the annual costs to the Medicare/Medicaid system exceeds $200 billion, and with the rising age of the population, annual costs of dementia care are expected to exceed $500 billion by 2040. As there is no cure for dementia, a consensus has formed that a more pragmatic goal of research should be developing interventions capable of slowing or preventing cognitive aging. We propose that this is a readily achievable goal. Cognitive impairment is closely linked to cerebral perfusion, and cerebral perfusion is a function of cardiac output. In turn, cardiac output is completely dependent on venous return, which in the upright human, relies on adequate soleus muscle activity. As modern adults rarely squat, which is necessary for maintaining the soleus muscle, soleus insufficiency develops early in adulthood in most people. However, soleus muscle insufficiency can be reversed, resulting in improved cardiac output, cerebral perfusion, and the prevention of cognitive aging.

Keywords: dementia prevention, cerebral perfusion, cardiac output, venous return, second heart, soleus muscle stimulation

1. Introduction

Dementia is a major cause of morbidity and mortality in the developed world. Dementia, in all of its forms, is a progressive condition, with an incidence of less than 5% through age 79, but reaching 40% for those over age 90 [1]. Given the aging demographics of the developed world, the economic impact of this condition could soon dominant healthcare costs in many countries.

There is currently no cure for dementia, and numerous pharmaceutical firms have abandoned the search for a cure. In particular, interventions based on the beta-amyloid hypothesis which has guided dementia drug therapy development for the last three decades has come under increasing scrutiny as drugs which effectively reduce beta-amyloid accumulation appear to exacerbate, rather than ameliorate, the symptoms associated with dementia [2]. It is therefore incumbent that we take a fresh approach to understanding dementia, in particular, we suggest it is important to develop a more thorough understanding of the numerous physiologic interactions associated with progression of cognitive impairment with age. Such understanding

will set the stage for innovative interventions, specifically, interventions focused on prevention, rather than treatment. This coupled systems, or complex systems, approach, is less intuitive than the more traditional scientific approach of establishing proximate cause. Indeed, in complex systems, cause may not be identifiable, rather, outcomes arise as emergent behaviors of interdependent coupled components of the system. Despite these challenges, it is becoming widely recognized that a complex systems mindset will be necessary for effectively addressing not only dementia, but also the wide range of functional disorders which modern medicine currently faces [3].

Perhaps the physiologic interactions of greatest current interest, with respect to dementia, are those between the cardiovascular and cerebral systems. Over the past three decades, numerous prospective and retrospective studies have identified strong associations between low cardiac output, low blood pressure, low cerebral perfusion, and the development of dementia. The majority of these studies have focused on older adults, but a review of cognitive and cardiovascular changes taking place from early adulthood provides important insights into why dementia may not have to be the scourge of old age which many people fear.

Here, we describe the development of cognitive decline starting in early adulthood and relate this decline to parallel changes in the cardiovascular and the musculo-skeletal systems, specifically, second heart function. The parallels in secular decline in these systems lead us to propose that inactivity based changes in skeletal muscle fiber structure plays a critical role in the age related decline in cardiac output, and correspondingly decreased cerebral blood flow. We propose that this decreased cerebral blood flow, beginning in middle age, is a dominant factor in cognitive decline, cognitive impairment, and eventually dementia, in those where cerebral perfusion is not corrected. We introduce preliminary evidence showing that enhancement of cardiac output through second heart (soleus muscle) stimulation is able to improve cognitive performance in those with both mild and advanced cognitive impairment.

2. Age related cognitive decline

Dementia is a syndrome characterized by memory loss, decline in executive function, behavioral changes, and ability to perform activities of daily living. The impact of dementia on the healthcare system is by far the highest of any health condition [4]. In the U.S., for example, cumulative five year care costs exceed $300,000 or roughly twice the cost of care for heart disease or cancer. With almost 6 million Americans currently affected, annual costs to Medicare/Medicaid exceed $300 billion, and with the aging of the population, these costs are expected to exceed $500 billion by 2040, unless an effective intervention is developed.

While prevalence within the elderly population is based on diagnosed cases, it has become clear that dementia is a slowly progressive condition initiated at a far earlier stage of life. For example, in our laboratory, we have utilized computer aided assessments (Cognivue, Inc., Victor, NY) to quantify cognitive function, including memory, motor skills, and executive function. We have observed (**Figure 1**) that by age 65, cognitive performance for more than 50% of individuals falls below established threshold for mild cognitive impairment. Moreover, by age 80, roughly one-half of the individuals we have screened in our laboratory score below the threshold for moderate to severe cognitive impairment.

Remarkably, we observe few individuals over the age of 55 who are able to score above 90 on the Cognivue scale (scores above 95 are readily attained by young adults). Linear regression leads to the suggestion that cognitive decline is initiated

while individuals are still in their 30s. This perspective is confirmed by the work of Hughes et al. who have investigated cognitive performance among middle-aged and older individuals through the use of telephone-based assessments [5]. In assessing over 2500 individuals using a range of validated assessments, small declines in cognitive performance were observed as people progressed from their 30s into the 40s, however, only one assessment (backwards counting) showed a significant decline in performance over this decade. Starting in the 40s, dramatic declines became evident relative to that of individuals in their 30s (**Figure 2**).

The characteristics of cognitive performance decline appear to be dependent on cognitive task. Short-term memory skills, such as repeating a digit sequence

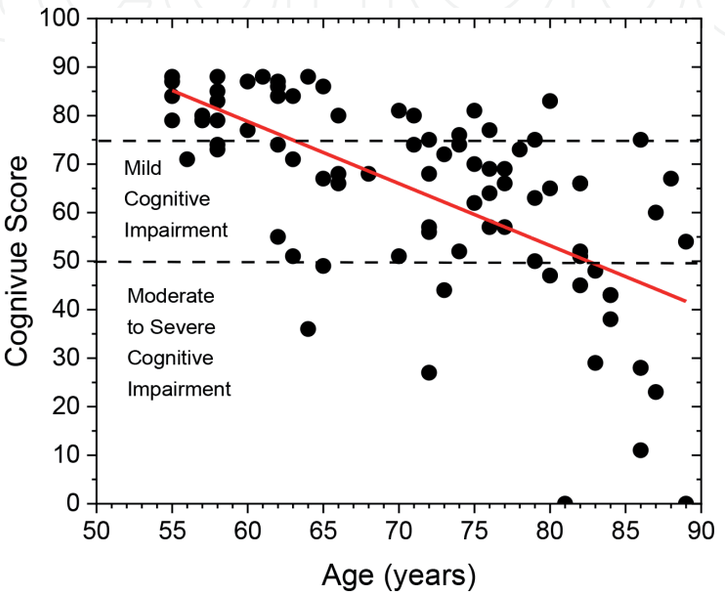

Figure 1.
Age related decline in cognitive performance (memory, motor, and executive function) in a convenience sample of middle aged and older subjects. By age 65, more than half of tested subject perform at a level characterized as mild cognitive impairment or worse. For those in their mid 80s or older, more than half perform at a moderate to severe cognitive impairment level.

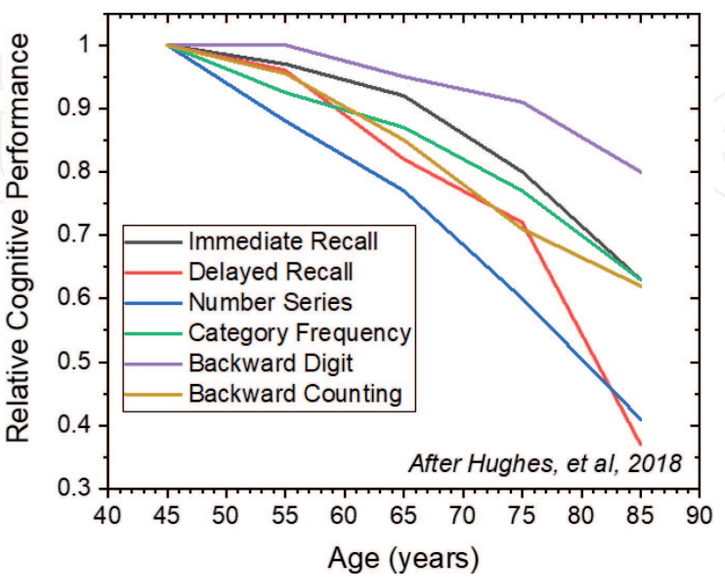

Figure 2.
Decline in cognitive function in middle aged adults. In phone evaluations of over 2500 middle aged and older adults, significant decline in backward counting capability becomes evident between 30 and 40 years of age. Beyond age 40, the majority of cognitive skills are found to decline, and beyond age 50, all cognitive skills evaluated decline with increasing age. After Hughes, et al., [5].

backward, declined slowly with age, along with immediate recall tasks. However, executive function tasks were found to already show substantial decline in early middle age.

3. Age related decline in cardiac output and blood pressure

The question naturally arises as to whether these observed "declines" in cognitive performance in middle-age individuals are, in fact, detrimental, or instead simply reflect more effective use of "brain power" which comes with experience. That is, individuals consistently show improved performance in day to day functions in this age range despite the decline observed in cognitive testing [6]. A generally accepted explanation for this apparent paradox is that, for young people, most daily experiences are novel, and so they retain a high ability to deal with novel exposures. Alternatively, by middle age, most people have obtained a knowledge base of serviceable answers to the most commonly encountered mental challenges, which they can recover with minimal cognitive effort. Because cognitive testing, by design, relies on the presentation of novel challenges, this gives young individuals a natural advantage independent of actual levels of cognitive capability. Certainly, many individuals retain "normal" levels of cognitive performance as measured by cognitive testing well into their 80s, as seen in **Figure 1**, perhaps indicating that these individuals have retained the ability to deal with fresh challenges through regular exposure to novel experiences.

Nonetheless, the consensus in the healthcare community is that while dementia is not a normal outcome of aging, some cognitive decline is to be expected with aging. Age related changes in cardiovascular system performance provides a physiologic basis for this consensus. Specifically, cardiac output has long been observed to decline with age. However, early demonstrations of this declining pattern have relied on invasive measurement techniques which were capable of creating a stress response which may have influenced these older measurements. To address this issue, Middlemiss, et al. [7] have recently utilized non-invasive cardiac output assessment techniques to evaluate changes in cardiac output across the adult age span (**Figure 3**).

These non-invasive measures confirm that cardiac output in the supine position declines substantially with age, specifically by almost 50% over the adult life span in both men and women. Moreover, these investigation shows that cardiac output declines by a further 25% during transition from the supine to the seated position, and falls by 50% when transitioning from supine to a standing position. The implication is that cardiac output in older adults who are standing quietly can be expected to be reduced, on average, by 75% in comparison to that of an average 20 year old.

Cardiac output is a key determinant of arterial blood pressure. In combination with peripheral vascular resistance, cardiac output establishes mean blood pressure. As sufficient blood pressure must be sustained throughout the cardiac cycle in order to ensure adequate blood flow to the brain, which is located at the top of the body when in upright posture, blood pressure becomes a critical factor in regulating cognitive performance. In principle, the declining cardiac output associated with aging should not necessarily lead to declining blood pressure, as vasoconstriction can raise peripheral vascular resistance in order to maintain blood pressure levels. In fact, given the dramatic decline in cardiac output when upright, in the majority of older individuals the ability to vaso-constrict is insufficient to maintain normal blood pressure.

In our lab, we focus on assessing resting diastolic blood pressure (DBP), as the lowest pressure during the diastolic phase of the heart contraction cycle represents the point at which cerebral blood flow is at a minimum. We obtain resting DBP with the subjects in a quiet, seated position for at least 10 minutes, and record the third of three brachial pressure measurements. We observe (**Figure 4**) that by age 55, average resting DBP is below 80 mmHg. By the 9th decade of life, average diastolic pressures are below 70 mmHg. Overall, we observe that among this convenience sample that approximately 20% are unable to maintain a resting diastolic pressure above 65 mmHg, a level at which symptoms of orthostatic hypotension (OH) become evident. For subjects over the age of 75, 30% are unable to maintain this threshold DBP level.

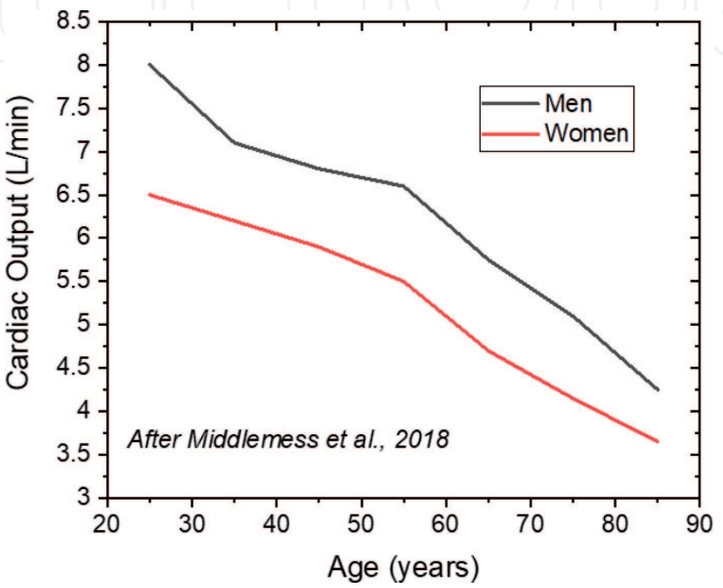

Figure 3.
Cardiac output (CO) as a function of age as measured utilizing non-invasive assessments. Cardiac output declines by approximately 50% in both men and women from the 3rd decade to 9th decade of life. CO decline occur at a relatively constant rate over this age range.

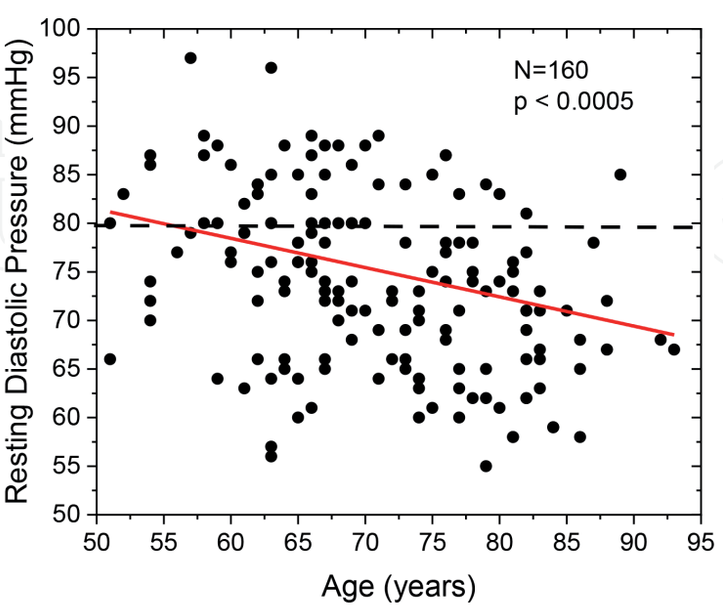

Figure 4.
Resting diastolic blood pressure (DBP) vs. age. A robust negative correlation ($p < 0.0005$) is observed between DBP and age with average DBP falling below 80 mmHg by age 55 in a convenience sample of men and women. By age 85, average DBP falls below 70 mmHg, and within the subject population, approximately 20% were unable to sustain a DBP above 65 mmHg after sitting for 10 minutes.

OH has been shown to occur in less than 3% of young adults, but up to 35% in individuals over the age of 75 [8]. Torabi, et al. [9] investigated the cardiovascular characteristics of individuals with both classical and delayed OH. In a study of over 2000 patients, over the age of 15, with unexplained syncope, 27% were found to be unable to maintain normal blood pressure levels during upright tilt testing. In this population, systolic blood pressure fell, on average to 95 mmHg, while diastolic blood pressure fell, on average, to 60 mmHg.

These observations indicate that asymptomatic postural hypotension is remarkably common in the adult population. That is, vaso-constrictive ability is insufficient in at least 20% of the adult population to maintain normal blood pressure during quiet sitting. Moreover, among the older population, symptomatic postural hypotension is evident in over one-third of individuals, who are unable to maintain blood pressure levels in the presence of declining cardiac output. The critical question is whether the health implications associated with chronic hypotension extend beyond the inconveniences of dizziness and occasional syncope. Extensive work on the association of hypotension with cognitive impairment suggests that hypotension, and correspondingly, cerebral hypo-perfusion, may be one of the most consistent risk factors associated with dementia.

4. Role of cerebral perfusion in cognitive function

Numerous lines of evidence lend strong support for the hypothesis that sustained cerebral hypo-perfusion as a result of chronically low blood pressure has significant negative effects on cognitive performance, and as well, leads to the development of dementia.

Recent computer aided cognitive assessments of men and women over the age of 50, for example, demonstrate a strong correlation between resting diastolic pressure and cognitive performance (**Figure 5**). Multivariate regression analysis on these data show that, after adjusting for subject age, resting diastolic pressure is a significant ($p < 0.02$) predictor of cognitive performance with close to a 1% decline in performance for each 1 mmHg drop in DBP. Notably, only for average diastolic blood pressures above 80, is normal cognitive performance (assessment score > 75) observed. Similarly, the regression analysis indicates that for diastolic pressures below 50 mmHg, average cognitive performance falls into the moderate cognitive impairment range.

These results are consistent with those first reported in the Baltimore Longitudinal Aging Study [10] where it was found that cognitive performance in an older (70 ± 8 years) population was significantly degraded at diastolic blood pressures below 80 mmHg. Confirmation is also obtained by comparison of age dependent cardiovascular and cognitive performance measures (**Figure 6**). Combining the results of Middlemiss et al. [7] with the results of Hughes et al. [5] demonstrates a robust ($p = 0.002$) association between cognitive performance and cardiac output. This analysis demonstrates that for a 30% decline in cardiac output, a 40% decline in cardiac performance can be expected in the 40–90 year old population.

Over the past two decades, numerous studies have provided substantial evidence that decreased cardiac output and chronically low blood pressure are associated with declines in cognitive performance, and also significantly increases the risk of developing dementia. Among the earliest of these studies was the Kugsholmen project undertaken in Sweden [11]. This study showed that, in an elderly population, those with a systolic blood pressure below 140 mmHg, or a diastolic blood pressure below 75 mmHg, had a 3x greater likelihood of being diagnosed with dementia. At that point in time it was unclear whether the lower blood pressures were a consequence of dementia, or played a causal role.

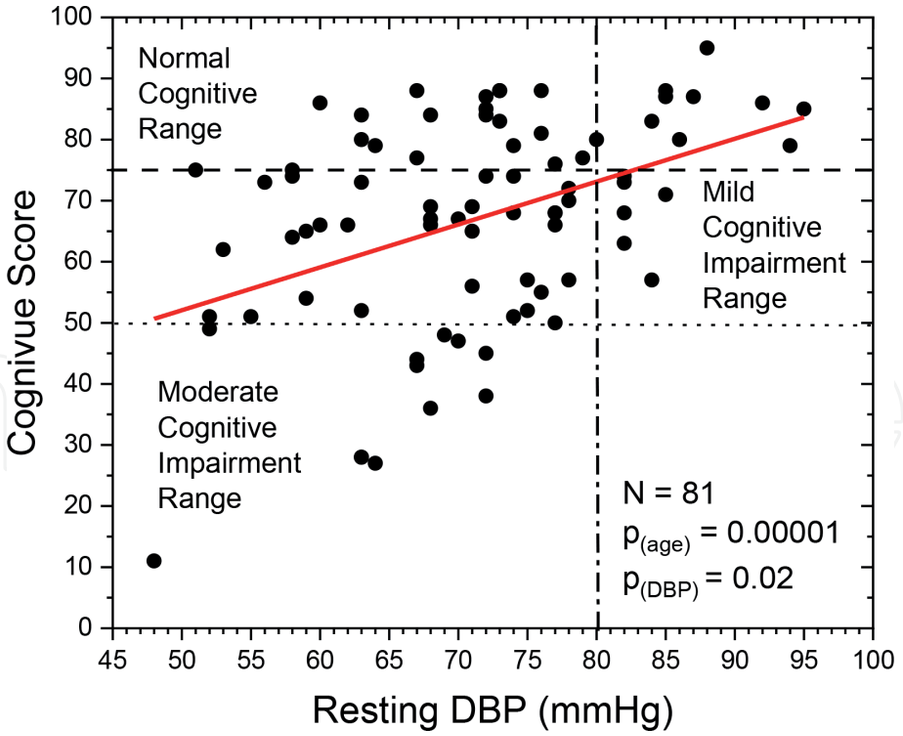

Figure 5.
Cognitive performance vs. resting diastolic blood pressure (DBP). After adjusting for age effects on cognition, declining DBP is strongly associated with declining cognition levels in a convenience sample of men and women. The average individual with a resting DBP below 80 mmHg falls into the category of mild cognitive impairment as assessed using the computer aided Cognivue assessment. DPB below approximately 50 mmHg is associated with transition into the range of moderate to severe cognitive impairment.

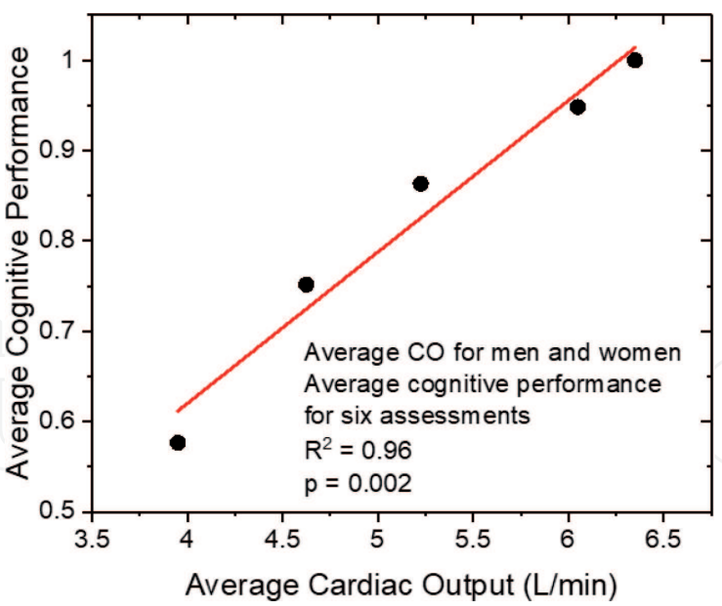

Figure 6.
Integrated analysis of age related cognitive performance data per Hughes et al. [5] with age related cardiac output data per Middlemiss et al. [7]. Cardiac output robustly predicts (p = 0.002) cognitive performance, consistent with a causal role for decreased cerebral blood flow mediating cognitive decline.

The East Boston study [12] addressed, in part, this question, by showing that there was an inverse correlation between risk of Alzheimer's diagnosis and blood pressures taken four years before diagnosis. Verghese, et al. [13] subsequently directly addressed this question in the Bronx Aging Study. They observed in this community based, longitudinal study that sustained low diastolic blood pressure (<70 mmHg) was associated with a 2x increased risk of developing Alzheimer's

disease over a 20 year period. More recently, in a cross-sectional study of more than 24,000 adults who did not have a dementia diagnosis, subjects were followed for up to 27 years [14]. Applying multiple linear regression to adjust for age, gender, education, and body mass index, significant negative correlations were observed between risk of developing Alzheimers, as well as all-cause dementia, across the full range of systolic and diastolic blood pressures.

Complementing these investigation, the established link between diabetes and risk of dementia [15], combined with the well-known influences of diabetes on vascular dysfunction, is currently leading to a broader acceptance that hypo-metabolism, and correspondingly, hypo-perfusion, plays a more significant role in the development of dementia than previously considered [16].

5. Mechanism of age related decline in cardiac output

The numerous demonstrated associations between declines in cardiac output, blood pressure, cognitive performance, and risk of developing dementia, provides a physiologic explanation for the age related cognitive decline, but provides limited insight into how this decline could be prevented or reversed. Our research has led us to propose that the critical factor linking these related outcomes is the inability to maintain adequate venous return during orthostasis.

Venous return refers to the flow of blood from the periphery of the body back to the right atrium. While venous return and cardiac output levels can transiently deviate, under normal physiologic conditions cardiac output is strictly a function of venous return. In the supine position, venous resistance contributes only about 15% to total vascular resistance, however, in upright posture, the venous system plays a much larger role in influencing venous return.

The largest influence of the venous system is through its role as a capacitance vessel. Veins are highly distensible, having thinner walls, with larger diameters, and a compliance of about 30 times that of arteries. They can, therefore, expand rapidly to accommodate large volumes of blood. Correspondingly, a transition from supine to upright posture typically leads to a rapid 500 ml redistribution of blood to the peripheral venous system, a fluid shift which continues to increase over time. The ratio of venous to arterial capacitance under orthostasis has been estimated to grow to as large as 18:1 [17].

In addition, the influence of gravity on the hydrostatic column of blood in the venous system is such that venous blood pressure in the feet can exceed 90 mmHg. As a result of these high lower limb pressures, fluid extravasation from the vascular system increases. Increased extravasation can lead to an additional loss of up to 750 ml over 30–40 minutes following the transition to upright posture. Not only does this cause a further decrease in circulatory system blood volume, but also increased interstitial fluid pressure which results in compression of the peripheral vasculature, and increased in vascular resistance.

The net effect of reduced circulatory volume and increased vascular resistance during upright posture is significantly decreased cardiac output. While vaso-constriction serves to partially support blood pressure during orthostasis, this additional increase in vascular resistance also serves to further reduce blood flow. In our lab, we have observed average sustained decreases in cardiac index, resulting from a transition to quiet sitting, of over 35% relative to that supported when individuals were supine (**Figure** 7).

Return of pooled blood and interstitial fluid which occurs during orthostasis is critically dependent on skeletal muscle pumping. While locomotion can play a role in this process, most adults are sedentary for 9–10 hours per day [18]. Under

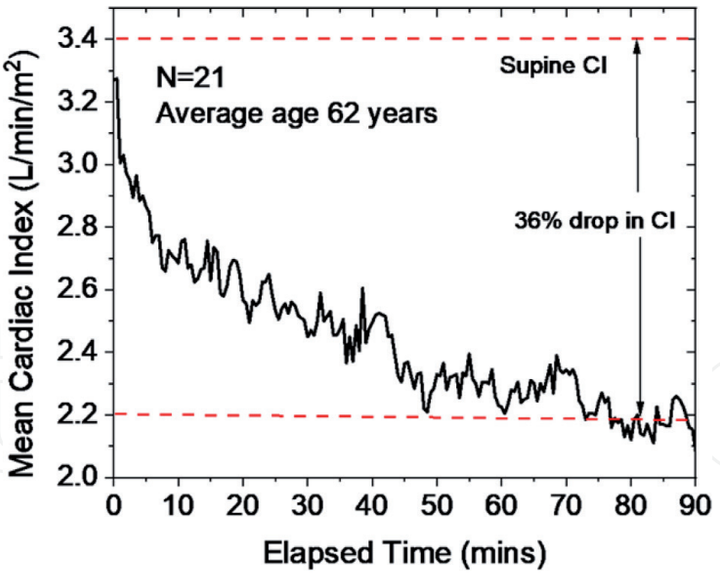

Figure 7.
Cardiac index as a function of time following transition from supine to upright sitting. A decline in CI of 36% from a supine CI of 3.4 L/min/m² is observed among healthy adult women with an average age of 62. This occurs despite an increase in metabolic rate associated with an upright posture, and arises due to gravity induced blood pooling in the lower exptremities.

sedentary conditions, skeletal muscle pumping activity is dominated by soleus muscle action. The essential role played by the soleus in ensuring venous and lymphatic return during orthostasis has led to these muscles commonly being referred to as the calf muscle pumps, or the "second hearts."

The soleus muscles are highly specialized muscles which contain up to 18 thin walled sinuses, each of which are able to hold large volumes of blood. Further, as deep postural muscles composed primarily of slow-twitch fibers, the soleus muscles can sustain contractions over extended time periods. A typical soleus contraction cycle lasts up to one minute, followed a relaxation phase of 60–90 seconds during which the sinuses are able to refill. In addition, because the soleus muscles originate on the posterior tibia and fibula, the muscle can pump effectively when a person is seated. These muscles can generate venous driving forces exceeding 200 mmHg, more than sufficient to drive blood and interstitial fluid back to the heart during upright posture.

6. Soleus muscle adaptation

Like all muscle tissues, the soleus muscle demonstrate changes in both structure and physiology with increasing age. The most commonly observed change in voluntary muscle with advancing age is reduction in muscle mass, with Type II muscle fibers decreasing in both numbers and in volume with age [19]. However the soleus muscle is a deep postural muscle and principally composed of Type I fibers, and Type I fibers do not change substantially in size or number with advancing age. Rather, Type I fibers are far more affected by usage patterns.

Specifically, lack of use of the soleus muscle results in fibers converting towards Type II behavior. Microvascular supply to the fibers is lost and correspondingly, the innate fatigue resistance expected in deep postural muscle tissue. This transition can occur rapidly, independent of age. NASA studies characterizing muscle fiber type changes in astronauts found more than a 20% loss in force generating capacity in both Type I and Type IIa fibers taken from the soleus after a remarkably short (17 day) space flight [20].

The postural role of the soleus muscle is plantar flexion. In fact, when an individual is in a bent knee position, the soleus is the only active plantar flexion muscle. The postural activities which require the most significant plantar flexion force in the bent knee position are squatting activities. Squatting is the natural human rest position, and our ancestors squatted regularly throughout the day - while cooking, eating, socializing, and of course, when defecating. Children also commonly squat during the day, but in the modern world, sitting has become the dominant resting position. While a small level of soleus activity occurs during sitting, squatting results in 4–5 times as much soleus muscle activity as sitting [21]. Therefore, while our ancestors were typically sedentary for 9 or more hours each day, similar to modern individuals, their natural resting posture required up to 5x more soleus muscle activity, thereby persevering the fatigue resistant qualities of the slow twitch muscle fibers in this muscle.

7. Soleus muscle stimulation

The critical observation is that the commonly observed declines in the venous return of adults is not a function of age, per se, but rather is the result of the transition to sitting as a dominant resting posture, in particular as people get older. The transition to sitting as the dominant upright resting posture for adults has resulted in two significant impacts on venous return. First, the soleus muscles are activated for only a small fraction of the time when people are sedentary, and correspondingly, muscle pump activity is limited. Second, soleus inactivity results in an adaptation of the soleus muscle fibers such that the muscle, even when activated, is unable to develop the sustained forces necessary to ensure adequate venous return.

Because the soleus fiber adaptations which occur in most people arise primarily from disuse and not due to aging, reconversion of the soleus muscle fibers back to Type I fibers should be possible through alteration of muscle activation patterns. The soleus muscles are activated, when in upright posture, when the center of gravity of the body moves too far forward; soleus contraction returns the body to a balanced position. This shift in the center of gravity is sensed by pressure on the frontal plantar surface, specifically by Meissner's Corpuscles, which activate short, and long, loop reflex arcs which trigger soleus contraction.

Retraining of the soleus muscle fibers therefore should simply require a sustained stimulation of the postural reflex arc in a pattern which mimics normal resting posture (i.e. squatting) activation. This can be achieved using micromechanical stimulation of the Meissner's Corpuscles periodically for sustained periods of time (one minute bouts) for extended time periods, over the course of the day (i.e. a significant fraction of sedentary time).

In our lab, we have undertaken such studies utilizing the soleus muscle stimulator (HeartPartner) developed by Sonostics, Inc. (Endicott, NY). We utilize electrical impedance plethysmography (Cheetah Medical; Wilmington, DE) to track cardiac output following a transition from the quiet standing position to quiet sitting. This represents a change in metabolic activity from about 1.74 METS to about 1.46 METS [22] or roughly a 17% decline in metabolic demands and therefore cardiac output (CO). Typically, the decline observed in adults in far greater. **Figure 8** provides an example of the observed cardiac performance in response to this shift in posture in an older adult. From an initial cardiac index (CI=CO/Body Surface Area) of 2.8 L/min/m^2, cardiac output drops by almost 40% during 60 minutes of quiet sitting.

These results demonstrate that, when seated, the soleus muscles are commonly not being stimulated sufficiently to sustain the venous return necessary to maintain

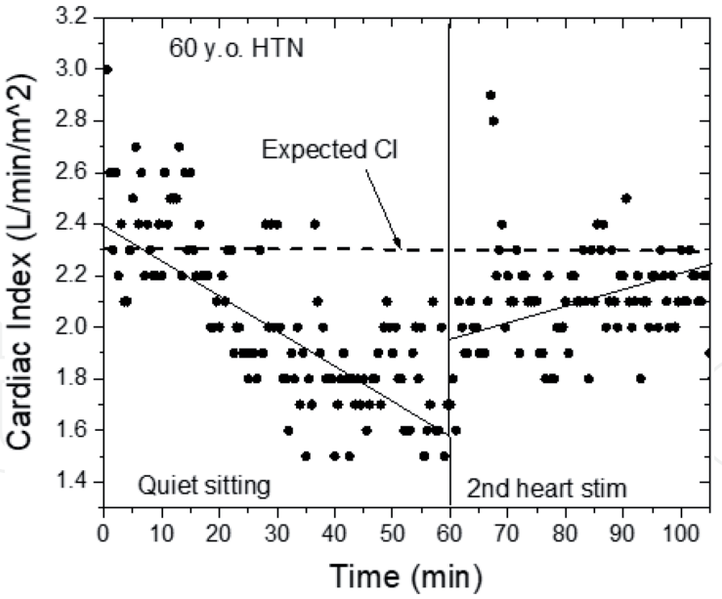

Figure 8.
Cardiovascular system response to soleus muscle stimulation in a 60 year old woman. A change in posture from standing to sitting results in this individual results in a 40% decline in cardiac index (CO/BSA) whereas 20% or less would be expected. While quiet sitting is incapable of stimulate the soleus muscles sufficiently to maintain the venous return necessary to sustain a normal level of cardiac output, external stimulation of the soleus muscles is seen to be capable of returning cardiac output to normal levels within 30 minutes. Initial abrupt rise in CI reflects return of blood pooled into lower limb veins, while the slower rise in CI reflects interstitial fluid return through the lymphatics.

normal cardiac output (CO). However, the soleus muscles still respond, at least over a relatively short duration (30 minutes), to external stimulation. The initial (within minutes) response to soleus stimulation is a rapid rise in cardiac output due to the return of blood pooled into the lower leg veins. Over tens of minutes, interstitial fluid return through the lower limb lymphatics serves to further increase cardiovascular volume resulting in a return to a cardiac output level expected for a sitting adult.

Importantly, just as the soleus muscle rapidly adapts to disuse, these muscles appear to be capable of rapidly "readapting" or more specifically, undergoing muscle fiber reconversion. **Figure 9** (left panel) illustrates the cardiovascular response to the orthostatic stress of quiet sitting in a young (35 year old) woman with severe second heart insufficiency. Upon transitioning from a standing to a sitting position, venous return is inadequate to maintain resting diastolic pressure above a hypotensive level. Specifically, following a transition from standing to quiet sitting, her diastolic pressure is seen to decline from about 80 mmHg, to less than 55 mmHg. Though sitting provides insufficient stimulation to the soleus muscles to maintain venous return, her soleus muscles remain capable of responding to external stimulation. Sustained soleus stimulation over 30 minutes returns her diastolic pressure back close to the normal range (~75 mmHg).

Three months of daily soleus muscle stimulation, for at least one hour per day, resulted in a substantially improved cardiovascular response to the orthostatic stress of quiet sitting in this subject (**Figure 9** right panel). While sitting still resulted in a drop in diastolic blood pressure, the decline it seen to occur at a much slower rate, and to a lesser extent (falling to about 65 mmHg over 90 minutes). These results are consistent with fiber reconversion occurring within the soleus muscles. The differential response is consistent with an increase in the ability of the soleus muscle fibers regaining their fatigue resistance, and correspondingly, their ability to produce the sustained contractions required to ensure adequate venous return to the heart while seated.

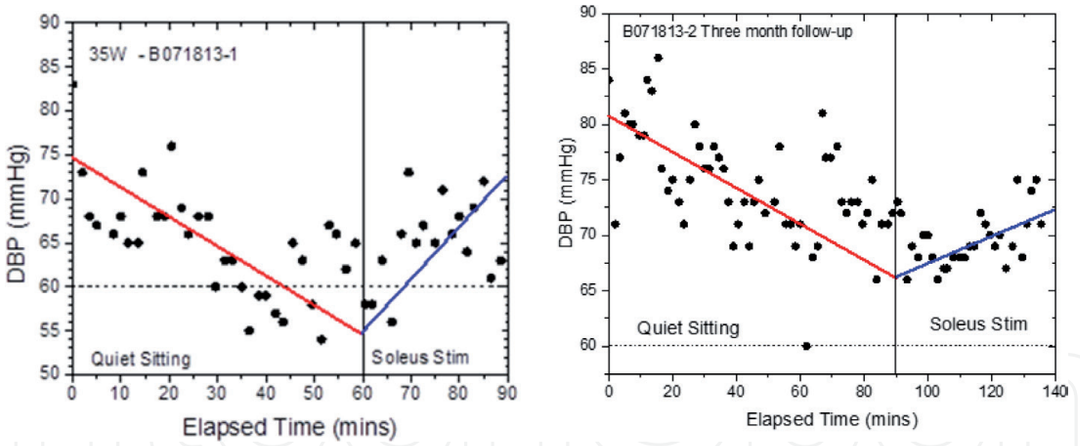

Figure 9.
Soleus muscle retraining following three months of daily, external stimulation. Left panel - In a young adult (35 y.o.) woman, sitting provides insufficient soleus muscle stimulation to sustain the venous return necessary to prevent diastolic blood pressure from falling into a severe hypotensive range. However, external stimulation of the soleus muscles is able to return diastolic pressure back to the normal range. Right panel – Following three months of daily use of soleus muscle stimulation the soleus muscles are capable of preventing severe hypotension even over a sitting duration of 90 minutes, but still unable to sustain a normal diastolic pressure.

8. Influence of soleus muscle stimulation on cognitive function

The ability of soleus muscle stimulation to normalize cardiac output and blood pressure, raises the obvious question of the extent to which such improvements in cardiovascular function can influence cognitive function. Two small pilot studies we have undertaken lead us to believe there is substantial potential for this simple, non-invasive, intervention to slow, and even reverse, the cognitive decline associated with chronic exposure to low cardiac output and the corresponding low cerebral perfusion.

In a three month study on individuals (average age of 82 years) residing in an assisted living center [23], cognitive performance was tracked weekly using the Incongruent Stroop Executive Function Test [24]. Five control subjects with normal blood pressure (resting diastolic blood pressure above 70 mmHg) and five intervention subjects with below normal resting diastolic pressure were recruited into the study. Intervention subjects self-treated to one hour per day of soleus muscle stimulation using a HeartPartner soleus muscle passive exercise device (Sonostics, Inc.). While at the start of the study, the intervention group required almost twice as long to complete the executive function test. Over the three month duration of the study, blood pressures and test times for the control group remained steady. However, the intervention group experienced improvements in both their resting diastolic pressures and their ability to complete the Stroop executive function test, such that at the end of study, test execution times matched that of the control group (**Figure 10**).

Because there is the potential for learning curve effects to play a role in traditional executive function tests such as the Incongruent Stroop when they are given repeatedly to the same study subjects over short separation times, we have also observed the influence of soleus muscle stimulation on cognitive function as assessed by a computer aided assessment which has been shown to have high repeatability and low learning curve effects, and which involves motor, memory, and executive function skills (Cognivue, Inc.). Six subjects, over the age of 65 years, who tested in the moderate to severe cognitive impairment range using the Cognivue assessment, were recruited. Each subject was provided with a soleus muscle stimulation device and encouraged to use the device for at least 2–3 hours per day. Subjects were tracked approximately every month, for six months, or until they cognitive performance returned to the normal range (Cognition score > 75).

All six subjects experienced a return to normal function during the course of the study, though the rate of return was dependent on age of the subjects (**Figure 11**). Subjects in their 60s demonstrated cognitive improvement rates of over 10%/week, while those in their 80s demonstrated improvement rates in the range of only 1–2% per week. Nonetheless, extrapolating over time, even these low rateswould mean

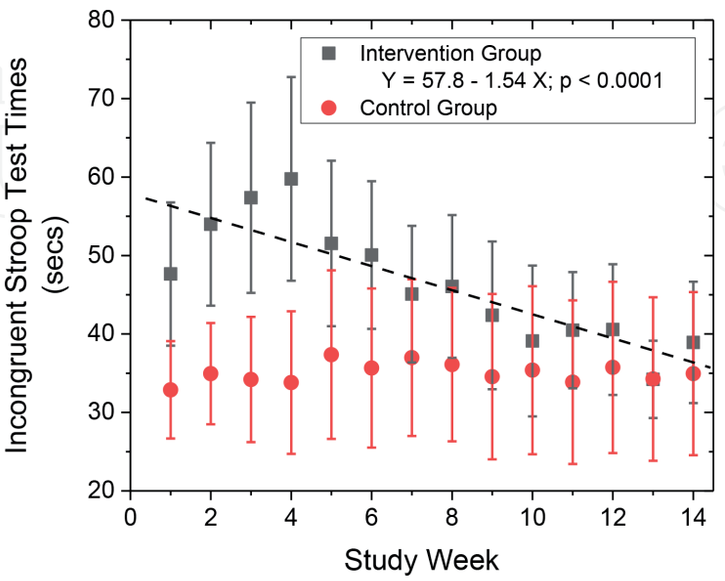

Figure 10.
Long term effects of daily soleus muscle stimulation on cognitive performance in an elderly (average age of 82) population residing in an assisted living center. Cognitive assessment relied on the incongruent Stroop executive function test. Control (normotensive) group test completion times did not vary significantly over three months. The intervention group (DBP < 70 mmHg at start of the study) received one hour per day of soleus muscle stimulation. While test completion times for the intervention group were initially almost twice that of the control group, over three months of daily soleus stimulation test times recovered to a level similar to that of the control group.

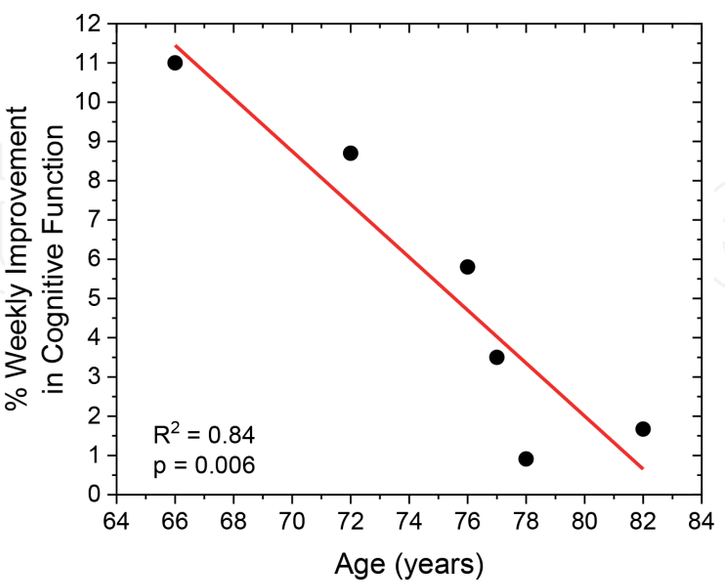

Figure 11.
Cognitive recovery rates as a function of age. Subjects with cognitive performance in the moderate to severe cognitive performance range undertook soleus muscle stimulation for 2–3 hours per day until cognitive performance reached a normal level (cognition score > 75). Individuals in their 60s experienced cognitive performance improvement at a relatively remarkable rate of 10% per week. Individuals in their 8th or 9th decades experience cognitive improvement, but at much lower rates (1–2%/week). A 2%/week cognitive improvement rate indicates that approximately 6 months of intervention would be required to move an individual from the moderate cognitive impairment level to the normal cognitive function level.

that an older individual starting out with severe cognitive impairment (Cognition score < 50) would still be able to return to normal cognitive function within a one year period of time.

9. Conclusions

The impact of dementia on both the healthcare system and society is already large and has the potential to become overwhelming in the near future. Alzheimer's Disease is the most prevalent form of dementia and the strong association between beta-amyloid accumulation in the brain and Alzheimer's provided some hope that if beta-amyloid production could be slowed, or its removal accelerated, dementia could be cured. To date, this strategy has failed to develop, and it is unclear if this strategy will be successful anytime in the near future.

As a result, the current consensus is that we need to identify a means of preventing the development of the cognitive aging which commonly progresses to dementia. Because this will require that any intervention will need to be implemented before there are indications of significant cognitive decline, successful interventions will have to be simple, inexpensive, non-invasive, and well accepted by older adults. Compliance is always challenging for healthcare interventions when the health condition is symptomless, and so it is always beneficial if the intervention produces benefits beyond the primary goal.

What has become clear over the past three decades is that reduced cardiac output, leading to reduced cerebral perfusion, is a robust predictor of cognitive aging and all cause dementia. Though cardiac output commonly declines with age, declining cardiac cardiovascular performance is not, per se, an age dependent outcome, but rather is a function of venous return. Venous return, correspondingly, is primarily dependent on the ability to maintain sufficient soleus muscle pump function whenever a person is in upright posture. The key, therefore, to maintaining cardiac output over a lifetime, is to maintain soleus function over an individual's lifetime.

Soleus muscles lose their ability to maintain adequate venous return, in large part, due to modern society's transition to chair sitting as the normal upright resting mode. Fortunately, like all muscles, the soleus muscles can be retrained and preliminary studies utilizing non-invasive soleus muscle stimulation technology has demonstrated that the improved cardiac output and normalization of blood pressure which results from soleus retraining leads to a reversal of cognitive decline even for those in their 9th decade of life. These preliminary results indicate that simple, well accepted, intervention techniques for the prevention, and even reversal, of cognitive aging, are a viable option for eliminating the devastating economic and social consequences of dementia.

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Conflict of interest

Dr. McLeod holds an equity position in Sonostics, Inc.

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