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Short Communication

Redefining Hypotension in Older Adults: Implications for the Prevention of Age Related Cognitive Decline

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Abstract

Chronically low blood pressure in older adults is associated with significantly increased long-term risks of dementia and all-cause mortality risk. Yet low blood pressure is generally not treated until an individual begins to experience the acute symptoms arising from very low cerebral perfusion. However, these acute symptoms, such as dizziness, balance difficulty, syncope, increased fall occurrence, vision impairment, and nausea, begin to occur only at very low blood pressure levels, such that mean arterial pressure levels as low as 65mmHg are often considered to be of limited concern. If the long-term consequences of chronic low blood pressure are to be prevented, an alternative approach to defining what constitutes too low a blood pressure for older adults, i.e. hypotension, will be required. Cognitive aging is a significant health concern for many older adults as it has significant impact on quality of life, and is widely considered a precursor to dementia. Here, we utilize an FDA cleared computer aided cognitive assessment tool to identify the relationship between resting brachial blood pressure in the upright seated position, and cognitive function in a convenience sample of independently living older adult men and women. We observed that resting diastolic blood pressure is significantly and positively correlated with cognitive function in adults over the age of 60 years. Specifically, cognitive performance was found to be significantly impaired for diastolic blood pressure levels below approximately 80 mmHg. Diastolic blood pressures (DBP)

below 80 mmHg in older adults have consistently been shown to increase the risk of dementia as well as all-cause mortality, but the influence of below normal DBP on quality of life (QoL) in older adults has not been extensively addressed. The present work shows that adults over age 60, with a DBP below 80 mmHg, are significantly more likely to demonstrate mild to moderate cognitive impairment, and correspondingly, the associated impacts on QoL. These results lead to the suggestion that maintenance of diastolic blood in older adults in the 80-90 mmHg range will not only improve quality of life in this population, but may also provide substantial clinical benefit in terms of preventing, or reversing, age-related cognitive decline.

Keywords
Hypotension; age-related cognitive decline; dementia prevention

1. Introduction

Both absolute and relative definitions of hypotension are used clinically. In absolute terms, an adult with a systolic blood pressure (SBP) below 90 mmHg, a mean arterial blood pressure (MAP) below 65 mmHg, or a diastolic blood pressure (DBP) below 40 mmHg, is considered hypotensive [1]. In relative terms, a sustained drop in blood pressure after transitioning from a supine to sitting or standing posture, of greater than 20 mmHg for SBP, or more than 10 mmHg for DBP, is an indication of hypotension [2]. When this drop occurs within 3 minutes, the individual is considered to have orthostatic hypotension (OH), while if the drop occurs after more than 3 minutes the individual is referred to as having delayed OH [3].

These threshold values are clinical standards because they reflect the blood pressures at which acute symptoms of hypotension (orthostatic intolerance) are consistently observed in individuals in upright posture. Symptoms of hypotension primarily arise from decreased brain blood flow. The DBP hypotension threshold of 40 mmHg reflects the minimum blood pressure required to pump blood from the heart to the top of the head in a standing or seated individual - a distance of approximately 18 inches (45 cm), against the force of gravity. DBP below this level leads to cerebral hypoxia and loss of consciousness. Loss of consciousness when standing, results in falling, which often has significant health impacts, particularly for the elderly. Hip fractures resulting from falls are associated with a 5× increase in one year mortality rates for those over 60 years of age [4].

However, there are also significant long-term health effects associated with chronically low blood pressure. Postural hypotension in older adults has been shown to be associated with increased risk of cerebrovascular disease and increased cardiovascular disease [5]. In addition, while mid-life hypertension has been associated with increased dementia risk [6], there is a growing recognition [7] that low late-life blood pressure is also associated with increased dementia risk. Cohort studies provided the first evidence of this low blood pressure-dementia link [8], and subsequently, numerous, large, prospective studies [9-12] have confirmed this observation. Combined with research demonstrating the strong influence of reduced BP on cerebral blood flow [13], these observations have led to the working hypothesis that sustained reduced brain blood flow plays a causal role in the development of dementia. This remains an active area of investigation, with numerous other parameters, such as blood pressure index [14], orthostatic hypotension [15, 16]

and blood pressure variability [17] also being proposed as critical factors mediating the progression to dementia.

Further, increased risk of all-cause mortality has been associated with below "normal" blood pressure levels. For example, recent work with the frail elderly has shown that all-cause mortality was significantly reduced at SBP levels of 140-160 mmHg and DBP levels of 80-90 mmHg compared to those with lower blood pressures [18]. In a population of individuals over 70 years of age undergoing antihypertensive therapy, those who achieved a target SBP below 140 mmHg or a DBP below 90 mmHg had a significantly higher risk of all-cause mortality compared to those with treated BPs above these levels [19].

While dementia and all-cause mortality risk are critical issues, these are health endpoints, and do not reflect quality of life for most adults over the bulk of their elder years. Conversely, mild/moderate cognitive impairment (MCI) is remarkably common among older adults, with a prevalence as high as 22% for those over age 70 years [20]. MCI not only has profound effects on quality of life [21] but it is also a strong predictor of dementia. Progression to dementia occurs at a rate of 12% per year among those with MCI, a rate 3-5 times greater than similarly aged individuals with normal cognition [22].

Cognitive impairment, therefore, represents a uniquely valuable health outcome from the perspective of understanding hypotension thresholds. While cerebral blood flow is traditionally considered to be well regulated [23], recent studies have shown that there is essentially a linear relationship between blood pressure and cerebral blood flow. This relationship is particularly robust for diastolic blood pressure, where a 10 mmHg reduction in DBP has been shown to be associated with a 10% reduction in cerebral blood flow [13]. The ability to identify, and effectively treat, those most at risk of reduced brain blood flow at an early age could result not only in greatly improved quality of life among this population, but also the prevention, or even reversal, of age-related cognitive decline, and correspondingly, the prevalence of dementia, and perhaps, reduced all-cause mortality.

Until recently, cognitive performance in the elderly has primarily relied on a wide range of pen and paper-based assessments, with the most popular including the Mini-Mental State Exam (MMSE), the St. Louis University Mental Status (SLUMS) exam, and the Montreal Cognitive Assessment (MoCA). These assessments were developed to detect dementia and do so effectively, but the qualitative aspects and narrow scoring ranges tend to result in poor sensitivity for milder forms of cognitive impairment or for tracking changes in cognitive performance [24]. Other issues which have been raised in regards to these assessments are that the MMSE does not include evaluation of executive function, and is sensitive to cultural factors, education and socio-economic status [25], and the more recently developed SLUMS and MoCA have been shown to have poor specificity [26].

This situation changed substantially in 2015 when the FDA approved the first computer based cognitive assessment aid (Cognivue) developed by Cerebral Assessment Systems (now Cognivue, Inc., Victor, NY). This computer based cognitive assessment was designed to improve on the sensitivity, specificity, as well as reliability on repeated testing, of cognitive assessment, in comparison to pen and paper assessments, as well as minimizing assessment bias associated with education and socio-economic levels [27]. Cognivue evaluates motor, memory, and executive function through a series of eight tests which can be completed by an individual in about 10 minutes total. Subsequently, more than a dozen short duration (less than 30 minute) computerized cognitive assessment aids have been developed [28], with the most recently FDA cleared assessment

(CognICA) being language independent. In all cases, these tools are considered by the FDA to be assessment aids and not diagnostic tools. Nonetheless, they provide simple, and reproducible, means of characterizing cognitive performance in older adults.

Given the importance of cognitive health in maintaining quality of life, and the development of cognitive assessment tools capable of characterizing mild to moderate cognitive impairment, we elected to undertake a pilot observational study directed towards characterizing the relationship between cognitive performance and blood pressure parameters. The underlying hypothesis was that, similar to dementia and all-cause mortality, a lower blood pressure level exists which will identify those at increased risk of early cognitive impairment. The study design involved a convenience sample of independently living older adults. Computer based cognitive assessments were regressed against resting blood pressure parameters in order to identify the presence of any significant relationships.

2. Methods

While postural hypotension is optimally evaluated in an individual in the standing position, obtaining accurate blood pressure shifts during postural transitions in the absence of tilt-table testing is remarkably challenging [29]. We therefore elected to obtain absolute brachial blood pressure levels following 10 minutes of quiet upright sitting. This measurement is convenient to obtain, reproducible, and widely used in clinical medicine. Three brachial blood pressure measurements were obtained from each subject using an electronic sphygmomanometer (Contec, Model 08A, Contec Medical Systems Co. Ltd., Qinhuangdao, PRC), immediately after being seated in a chair with arm and back support and with the subject's feet on the ground, and at five minutes intervals. The third blood pressure measurement (reflecting adaptation to 10 minutes of quiet sitting) was utilized in the analyses. SBP, DBP, and HR were recorded, and MAP was calculated as 1/3 SPB + 2/3 DBP. While 30 minutes or more of seated rest would be required to identify all of those with delayed OH, we felt such a long protocol was impractical for an assessment that would be useful in the primary care environment.

Cognitive performance was assessed using the Cognivue Advanced system (Cognivue, Inc. Victor, NY). The Cognivue Advanced assessment was selected as it is an FDA cleared cognitive assessment aid, and it utilizes the results of a range of cognitive tests addressing reflex, visual/spatial, executive, language, memory, delayed recall and abstraction functions. This system has been validated for adults over the age of 55 years and provides a combined cognitive performance score on a scale of 1-100. Scoring has been referenced to standard SLUMS criteria, such that a combined scores of 75 or greater reflects normal cognitive performance (SLUM >26), and a score below 50 consistent with a SLUM <21, or cognitive impairment. Scores in the 50-74 are interpreted as mild cognitive impairment. R^2 for repeated testing with the Cognivue is 0.81 which is higher than that for pen and paper assessments [27].

As the Cognivue cognitive assessment has been validated only for those over 55 years of age, we limited study participation to that age range. Inclusion criteria were: Living independently; and fluency in reading and understanding the English language. Exclusion criteria included self - reported visual challenges which would prevent reading a computer screen, or manual dexterity challenges which would prevent operation of the manipulandum of the device. Subject recruitment was promoted through advertisements in the local community as well as through participating physician

referrals. After obtaining informed consent, both age and self-reported gender were recorded along with SBP, DBP, HR, and cognitive performance values. A minimum sample size of 90 was selected based on the study size utilized in the Cognivue validation study (Hildago) where computer assessment outcomes were shown to be equivalent to the SLUMS exam.

Univariate statistics, linear regressions, and multivariate linear regression analyses were performed using Origin 2023 (OriginLab Corp, Northampton, MA). p-values < 0.05 were considered statistically significant.

The study protocol was determined to be IRB exempt as the study involved only a single clinical lab visit where two short and simple non-invasive tests (BP and cognitive assessment) would be performed, and no other health data would be collected.

3. Results

Ninety-three subjects were recruited (38 M/55 F). Subject age ranged from 55 to 89 years (mean = 70.9 years). Resting SBP following 10 minutes of quiet sitting ranged from 97 mmHg to 167 mmHg (mean = 134 mmHg), while resting DBP ranged from 48 mmHg to 95 mmHg (mean = 71.8 mmHg). Resting heart rates ranged from 54 bpm to 89 bpm (mean = 68.4 bpm). Based on standard SBP, DBP and MAP definitions of hypotension, none of the recruited subjects would be described as hypotensive.

Six subjects could not complete the Cognivue assessment due to either frustration, vision difficulties, or motor coordination difficulties. For the 87 subjects completing the cognitive assessment, scores ranged from 11 to 95 (mean = 67). Cognitive performance as a function of age demonstrated a significant negative correlation ($p < 10^{-9}$) with increasing age, with the average rate of decline of 1.1 points per year of additional age (Figure 1). For those younger than 60 years of age, over 80% (13/16) scored over 75 on their cognitive assessment. For those 70 years of age or older, over 85% (39/46) had a cognitive performance score below 75 (mild or more severe cognitive impairment, and 24% (11/46) had a cognitive performance score of less than 50, that is, in the impaired cognitive function range.

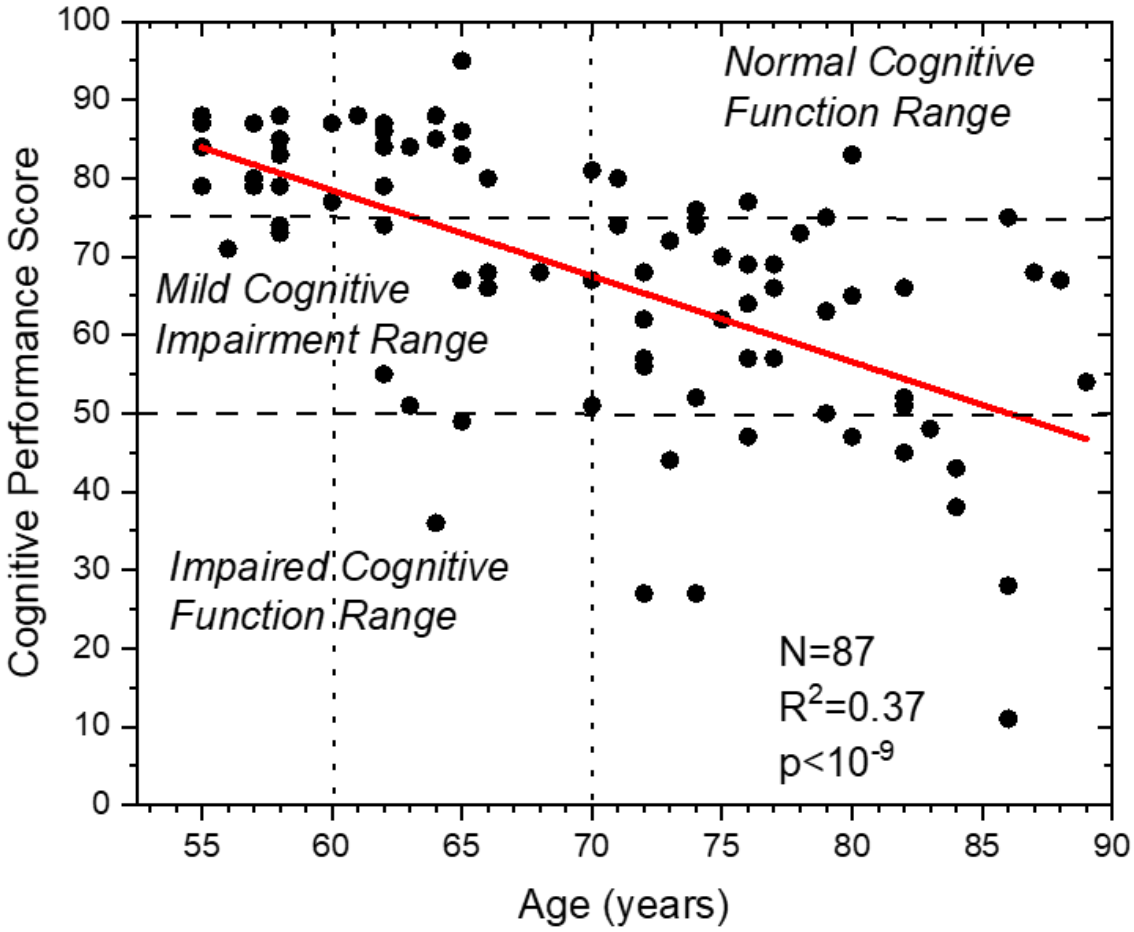

Figure 1 Cognitive performance vs. age. For subjects 55-60 years of age, 81% demonstrated cognitive behavior in the normal cognitive function range as defined by the Cognivue Advanced computer based cognitive assessment aid. For those subjects 70 or older, 85% of subjects demonstrated cognitive performance characterized as being in the mild cognitive impairment or impaired cognitive function ranges.

Demographic determinants of cognitive performance score were identified through multiple linear regression (Table 1). Age, SBP, DBP, HR, and gender were included in the analysis. Only age ($p < 10^{-5}$) and DBP ($p = 0.009$) were found to be significant predictors of the cognitive performance score. Cognitive performance declined with age at a rate of 0.85 points per year of age. Conversely, DBP was positively correlated to cognitive score, with cognitive performance scores increasing 0.41 points per 1 mmHg increase in pressure.

Table 1 Results of multiple linear regression analysis of Cognitive Performance Scores against age, blood pressure, heart rate and gender.

	Regression Coefficient	**Standard Error**	**t-Value**	**p Value**
Intercept	129.7	21.5	6.02	$4.9 * 10^{-8}$
Age (years)	-0.851	0.166	-5.11	$2.1 * 10^{-6}$
SBP (mmHg)	-0.046	0.090	-0.51	N.S.
DBP (mmHg)	0.410	0.155	2.65	0.009
HR (bpm)	-0.345	0.171	-2.02	N.S.

Gender (1 = Male)	-5.08	3.14	-1.62	N.S.

Only age and diastolic blood pressure were found to be significant predictors of cognitive performance in the study group of 55-89 year old men and women.

Further analysis addressed the relationship between age and DBP (Figure 2). Age was found to be a significant predictor of resting DBP ($p = 0.001$) in the study population, with DBP declining 0.33 mmHg for each additional year of age. Average DBP was observed to be below normal (i.e. <80 mmHg) across the entire age range evaluated, declining from an average of 77 mmHg at age 55 years, to 66 mmHg by age 89.

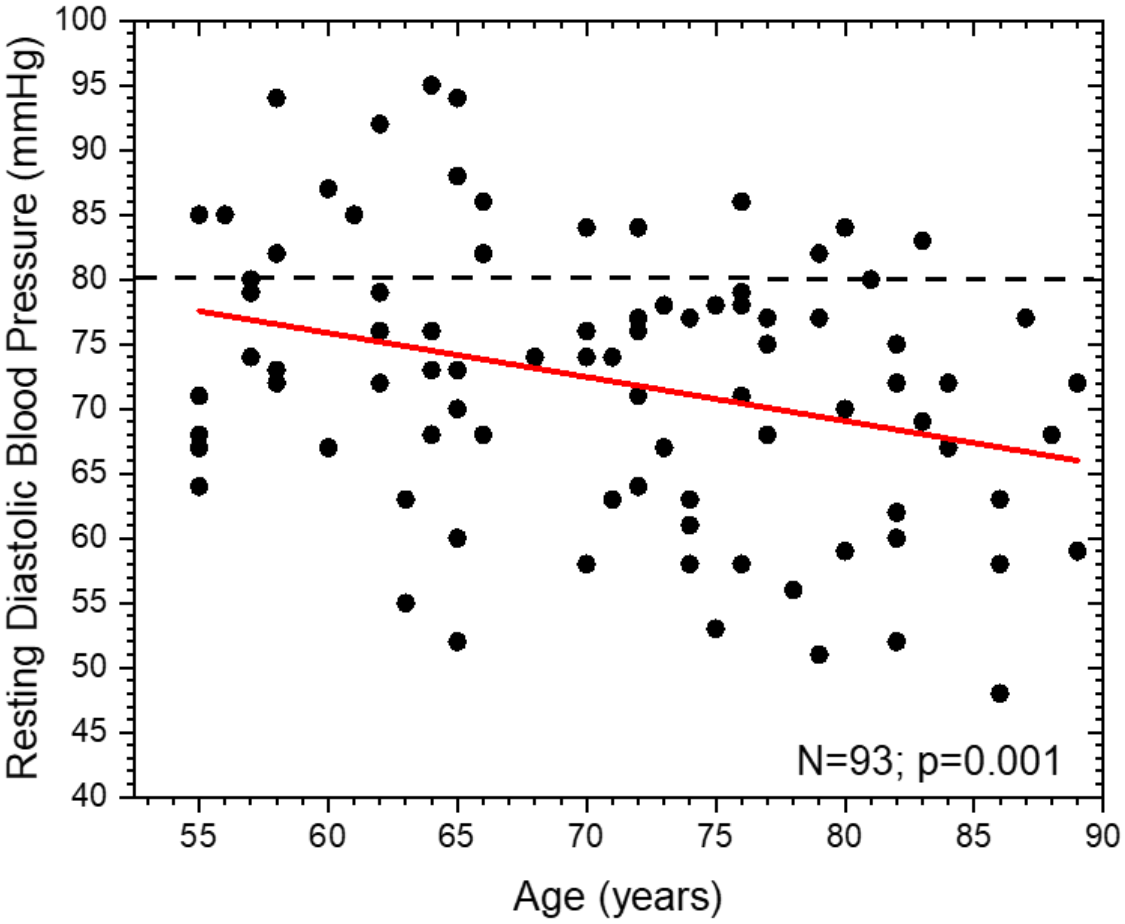

Figure 2 Average diastolic blood pressure declines significantly with age ($p = 0.001$). Average DBP was found to be below normal (<80 mmHg) across the age range from 55-89 years. However, no subject was found to have a DBP in the classically defined hypotensive range (i.e. below 40 mmHg).

Utilizing the calculated multiple regression coefficients to remove the influence of intercept and age from the cognitive performance scores, the relationship between DBP and cognitive score for each subject was determined (Figure 3). This analysis was undertaken for subjects 60 or older, the age at which cognitive performance began to decline in the subject population. The correlation between DBP and cognitive performance score was more positive for this subgroup, with cognitive scores increasing approximately 0.47 points per 1 mmHg increase in DBP ($p = 0.001$). Over the range of DBP values in the subject population, (48-95 mmHg) there was a 22 points improvement in

cognitive performance score at the highest DBP compared to the lowest DBP (p = 0.004). In addition, this analysis indicated that the point where DBP transitions from having a positive impact on cognitive performance scores to having a negative impact on cognitive scores occurred at a DBP of approximately 80 mmHg.

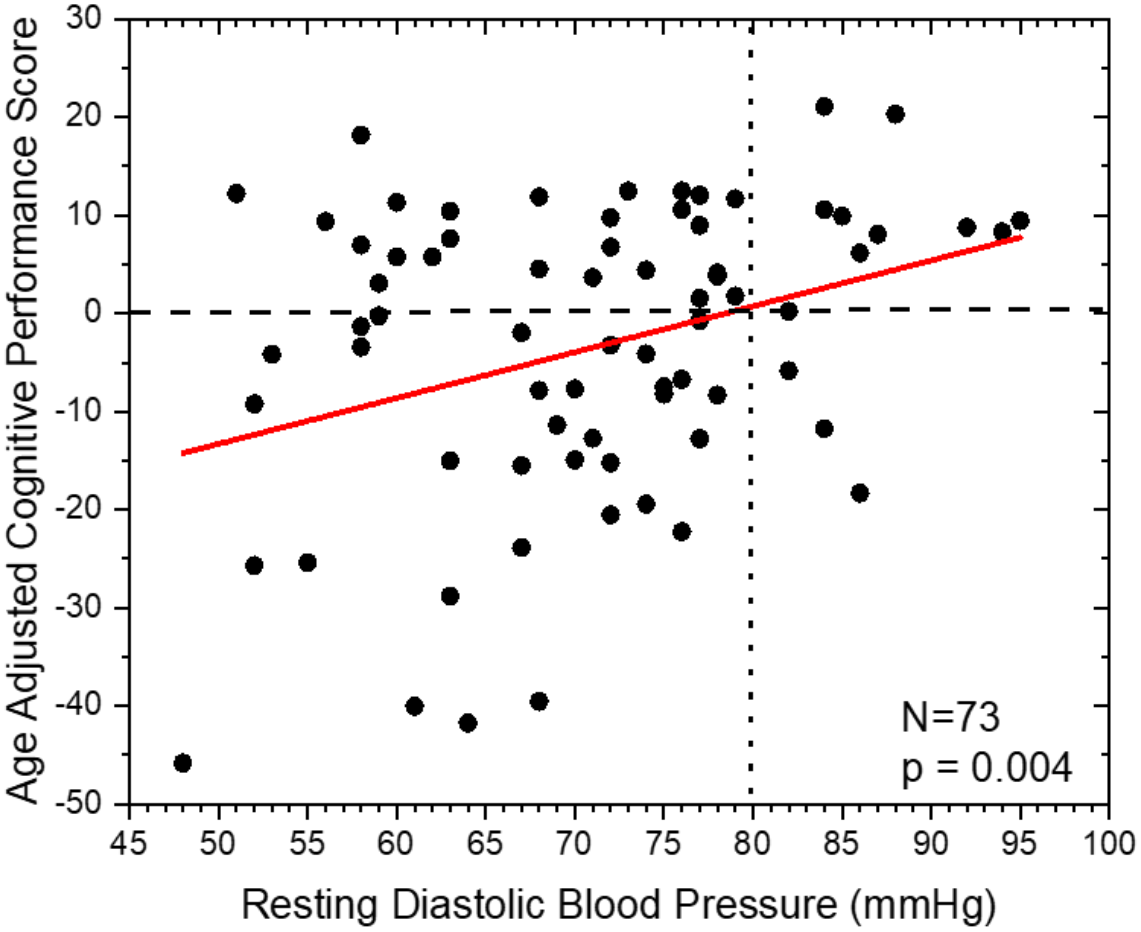

Figure 3 Diastolic blood pressure is a significant and independent predictor of cognitive performance as assessed using the Cognivue Advanced computer based cognitive assessment aid, in particular, for subjects over the age of 60 years where early cognitive decline becomes evident. After removing the effects of age and intercept from the cognitive performance score, the independent effect of DBP on cognitive performance can be observed. Cognitive performance is negatively affected by DBP levels below 80mmHg. On average, each 10 mmHg decrease in DBP below 95 mmHg was found to be associated with a drop in cognitive performance of 4.7 points on a 100 points scale.

4. Discussion

Consistent with the concept of cognitive aging, we observed a strong dependence of cognitive performance on age when utilizing a computer based cognitive assessment aid. While the vast majority of study subjects below age 60 demonstrated normal cognitive function, the vast majority of subjects over the age of 70 demonstrated below normal cognitive performance, and 24% of this group demonstrated cognitive impairment, consistent with previous reports [20]. The age range of

60-70 years, in this group, was associated with a particularly rapid transition in cognitive function. Yet, very few subjects in this age range showed declines beyond mild cognitive impairment. This observation is consistent with the widely held understanding that while dementia can develop suddenly, in general, it is not a rapid onset condition but the result of a progressive condition initially manifesting as mild cognitive impairment. These results add support to the contention that if cognitive impairment can be slowed or reversed in its earliest stages, then progression to more advanced stages of cognitive decline may never occur.

Access to signs associated with early cognitive impairment, however, will not be sufficient to slow or prevent progression unless an effective intervention is available. That mild to moderate cognitive impairment is significantly associated with resting diastolic blood pressure suggests both a means to intervene and an indication of when to intervene. The results from this study show that the threshold at which DBP begins to have a negative influence on cognitive function is about 80 mmHg. That is, at least from a cognitive function perspective, diastolic blood pressures below 80 mmHg should be considered hypotensive for the over 60 population. This 80 mmHg threshold for DBP is consistent with current medical practice guidelines. For example, in December of 2022, the American Academy of Family Physicians updated their hypertension guidelines to recommend treatment of adults with hypertension to a standard blood pressure target of 140/90 mmHg [30].

In the present study, only about 20% of participants met this diastolic blood pressure threshold (only 4 subjects had a resting DBP >90 mmHg). If 80 mmHg is accepted as an appropriate lower threshold for defining hypotension, and if the subjects of our study are representative of the U.S. population, then these data indicate that a very large segment of the elderly population will require some intervention to assist them in normalizing their resting DBP.

Below normal blood pressures can arise for a variety of medical or physiologic reasons. Polypharmacy commonly results in decreased blood pressure as well as overmedication with diuretics, anti-hypertensives or anti-depressants. Concerns over the widespread complications of polypharmacy resulted in the initiation of the National Institutes of Health “de-prescribing” program to assist physicians in reducing medication levels among their elderly patients [31]. Similarly, for elderly patients with DBP <80 mmHg and taking blood pressure lowering drugs, medication levels should be reviewed.

From a physiologic perspective, as blood pressure is the product of cardiac output and vascular resistance, low resting blood pressure reflects either a loss of vascular compensation in the upright individual, or a decline in cardiac output. Vascular resistance can be increased through pharmacotherapy in some patients. Midodrine is currently the FDA approved medication for treating hypotension [32]. However, midodrine use is contraindicated for those with heart or kidney disease, and complications of use include supine hypertension as well as numbness, paresthesia, backache, and difficulty urinating. These complications and restrictions limit the usefulness of this medication in the elderly, and so alternative pharmacologic approaches to treating chronic hypotension are under investigation [33].

That cardiac output declines with age (about 1%/year) has long been known [34, 35]. A common cause of reduced cardiac output, in the absence of heart failure or autonomic dysfunction, is insufficient cardiac return. When upright, blood and interstitial fluid return to the heart is highly dependent on skeletal muscle pumping activity [36]. While all muscles of the leg can play a role in this process, the soleus muscles in the lower leg are responsible for over 70% of cardiac return. In the absence of adequate soleus muscle activity, blood will pool into the lower limb venous system

and interstitial fluid will pool into the lower limb tissues during sedentary activity. This fluid pooling suggests two approaches for addressing low cardiac output - either prevent lower limb fluid pooling, or enhance calf muscle pumping activity.

Various approaches are available to assist patients in their efforts to limit lower limb fluid pooling and maintain diastolic blood pressure. Fluid pooling can be reduced through use of leg elevation, compression stockings, or sequential pneumatic compression, though compliance with these interventions, particularly among the elderly, can be challenging. Enhancement of calf muscle pump capability can be achieved through several different approaches. As with any muscle, the soleus muscles can be retrained with appropriate exercise, and exercise is commonly prescribed for individuals with chronically low blood pressure. However, because the soleus muscles are deep postural muscles, they are optimally retrained using low level, long duration, exercise regimen such as squatting or toe standing, for which there is generally poor compliance in unsupervised settings. Alternatively, external activation of the lower leg muscles can be utilized. Transcutaneous peroneal nerve stimulation has been shown to enhance venous return, and this technology has recently been approved by the FDA as an approach for reducing the risk of deep vein thrombosis [37]. In addition, micromechanical stimulation of the soleus reflex arc has been shown capable of significantly increasing resting cardiac output via increased cardiac return, thereby normalizing DBP levels in the older population [38] and improving cognitive function [39].

The relatively small sample size represents a limitation of this study. The sample size of 93 subjects limited the number of factors which could be investigated in terms of identifying the underlying causes of the observed variation in diastolic blood pressure as well as other factors which may be influencing cognitive performance. Polypharmacy, anti-hypertensive and anti-depression therapy, heart failure, autonomic dysfunction, and numerous other factors could be playing a role in both of these measures, and to discriminate the role of these various factors would require a much larger dataset. However, many of these factors are age related, and so by removing the age dependent effects on cognitive performance, we have made an initial attempt to identify the independent influence of low blood pressure on cognition in the older adult population. Further investigation, such as case-control or longitudinal studies will be required to clarify how these factors may influence the development of mild cognitive impairment, either through their influence on blood pressure or some alternative mechanism.

5. Conclusions

Using a computer aided cognitive assessments, we observed that individuals who are over the age of 60, and have resting diastolic pressures below 80 mmHg, are significantly more likely to demonstrate mild or moderate cognitive impairment than their peers. We interpret these results to suggest that a preventative health focus for the older patient should be to maintain their resting diastolic blood pressure in the 80-90 mmHg range. While these blood pressure levels are well above traditional definitions of hypotension, it would appear that such pressures are necessary to ensure adequate cerebral blood flow in older individuals and thereby prevent the progression of age related cognitive decline towards dementia. From the clinical perspective, a further benefit of this strategy is that this DBP range has also been shown to be associated with reduced all-cause mortality rates in the older individual. We propose that it would be appropriate to consider 80 mmHg the threshold for defining hypotension in the population over 60 years of age.

Hypotension is a rarely treated condition as the acute symptoms arising from the reduced brain blood flow are associated with blood pressure levels only rarely seen in the primary care clinic. Acute symptoms, such as dizziness, blurred vision, nausea, etc. most typically occur at diastolic blood pressure levels below 40 mmHg. In our study, none of our subjects demonstrated DBP levels this low and so would not normally be considered hypotensive. However, over 80% of our subjects had a resting diastolic pressure below 80 mmHg. Correspondingly, these individuals appear to be suffering from insufficient cerebral blood flow and the resulting cognitive decline commonly seen in older adults. From a clinical perspective, if our subject population is close to representative of the nation's older adult population, a very large fraction of the over 60 population are likely hypotensive, in the context of this newly proposed hypotensive definition (DBP <80 mmHg). Correspondingly, intervention to normalize DBP should be considered to reduce the risk of mild cognitive impairment, as well as the increased cardiovascular complications and all-cause mortality risks which have previously been reported.

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Author Contributions

The author did all the research work of this study.

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Competing Interests

Dr. McLeod serves as Chief Scientific Officer at Sonostics, Inc. and holds an equity interest in the company.

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