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Postural Hypotension and Cognitive Function in Older Adults

Kenneth J. McLeod, PhD[1] and Teesta Jain, PhD[1]

Abstract

Background: Cognitive decline in the elderly is associated with chronic cerebral hypoperfusion. While many forms of exercise can slow or reverse cognitive decline, compliance in unsupervised exercise programs is poor. **Objective:** We address whether passive exercise, that is, muscle stimulation, is capable of reversing postural hypotension in an older adult population sufficiently to significantly improve cognitive function as measured by executive function tests. **Subjects and Methods:** In this study, 50- to 80-year-old women underwent cognitive testing, long-duration cardiac hemodynamic recordings during quiet sitting, and 60 min of soleus muscle stimulation with continued hemodynamic recording. **Results:** Two thirds of our subjects were hypotensive (diastolic blood pressure [DBP] < 70 mmHg) after 30 min of quiet sitting. Cognitive performance was significantly better in individuals with higher DBPs (0.79 s per 1-mmHg increase in DBP). Soleus muscle stimulation resulted in an average increase in DBP of 6.1 mmHg, which could translate into a 30% or greater improvement in cognitive performance. **Conclusions:** Incongruent Stroop testing provides high statistical power for distinguishing differential cognitive responses to resting DBP levels. These results set the stage to investigate whether regular use of calf muscle pump stimulation could effectively reverse age-related cognitive impairment.

Keywords

dementia, hypotension, exercise, calf muscle pump

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Introduction

Loss of memory or other cognitive function is a widely feared outcome of aging due to the dependence and disability created by these deficits, as well as the significant financial costs associated with caring for individuals with cognitive impairments (Satizabal et al., 2016). Currently, more than 5 million older adults in the United States suffer from dementia or cognitive impairment without dementia, representing an economic burden exceeding US$200 billion per year (Hurd, Martorell, & Langa, 2013). Encouragingly, recent studies have indicated that age-specific incidence of both dementia and cognitive impairment in individuals older than 65 years is declining. This appears to be a result, at least in part, of higher levels of educational attainment, which is associated with greater physical activity, better access to healthcare, improved diet, decreased smoking rates, and more cognitively complex occupations (Langa, 2017). Nonetheless, the aging of the population is still expected to lead to more than a doubling of the total number of individuals with cognitive impairment/dementia by 2050 (Hebert, Weuve, Scherr, & Evans, 2013). It is therefore imperative that the search for interventions which could significantly slow or reverse age-related cognitive decline continues.

A critical factor influencing cognitive function is cerebral perfusion, which itself is significantly influenced by blood pressure (BP). Historically, it has been assumed that autoregulation served to maintain cerebral blood flow at approximately 50 ml/min per 100 g of brain tissue, over the cerebral perfusion pressure (CPP) range of 60 and 150 mmHg (Cipolla, 2009). As CPP is typically about 10 to 15 mmHg below mean arterial pressure, this would suggest that depressed cerebral perfusion is a concern only for mean arterial pressures below 70 mmHg. More recent work, however, has indicated that the low end of the autoregulatory range can vary widely among individuals, ranging between approximately 50 mmHg to higher than 100 mmHg (Waldemar et al., 1989). Correspondingly, it has been demonstrated that even remarkably small reductions (<10 mmHg) in BP below normal levels are associated with significant decrements in reaction times and cognitive performance even in young healthy adults

[1]Binghamton University, NY, USA

Corresponding Author:
Kenneth J. McLeod, Director, Clinical Science and Engineering Research Laboratory, Binghamton University, Biotechnology Building, Room #2109, Binghamton, NY 13902-6000, USA.
Email: kmcleod@binghamton.edu

(Duschek, Weisz, & Schandry, 2003). Consistent with this observation, randomized, placebo controlled trials have shown that the pharmacologic raising of BP by just 10 mmHg can significantly enhance both cerebral blood flow and cognitive performance (Duschek, Hadjamu, & Schandry, 2007).

The strong dependence of cognitive performance on BP is a particular concern in older adults for several reasons. First, BP, in particular diastolic blood pressure (DBP), commonly falls in individuals above the age of 60 (Cheng, Xanthakis, Sullivan, & Vasan, 2012). In addition, age-related drops in BP can be significantly exacerbated by orthostatic influences (Pan, Benoit, & Girardier (2004). Upon taking an upright posture such as quiet sitting, gravitational forces acting on the blood supply produce a rapid translocation of 300 to 800 ml of blood into the legs, and continued upright posture leads to extensive fluid extravasation into the lower limb tissues. These processes result in significantly decreased venous return to the heart, diminished cardiac preload, and a corresponding drop in cardiac output by up to 50% (Ziegler & Rizos, 2004).

Numerous studies have confirmed an association between chronic hypotension and/or hypoperfusion with dementia in the elderly. Direct assessment of cerebral blood flow, via magnetic resonance imaging (MRI), has been shown to be an accurate marker of mild cognitive impairment (Binnewjizend et al., 2013). A study on individuals with dementia showed that orthostatic hypotension (OH) was severely underdiagnosed in this population (Bengtsson-Lindberg, Larsson, Minthon, Wattmo, & Londos, 2013). These investigators observed OH rates of 69% in dementia with Lewy bodies, 38% in Alzheimer's, but only 13% in age-matched controls. In a cross-sectional population-based study performed in Kungsholmen, Sweden, Guo, Viitanen, Fratiglioni, and Winblad (1996) reported that individuals with systolic blood pressure (SBP) <120 mmHg had a five to 10-fold increased likelihood of having dementia, and similar associations were observed with low diastolic BP. In the community-based, longitudinal Bronx Aging Study, it was observed that sustained low diastolic BP (<70 mmHg) was associated with a twofold increased risk of developing Alzheimer's disease over a 20-year time period (Verghese, Lipton, Hall, Kuslansky, & Katz, 2003). In addition, an association between hypoperfusion and the onset of dementia was observed in the Rotterdam Aging Study (Ruitenberg et al., 2016). Finally, in the Baltimore Longitudinal Aging Study, cognitive performance in an older (70 ± 8 years) population was observed to be significantly degraded at diastolic BPs below 80 mmHg (Waldstein, Giggery, Thayer, & Zonderman, 2005).

The association of chronic hypotension with cognitive dysfunction and increased risk of dementia, as well as the influence of posture on BP, suggests several potential pathways for slowing or reversing the onset of dementia in the elderly. Reduction in orthostatic exposure time, that is, reduction in sedentary activity time, could potentially play an important role in limiting chronic hypotension given the extensive sitting times of most older individuals. The average daily sitting time for those above the age of 60 exceeds 9 hr (Dunlop et al., 2015); moreover, the orthostatic stress of sitting tends to cause particularly large drops in BP in individuals with heart failure (Gorelik et al., 2009). The reality, unfortunately, is that the vast majority of modern activities of daily living (eating, watching television, reading, working on a computer, traveling) involve quiet sitting, and significantly reducing the duration of these activities is likely to have perceived negative influences on quality of life.

Leg elevation, compression stockings, and compression bandages have all been shown to assist in limiting lower limb fluid pooling during orthostasis, but compliance with these intervention modalities remains problematic whenever vigilant supervision is lacking.

Importantly, a recent meta-analysis of randomized controlled exercise studies indicates that essentially all forms of exercise improve cognitive function in the elderly (Cai, Li, Hua, Liu, & Chen, 2017), though again, initiation and adherence remain major issues (Vidoni et al., 2017). An alternative strategy, therefore, may be to utilize a passive exercise regimen. Calf muscle pump activation, via micromechanical stimulation of the lower leg postural reflex, produces sufficient soleus muscle contraction to significantly reduce lower limb fluid pooling and prevent hypotension in middle aged women (Goddard, Pierce, & McLeod, 2008; Madhavan, Stewart, & McLeod, 2004). As this intervention can be implemented whenever an individual is seated, compliance with usage may be greater than with traditional exercise interventions. To set the stage for the design of such an intervention study, we investigated the relationship between cardiac hemodynamics and cognitive function, using multiple executive function tests, in a population of community dwelling older adults during quiet sitting. We then investigated the ability of calf muscle pump stimulation to reverse the long-duration changes in cardiac hemodynamics arising during orthostasis using non-invasive cardiac output monitoring. Finally, we evaluate which executive function tests are sufficiently sensitive to BP changes to incorporate into a prospective clinical trial of this "passive" exercise intervention.

Method

The study protocol was approved by the Binghamton University Institutional Review Board (Protocol #3559-15) and executed in the Clinical Science and Engineering Research Laboratory at Binghamton University. Community dwelling older adults (above the age of 45 years) who were fluent in English were recruited using advertisements on campus, as well as flyers distributed in local healthcare clinics. Inclusion criteria included personal concerns about developing memory loss or other cognitive dysfunction (e.g., difficulty concentrating), willingness to make two visits on separate occasions to the lab, and ability to sit for 2.5 hr without a break. Exclusion criteria included uncontrolled BP (systolic >140 mmHg; diastolic >90 mmHg) or color blindness.

During the first visit to the lab, subjects took a seated position, the research protocol was described, inclusion/exclusion criteria reviewed, written informed consent obtained, and demographic information recorded. Following this orientation, requiring approximately 30 min, a series of three executive function tests were given to the subjects: the Congruent Stroop, the Incongruent Stroop, and the Trailmaking B tests. The Congruent Stroop test is primarily a measure of basic reading rate where the color of the word (red) matches the name of the word ("red"). Conversely, in the Incongruent Stroop test, the color of a word and the word are discordant; that is, the name of a color is printed in a color that does not match the name (e.g., blue or green is printed in red ink) and the subject is asked to read the color. This test is considered to be a measure both of mental flexibility and the ability to deal with interference (Wecker, Kramer, Wisniewski, Delis, & Kaplan, 2000). A total of 21 items, in 24-point font, were presented to the subjects in the two Stroop tests. The Trail Making B test evaluates visual attention and task switching in which the subject is instructed to draw lines to connect a set of 24 alternate numbers and letters as quickly as possible while maintaining accuracy. Each test was explained to the subject with the opportunity given to complete a short practice run. The test was then issued on an 8½ × 11 sheet of paper and timing was initiated; if the subject made a mistake, the investigator notified the subject, who then needed to correct the mistake and then continue with the timed test. All test results are reported as the number of seconds required to complete the task. Total time to complete the first phase of testing was typically less than 1 hour.

On the second visit to the lab, cardiac hemodynamics, including heart rate (HR), BP, and stroke volume (SV), were recorded under conditions of orthostatic stress, both without and with calf muscle pump stimulation. Subjects were seated in an electrically powered easy chair with the position adjusted so that their feet could be placed firmly on the floor. Hemodynamic measurements were obtained using electrical impedance plethysmography (Cheetah NICOM™; Cheetah Medical, Newton Center, MA). This assessment requires the placement of four electrode pairs on the subject's chest, two at the shoulder level and two at the abdominal level, in addition to a brachial pressure cuff for BP monitoring. The NICOM was set to capture HR and SV at 1-min intervals, while BP was recorded every 3 min. Following system calibration, the subjects were asked to stand and complete toe-standing exercises to clear fluid out of the lower legs, then to retake a seated position. The calf muscle pump stimulation apparatus (HeartPartner®; Sonostics, Inc, Endicott, NY) was placed under the feet so that the frontal plantar surface could be stimulated. Calf muscle pump stimulation serves to increase venous return to the heart resulting in increased cardiac output and normalization of BP. Hemodynamic measurements were then obtained during 90 min of quiet sitting with no stimulation (subjects were allowed to read or watch video during this time period, but to otherwise minimize motion) after which the calf muscle pump stimulator was activated and recording continued for another 60 min.

The NICOM device automatically calculates body surface area (BSA) based on the inputs of body height and weight, from which cardiac index (CI) is calculated as HR × SV / BSA. The hemodynamic data, along with executive function test times, were downloaded into Origin 2016 (OriginLab, Northampton, MA) which was utilized for all calculations. Time-dependent data, including HR, SBP, DBP, and CI, were averaged, and correlations to test times were undertaken using linear regression. Average individual BP values following 30 min of orthostasis and at the end of the orthostatic stress period were calculated based on 15-min averages collected over the time span of 30 to 45 min and 135 to 150 min, respectively. Data are reported as means ± standard deviation unless otherwise noted.

Results

A total of 29 subjects volunteered for the study with all but one being women and so we elected to exclude the one male subject due to the potential for gender differences which would not be testable. Twenty-one of the remaining subjects met all of the inclusion criteria, none of the exclusion criteria, and completed both testing phases. Seven subjects could not be rescheduled for the second lab session. Subject ages ranged from 50 to 82 years (mean 61.5 ± 6.6 years). Congruent Stroop test results were consistent with this group being fluent in English, with scores ranging from 7.8 to 16 s, with an average of 11.1 ± 2.4 s, or approximately 0.5 s per word. Incongruent Stroop and Trailmaking B test times demonstrated greater variation. Incongruent test times ranged from 20 to 75 s (mean 35.9 ± 12.8), while Trailmaking B test times ranged from 27.1 to 127 s (mean 51.6 ± 27.1). Neither the Coherent Stroop or Trailmaking B test times demonstrated any significant dependence on subject age, while Incoherent Stroop test times increased significantly with subject age (p = .02; Figure 1).

During the quiet sitting recording period, all cardiac hemodynamic measures (SBP, DBP, HR, and CI) demonstrated substantial declines (Figure 2). For the 21 subjects, average SBP upon sitting was 122 mmHg, declining to about 115 mmHg over 30 min, after which SBP levels largely stabilized. Similarly, DBP upon sitting averaged 78 mmHg, declining to about 71 mmHg over 30 min, and then also stabilized. HR, however, declined continuously over the full 90-min recording period, from a starting rate of 79 to 70 bpm at 90 min.

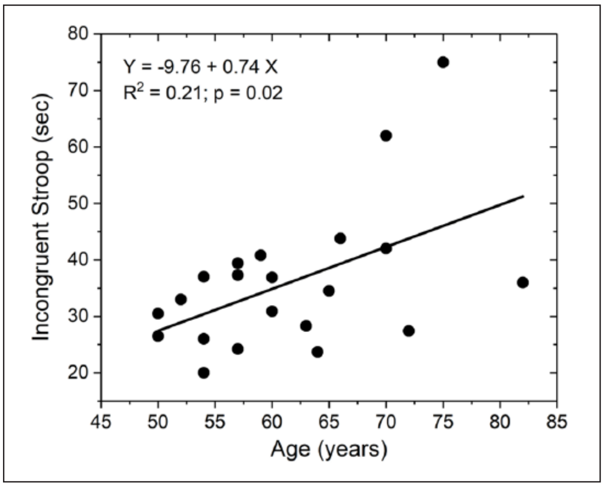

Figure 1. Incongruent Stroop test times as a function of age.
Note. Test times increased significantly (p = .02) over the age range of the subjects, approximately doubling between the ages of 50 and 80 years.

Correspondingly, cardiac index also declined continuously over the 90 min of quiet sitting, from an initial average value of 3.3 L/min/m^2 down to 2.3 L/min/m^2, representing an average decrease of 30%.

Only one of the cardiac hemodynamic parameters, DBP, demonstrated any significant age dependence. Focusing on resting levels (after 30 min of quiet sitting), DBP was significantly, and inversely, correlated to subject age ($p < .02$; Figure 3). Furthermore, 13 of 21 subjects (62%) had a resting DBP level below 70 mmHg (threshold for CPP falling below 60 mmHg), and four of these subjects had a resting DBP below 60 mmHg, that is, below the threshold defining clinical hypotension.

DBP was also the only hemodynamic parameter to show significant correlation to cognitive function, with the Incongruent Stroop test times demonstrating a highly significant inverse correlation with resting DBP levels (0.79 ± 0.27 s/mmHg; $p < .01$) such that test times at 50 mmHg were more than twice that observed at 90 mmHg (Figure 4). Focusing on the hypotensive subpopulation (resting DBP < 70 mmHg), the association between DBP levels and test times was more than twice as large (1.68 s/mmHg). Multiple regression analysis demonstrated that the dependence of Incongruent Stroop test times on DBP was independent of the age influence on test times described above.

Calf muscle pump stimulation raised average SBP, DBP, and HR, and correspondingly, CI levels. The most significant effects observed were on resting DBP levels, where DBP increased in 17 of the 21 subjects, and no subject experienced a decrease in DBP beyond measurement error. Sixty minutes of calf muscle pump (i.e., soleus muscle) stimulation was associated with an average increase in DBP of 6.1 mmHg (SE = 1.3), with effects ranging from −0.7 to 18.9 mmHg (Figure 5). Furthermore, 13 of 21 (62%) of the subjects had a DBP above 70 mmHg following 60 min of soleus stimulation, whereas a single subject had a DBP below 60 mmHg at the end of the stimulation period. In addition, the enhancement of DBP appeared stronger in older subjects such that the age dependence in resting DBP at 30 min was no longer evident after 60 min of soleus stimulation.

Discussion

The role of cerebral perfusion in mediating cognitive function is well established. The challenge facing caregivers, however, is extrapolating this knowledge into simple and actionable diagnostic information which can be utilized to initiate appropriate intervention for older individuals living at home or in senior living centers. Here, we addressed this challenge in a three-part physiologic study. We utilized a series of executive function tests to identify which of these commonly used cognitive assessments demonstrate the greatest sensitivity to aging. Next, we investigated which easily obtainable surrogate measure of cerebral perfusion best correlated to cognitive function. Finally, we investigated the extent to which calf muscle pump stimulation reverses orthostatically driven fluid pooling in this population to obtain the necessary data for the power calculations required for the design of prospective clinical study of this "passive" exercise modality.

In this study, cardiovascular hemodynamics were tracked continuously for 90 min while the subjects were under orthostatic stress (quiet sitting). This extended recording time is in contrast to the majority of studies on postural hypotension as the clinical definition of OH is a 20-mmHg drop in SBP, or a drop of 10 mmHg in DBP, within 3 min of transition to an upright position. Correspondingly, studies addressing postural hypotension in the elderly typically focus on relatively short-term changes in BP during orthostasis. Nonetheless, even these short-term studies have identified a remarkable incidence of OH, ranging from 25% to 65% among the elderly (Hiitol, Enlund, Kettunen, Sulkava, & Hartikainen, 2000; Weiss, Grossman, & Beloosesky, 2002).

Consistent with these previous reports, in our subject population, both BP and CI were observed to fall significantly over the 90-min recording period. Importantly, the predominant drop in BP occurred within the first 30 min of sitting, with resting DBP values dropping below 70 mmHg in more than 60% of the subjects. This suggests that, for this population, for most of the time they are sitting during the day, their DBP level is below that which studies have indicated is a threshold associated with increased risk of developing dementia.

Unlike BP, CI declined continuously over the 90 min of sitting. Average Cardiac Index levels started out at 3.3 L/min/m^2 upon sitting, consistent with the CI expected of this age group when supine ($4.87-0.023 \times$ age; Katori, 1979), then fell by one third to below 2.2 L/min after 30 min of sitting. This long-duration continuous drop in CI

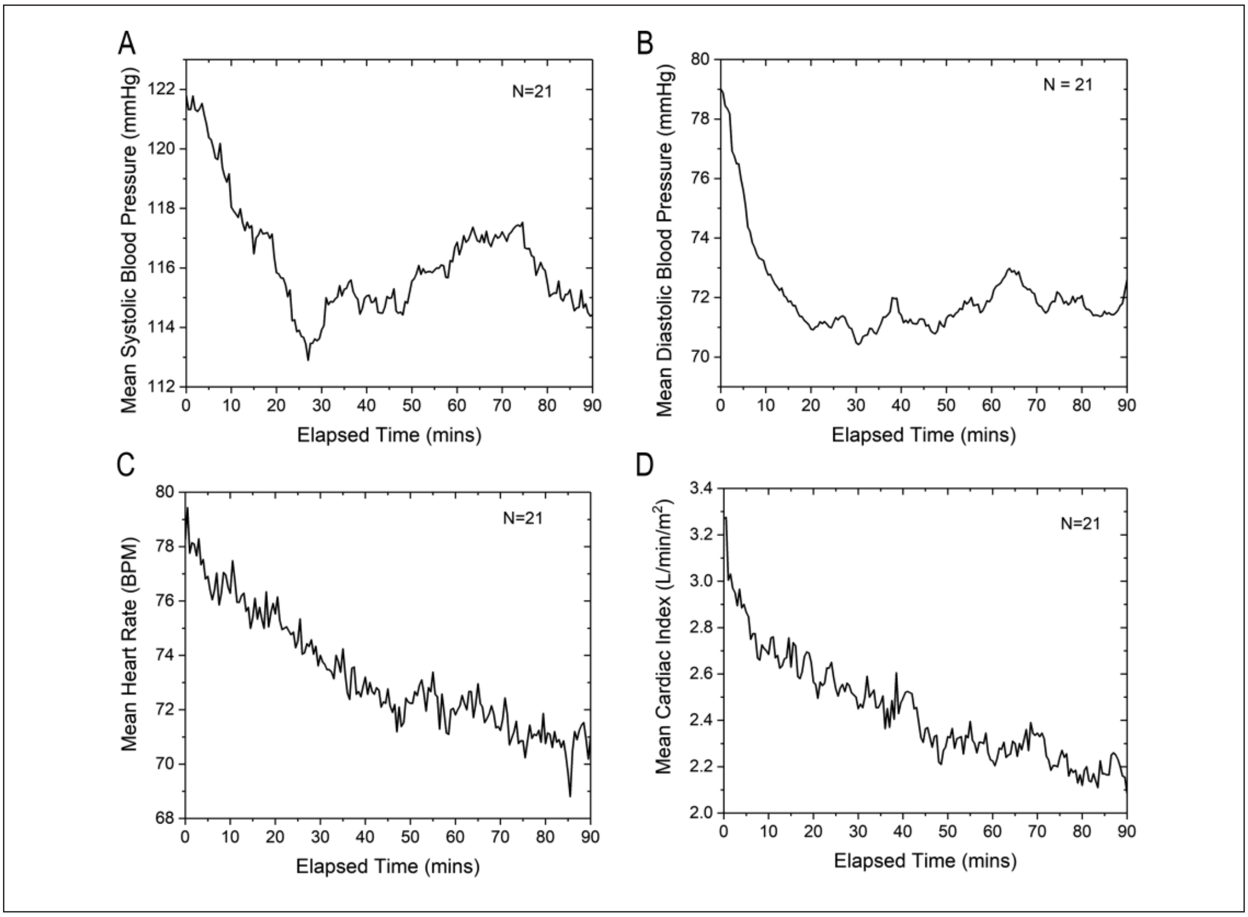

Figure 2. Cardiac dynamics, averaged over 21 subjects, as a function of duration of quiet sitting.
Note. Systolic blood pressure was observed to decline about 5% over the first 30 min of quiet sitting, then plateaued (A). Diastolic blood pressure declined approximately 10% over the first 20 to 30 min, then plateaued near 70 mmHg, a level where cerebral perfusion begins to be significantly affected (B). While heart rate was observed to decline by only 10% over the 90 min (C), cardiac index fell by one third over the 90 min of quiet sitting as a result of significant reductions in stroke volume as well as heart rate (D).

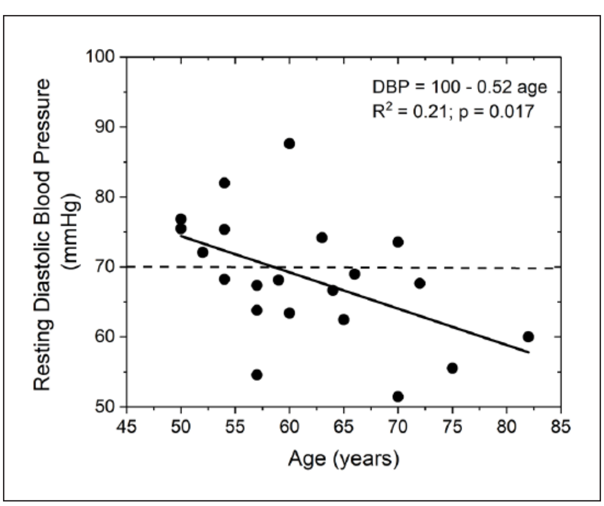

Figure 3. Resting diastolic pressure as a function of subject age.
Note. DBP following 30 min of quiet sitting was significantly dependent on subject age. Two thirds of the subjects demonstrated resting DBP levels below 70 mmHg, while the DBP of four subjects (20%) fell below 60 mmHg, the threshold for clinical hypotension. DBP = diastolic blood pressure.

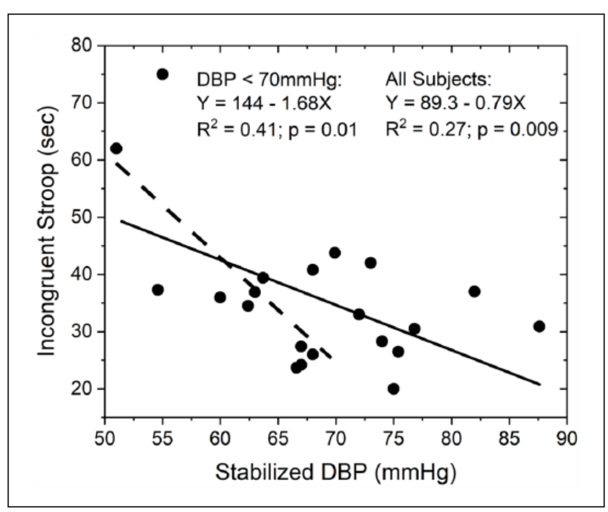

Figure 4. Incongruent Stroop Test times versus resting DBP.
Note. Incongruent Stroop test times demonstrated a significant inverse correlation to resting DBP levels ($p < .01$). Test times more than doubled as DBP ranged from 90 to 50 mmHg. Focusing on the hypotensive subset of subjects (resting DBP < 70 mmHg), test times were 1.7 s longer for each 1-mmHg decrease in blood pressure. DBP = diastolic blood pressure.

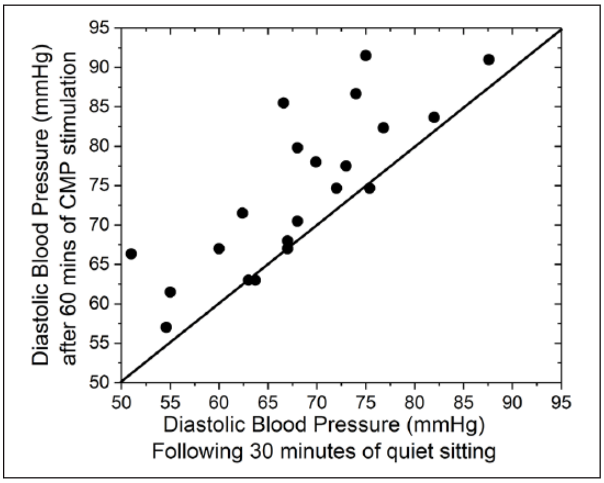

Figure 5. Change in resting diastolic blood pressure following 60 minutes of calf muscle pump stimulation.
Note. Soleus (calf muscle pump) stimulation increased resting DBP in 17 of the 21 subjects. Average increase was 6.1 mmHg among all subjects, and 8 mmHg among the responders, a magnitude which would be expected to lead to a 14-s improvement in Incongruent Stroop test scores, or approximately a 40% improvement. DBP = diastolic blood pressure; CMP = calf muscle pump.

is very different than that seen in young adults, where changes in resting metabolic rate (a surrogate measure of cardiac index) have been shown to plateau in 10 to 15 min (Popp, Risch, Sakarcan, Bridges, & Jesch, 2016). However, these results are consistent with recent work assessing lower limb fluid pooling which show that fluid pooling in older adults (40-70 years) can progress for more than 4 hr (Singh, Yadollahi, Lyons, Alshaer, & Bradley, 2017).

Our subjects demonstrated Stroop test times similar to published normative data (Bayard, Erkes, & Moroni, 2011). Moreover, consistent with what has previously been reported with respect to the relationship between BP and cognitive function, we observed a significant inverse correlation between DBP and performance times on the Stroop tests. Of particular note is the performance of the subpopulation which had a resting DBP in the hypotensive range (DBP < 70 mmHg). For this group, each 1-mmHg decrease in BP was associated with an increase in test times (Incongruent Stroop) of 1.7 s (approximately 5%). As age-related dementia is associated with increased Stroop test times of just 25% (Bayard et al., 2011), this increase may be quite significant clinically.

We found that 60 min of calf muscle pump (soleus muscle) stimulation was sufficient to increase DBP in 17 of the 21 subjects, with no evident change in the remaining four. From an intention-to-treat perspective, the average increase in DBP was 6.1 mmHg. However, as it would be a simply process to prescreen subjects to determine responsiveness to the intervention, we also considered effectiveness excluding nonresponders. Excluding the four nonresponders, average DBP increased 8 mmHg, from 68 to 76 mmHg. Whether an 8-mmHg average increase in DBP would be sufficient to significantly improve cognitive function remains to be tested; however, this increase is quite similar in magnitude to that achieved with pharmacologic intervention and which has been shown to significantly improve both cerebral perfusion and cognitive performance in chronic hypotensives (Duschek et al., 2007). Furthermore, based on the initially observed relationship between DBP and Incongruent Stroop test times, an 8-mmHg increase in DBP should correspond to a 14-s reduction in test times, reflecting approximately a 40% improvement in cognitive performance.

Limitations of this study include the relatively small population evaluated. Because of the small number of subjects, we were unable to test for the confounding influence of numerous variables which affect cardiovascular performance and BP beyond age. These factors would include the influence of hypertension medications, medications which influence metabolic activity, the role of polypharmacy (drug interactions), gender, physical/athletic activity levels, and psychosocial factors (Huang, Webb, Zourdos, & Acevedo, 2013). Furthermore, hemodynamic recordings were not obtained on the same day as the cognitive testing. The experiment was designed to prevent the subjects from having to spend a large portion of their day in the laboratory, with the assumption that day-to-day variations in cardiac hemodynamics as well as cognitive function would not vary substantially; however, this may not be the case. Finally, we only investigated the influence of calf muscle pump stimulation on cardiac hemodynamics following 90 min of fluid pooling during orthostasis; the ability of soleus stimulation to prevent orthostatic fluid pooling remains to be evaluated.

In summary, an important aspect of mild cognitive impairment is that it is reversible (Ganguli, Fu, Snitz, & Chang, 2013). Exercise, in particular, is widely regarded as an effective means to slow or reverse cognitive decline (Ballesteros, Kraft, Santana, & Tziraki, 2015), and remarkably, mild exercise programs (walking, 2-kg dumbbells, etc.) albeit of long duration (60 min, 3 times per week) have been shown to significantly improve cognitive performance in older adults (Lu et al., 2016). These observations naturally raise the question of whether the effectiveness of the exercise programs is simply a function of exercise effects on BP, and therefore cerebral perfusion, in the elderly subjects. Unfortunately, compliance with exercise programs tends to be quite poor in the absence of supervision. Calf muscle pump stimulation is a form of passive exercise wherein the soleus muscles is activated while the individual sits quietly, and does not require the individual to remove their shoes and socks/stockings, and may have potential for providing long-duration exercise sufficient to slow or reverse cognitive decline in older adults. The data obtained here set the stage for a prospective pilot clinical trial of this intervention.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Kenneth J. holds an equity position in Sonostics, Inc. and so could possibly benefit financially from the publication of this research.

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