ATCOR

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A New Approach to Detection and Prevention of Cognitive Decline Using Central Blood Pressure

Introduction: Physiology of Cerebral Blood Flow and Pressures

Central blood pressure (cBP) is the pressure measured in the ascending aorta, the point where blood is ejected from the heart. The terms central and aortic blood pressure are often used interchangeably.

Blood pressure is almost always higher at peripheral locations such as the upper arm (where blood pressure is traditionally measured) than it is near the heart. This phenomenon is known as pressure amplification. Importantly, amplification varies greatly between individuals. Therefore, if you want to know an individual's central BP, you cannot simply measure their brachial BP.

Central BP is the pressure experienced directly by the target organs—the brain, kidneys, and the heart itself. As a result, these organs experience that pressure directly, with no buffering. The pulsatile pressure and flow phenomena that result from intermittent cardiac ejection penetrate the brain's microcirculation, leaving the cerebral microvasculature fully exposed to this pulsatility. In young people, the large elastic arteries (like the aorta) expand, or stretch, to absorb this pulsatile energy, and then slowly recoil, transferring it to the microcirculation (such as the capillaries) in a more controlled manner. In this respect, the large arteries act as a buffer for the downstream vessels and organs. With increased arterial stiffness from aging and certain diseases, the large arteries become less elastic and lose their ability to absorb this pulsatile energy. Consequently, these pulsations are transmitted peripherally into smaller vessels. In the case of the brain, the cerebral vasculature is therefore subjected to an increase in central pulse pressure and blood flow pulsatility, which may lead to vessel wall damage and endothelial dysfunction. This may ultimately result in microbleeds, lacunar infarcts, thrombosis, hemorrhage, and beta-amyloid production or decreased clearance—all of which are associated with cognitive impairment and dementia, including Alzheimer's disease. (1) (2) (see Glossary for definitions of clinical terms)

Central Hemodynamics and the Brain: Overview of Published Literature

1) Arterial Stiffness and Brain Structure

In 100 patients with a recent transient ischemic attack or minor stroke, Webb et al. found aortic pulse pressure (PP) and aortic pulse wave velocity (PWV) to be strongly associated with middle cerebral artery pulsatility. Furthermore, there was a strong association between middle cerebral artery pulsatility and the presence and severity of leukoaraiosis (white matter hyperintensities, WMH). Aortic PP and aortic PWV were also strongly and positively associated with the severity of WMH. These results suggest that increased arterial stiffness leads to increased transmission of pulsatility to the cerebral circulation and may play a role in the development

of white matter hyperintensities. (3) Subsequent research by Kim et al. showed that the aortic waveform is similar to the intracranial pressure waveform, lending further support to these findings (4).

Several studies have shown increased arterial stiffness to be associated with greater WMH volume and silent brain infarction (5) while central pressure waveform parameters (e.g. augmentation index) have also been shown to be correlated to the grades of white matter lesions (6). Matsumoto et al., in almost 1,000 older subjects (mean age 71.7 years old), showed that central pulse and systolic pressures were significantly associated with WMH volume. Conversely, brachial blood pressures were not associated with WMH volume (Figure 1). The authors also point out that central BP has the potential to be clinically useful as an indicator of

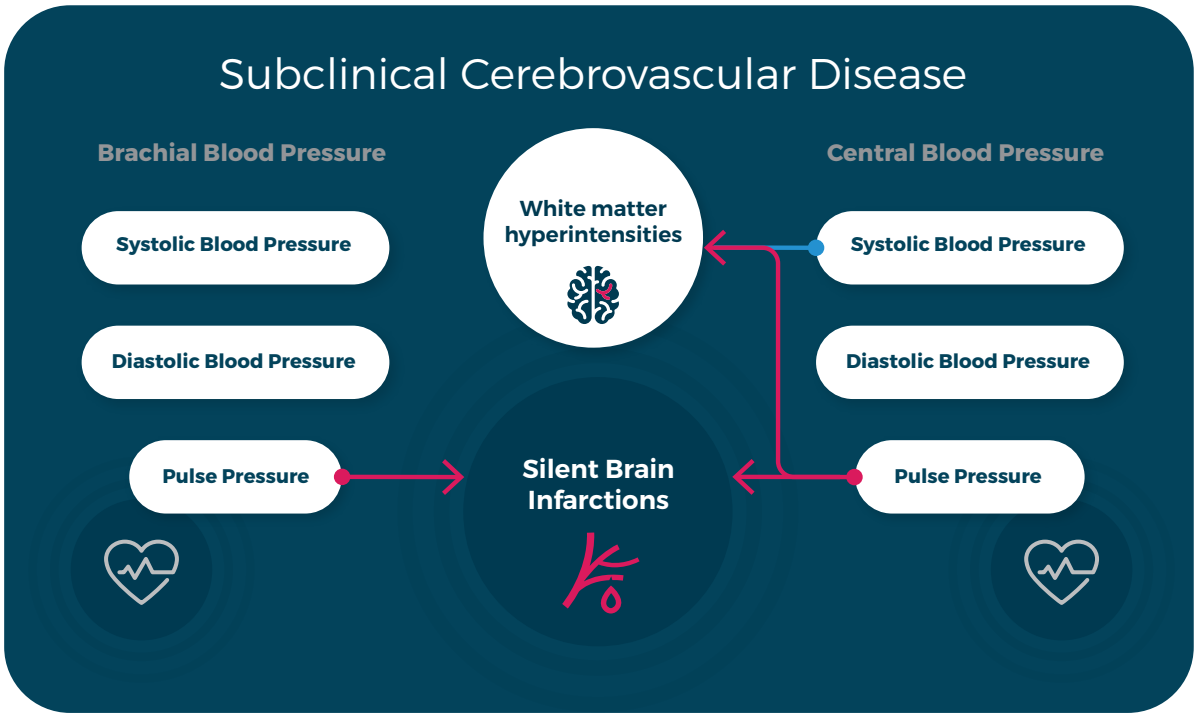

Figure 1. Only central systolic and pulse pressure are associated with white matter hyperintensity volume, not brachial pressures. (Matsumoto, 2020)

subclinical brain damage and may be important for implementing more effective stroke prevention strategies. (7) In an accompanying editorial King states, “Determining that only central blood pressure assessments were linked with increased white matter hyperintensity burden may have important clinical implications for management of blood pressures among the elderly to promote healthy brain aging.” (8)

Additionally, it has been demonstrated that increased arterial stiffness at baseline is predictive of increased WMH volume at follow-up (5). Recent findings suggest that a carotid-femoral pulse wave velocity (cf-PWV) cut-off value of approximately 8.5 m/s (calculated via 80% direct distance method) is more promising for classification of risk groups for individuals with targeted brain damage and cognitive dysfunction than the 10 m/s threshold previously proposed by the European guidelines. (9)

ß-amyloid plaques are a hallmark of Alzhemier’s Disease. One study recently reported that healthy elderly subjects with greater aortic stiffness had a higher rate of ß-amyloid accumulation after two years of follow-up (10). The exact mechanisms by which arterial stiffness may promote ß-amyloid accumulation has yet to be identified, but one hypothesis suggests that the increased penetration of pulsatility into the cerebral microvasculature predisposes those vessels to microhemorrhages and a subsequent cascade of events which promote the aggregation of ß-amyloid (11).

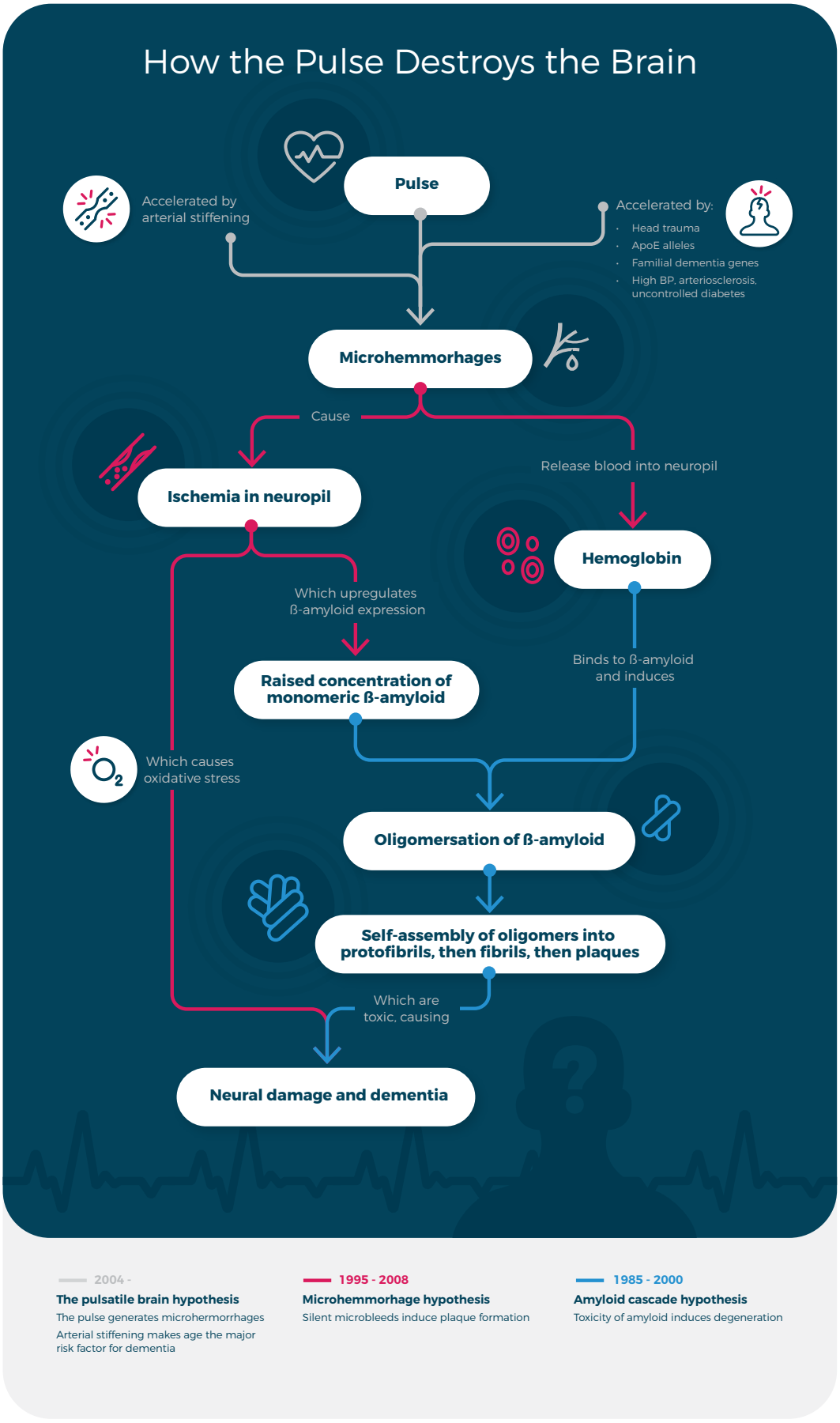

Figure 2. How the pulse destroys the brain. (Stone, 2015)

2) Arterial Stiffness and Cognition

Most research examining the relationships between arterial stiffness and cognition has used carotid-femoral pulse wave velocity (cf-PWV) to measure aortic stiffness.

Several investigations have assessed the relationship between central hemodynamic parameters and assessments of cognitive function. The results of cross-sectional studies consistently show an association between increased pulse wave velocity and impaired cognitive function (12) (13). At least one study has also shown cf-PWV to be significantly increased in mild cognitive impairment, vascular dementia, and Alzheimer's disease compared to subjects with normal cognitive function (Figure 3) (14).

Augmentation Index (AIx) and low pulse-pressure amplification have been found to be associated with poor executive function and language cognitive domain deficits in a study of 50 subjects (15). In a study of 493 independently living adults aged 20–82, Pase et al. showed higher central systolic and pulse pressures and lower pulse pressure amplification were associated with poorer performance across multiple cognitive domains. These central parameters predicted aspects of cognition not associated with brachial BP, indicating central parameters are more sensitive predictors of cognitive aging (16). Conversely, it is important to note that one population-based investigation found central blood pressure did not show a stronger association with cognitive function than brachial blood pressure (17).

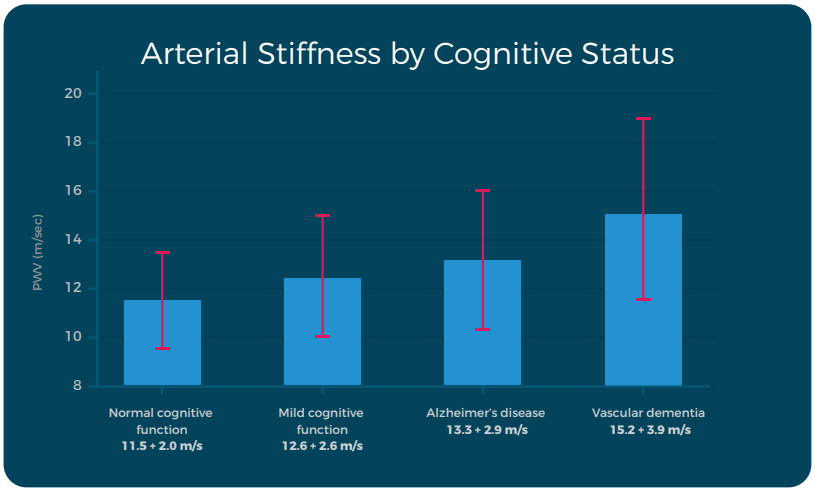

Figure 3. Relationship between PWV and cognitive status (normal cognitive function, MCI, AD, and VaD). P<0.0001, adjusted for age, gender, SBP, education level, antihypertensive therapy, presence of cardiovascular diseases. (Hanon, 2005)

As for the ability of cf-PWV to predict future changes in cognition, studies encompassing more than 20,000 subjects have been published. The results of these investigations have been remarkably consistent in demonstrating that increased cf-PWV was a significant predictor of cognitive decline or incident dementia. This is true for both cognitive healthy individuals and those with mild cognitive impairment and included follow-up durations from as short as 2 years up to 15 years. A detailed breakdown of these publications can be found in the table that follows.

A recently published review and meta-analysis of 29 cross-sectional and 9 longitudinal studies investigating the relationship between arterial stiffness and cognitive function concluded;

> *"Evidence reveals a negative association between arterial stiffness, measured using pulse-wave velocity, and cognition, specifically executive function, memory, and global cognition. This association seems to be independent of demographic, clinical, and assessment characteristics. These results accumulate evidence supporting that pulse-wave velocity assessment could be a useful tool to identify individuals at high risk of cognitive decline or early stages of cognitive decline, to implement interventions aimed at slowing the progression to dementia." (18)*

One longitudinal study exploring the relationship between cognition and central pressure parameters has been published. This study of frail, elderly nursing home inhabitants at least 80 years old found low pulse pressure amplification to be predictive of "decliner" status (19).

First Author	Mean Age	N	Cognitive Status	Cognitive Parameters	Follow-up Duration	Findings
Araghi (20)	65	4,300	Non-demented	Global cognitive score based on tests of memory, reasoning, and verbal fluency	7 years	Higher aortic stiffness associated with faster cognitive decline
Cui (21)	78	356	Non-demented	Battery of Neuropsychological tests	15 years	Risk of incident dementia was significantly related to higher baseline aortic stiffness, not brachial BP
Hajjar (22)	49	591	Healthy	Cognitive scores for executive function, memory and working memory	Up to 5 years	Increased arterial stiffness is superior to blood pressure in predicting cognitive decline in all domains and in explaining the hypertension-executive function association
Rouch (23)	75	375	Mild cognitive impairment	Mini-Mental State Examination; the cognitive efficiency profile	4.5 years	PWV was associated with conversion to dementia, whereas intima-media thickness, carotid plaques, or carotid artery diameter were not after controlling for age and other confounding factors.
Watfa (19)	87	682	Unspecified	Mini-Mental State Examination	2 years	Low pulse pressure amplification and high cf-PWV at baseline were independent predictors of cognitive “decliner” status
Al Hazzouri (24)	74	2,488		Modified Mini-Mental State Exam	9 years	Our findings confirm that higher arterial stiffness, as measured by PWV, is associated with faster rates of cognitive decline over 9 years of follow-up and with greater odds of cognitive impairment among community-dwelling older adults, beyond traditional cardiovascular risk factors, such as BMI, type2 diabetes mellitus, hypertension, and mean arterial blood pressure.
Pase (25)	69	1,101	Dementia-free	Societal guidelines for diagnosis of dementia and Alzheimer’s disease	10 years	Aortic stiffness was an independent predictor of incident mild cognitive impairment in the whole sample and with incident dementia in nondiabetic patients
Menezes (26)	59	6,927	Free of severe cognition or communication impairment	Memory test, fluency test, Trail B test	3.8 years	A higher cf-PWV remained longitudinally associated with poorer Memory and Verbal Fluency Test results
Waldstein (27)	54	582	Non-demented	Numerous tests	1.6 years	The present findings indicate that, among nondemented individuals, markers of arterial stiffness are associated with prospective decline in verbal and nonverbal memory, working memory or concentration, and a cognitive screening measure weighted for memory and concentration.

3) Arterial Stiffness as a Therapeutic Target

It is well established that there is considerable overlap in risk factors for cardiovascular disease and dementia. Therefore, it has been hypothesized that reducing vascular stiffness, as part of a broader cardiovascular regimen, may prevent, reduce, or postpone amyloid accumulation and subsequently reduce or postpone the incidence of Alzheimer's Disease as well as a general decline in cognition (29).

Offering further support to the role of hemodynamics in cognitive decline, the recently published SPRINT-MIND results showed that patients allocated to the intensive treatment group (brachial systolic BP goal of <120 mmHg) in the SPRINT study were significantly less likely to progress to mild cognitive impairment or the combined endpoint of mild cognitive impairment and dementia (30). These findings indicate that better management of blood pressure, and specifically central blood pressure, can confer protection to the cerebral microvasculature, thus mitigating age-related cognitive decline.

To date, investigations of traditional hemodynamic assessments and cognition have not been able to fully explain the relationship between the two. The robust and consistent results presented here strongly support that arterial stiffness, and the resultant increase in central pressure pulsatility, is the missing link that ties subclinical cardiovascular disease to decline in cognitive function. Therefore, individualized management of blood pressure with a goal of reducing central pressure pulsatility, delaying age-related arterial stiffening, and targeting a reduction in wave reflections may be an effective preventative strategy for mitigating cognitive decline and incident dementia.

Summary

There is a growing body of clinical evidence suggesting significant overlap between risk factors for cardiovascular disease (e.g. heart disease) and risk markers for cognitive decline—up to and including Alzheimer's disease and other forms of dementia.

Mid-life blood pressure seems to be predictive of subsequent dementia. Targeted central BP and arterial stiffness management would be a powerful therapeutic approach for early intervention and possible prevention of cognitive decline.

Central BP and arterial stiffness assessment are more strongly correlated with brain health than brachial BP—largely due to their relative proximity to the cerebral microvasculature. Consequently, central pressure waveform analysis can help clinicians identify individuals at greater risk of dementia. Central pressure waveform analysis (PWA) also facilitates targeted therapeutic protocols which can help delay and/or prevent future cognitive decline.

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