

Review

Pulse Wave Velocity in Association with Cognitive Function

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Dementia is an important public health issue in the ageing society; however the cause of dementia has not been clear yet except for age and genes. Cardiovascular risk factors have been suggested to contribute to dementia, such as high blood pressure, but the evidence from clinical trials has not been conclusive. The biological mechanism of cardiovascular disorders in association with cognitive function needs further study. Aortic pulse wave velocity (PWV), a “gold standard” measurement of arterial stiffness, has been established as an independent predictor of CVD events. Understanding the association of PWV and cognitive function can further help to understand the role of vascular risk factors in cognitive decline and dementia. Studies on the association of PWV and cognitive function have emerged recently. This manuscript introduced the measurement of aortic PWV, summarized the studies of its association with cognitive function, and commented on the possible mechanism of the association between arterial stiffness and cognitive function. Because of the link between cardiovascular disorders and dementia, intervention of cardiovascular risk factors may have additional benefits on cognitive function with ageing.

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INTRODUCTION

Dementia is an important public health issue in the ageing society. According to the Alzheimer's Association, 1 in 8 adults aged 65+ years has dementia in the USA (2011 Alzheimer's Disease Facts and Figures, http://www.alz.org/alzheimers_disease_facts_and_figures.asp). Worldwide, it was estimated that a total of 35.6 million people living with dementia in 2010, which would increase to 65.7 million by 2030, and 115.4 million by 2050. The estimated worldwide costs of dementia were \$604 billion in 2010, and if dementia were a company, it would be the world's largest by annual revenue exceeding Wal-Mart (see reference: <http://www.alz.co.uk/research/world-report: World Alzheimer Report 2010>). Although such an important disease, the etiology of dementia is not clear yet. Advanced age and genes are the two established risk factors, but neither of them can be modified.

Recent studies now suggested that cardiovascular risk factors have important roles in cognitive decline and dementia.¹ Stroke, a form of CVD, is one of the leading causes of vascular dementia. In the US, roughly 660,000 persons experience a stroke each year, and cognition declines usually culminate in dementia 1-4 years after stroke.² Some conventional cardiovascular risk factors, such as high blood pressure and diabetes have been widely studied to assess their associations with cognitive decline and dementia, and clinical trials have been conducted, but the results have not been consistent.^{3,4} The link between cardiovascular risk factors and cognitive decline and dementia remains to be understood.

Studies on direct vascular measurements, such as measurements of atherosclerosis and arterial stiffness may help to further elucidate the relation between cardiovascular disorders and dementia, but such studies are few compared to studies of conventional cardiovascular risk factors and cognitive function. The following is a review of epidemiological studies on the association of pulse wave velocity (a measurement of arterial stiffness) and cognitive function.

PULSE WAVE VELOCITY MEASUREMENT

Pulse wave velocity is one of the many indices (such as Young's modulus, characteristic impedance, stiffness index, and so on) of arterial stiffness. Arterial stiffness, or arterial compliance, is a mechanical property of arteries, determined by the smooth muscle cells which composed the arterial wall. Due to the non-homogeneous structure of arterial wall, arterial stiffness varies by different arterial segments and locations. Arterial stiffness changes with age. With increasing age, the large elastic arteries become “stiff”, and the orderly arrangement of elastic fibers and laminae is gradually lost and thinning, splitting, fraying; the collagenous material is increased in ground substance, often accompanied by calcium deposition.⁵ Because blood travels through the vessel forming a forward wave and is reflected back by the peripheral arteries forming a backward wave, the wave velocity is related to the compliance of arteries.

Three types of arterial stiffness can be measured: systemic arterial stiffness, regional arterial stiffness, and local stiffness.⁶ Systemic arterial stiffness is the measurement of overall opposition of large arteries to the pulsatile effects of ventricular ejection. Usually it is calculated based on

theoretical approximations after a direct measurement of a single peripheral artery.⁶ Regional arterial stiffness is measured at arterial sites of major physiologic importance such as the aorta. Aortic pulse wave velocity (usually measured from the carotid to the femoral artery) has been the “gold standard” for arterial stiffness measurement, and has been established as an independent predictor of CVD outcomes.⁷ Aortic PWV is also a marker of subclinical organ damage by the European Society of Hypertension/European Society of Cardiology.⁸ Local arterial stiffness is the measurement of cross-sectional arterial distensibility. It's the change in pressure driving the change in volume. Because this measurement requires a high degree of technical expertise and takes longer than measuring PWV, it is rarely used in epidemiological studies.⁶

Different methods and devices can be used to measure the PWV, including the Complior System device, SphymoCor System device, ultrasound scanning and so on. Both the SphymoCor and the Complior system have acceptable repeatability.⁶ Since the PWV is calculated as the ratio of artery distance over the pulse transit time, one major source of error for PWV measurement is from the superficial measurement of the artery distance. Obesity, especially the abdominal obese can make the measurement of distance of the aorta (from carotid artery to the femoral artery) inaccurate. Other factors should also be controlled when measuring PWV to standardize the measurement, such as room temperature, rest, time of the day, smoking, eating, alcohol, and speaking.

During the lifetime, aortic stiffness decreases sharply with age in the first decade of life, reaching a minimum at 10 years of age, and thereafter increases with age.⁹ Typical values of PWV in the aorta range from approximately 5m/s to >15m/s. A number of CVD risk factors are associated with arterial stiffness, including obesity, smoking, hypertension, diabetes, hypercholesterolemia, glucose tolerance, metabolic syndrome, and inflammation.⁷ More importantly, aortic PWV has significant implications on the cardiovascular system. Because the proximal arteries are more elastic than the distal arteries, waves are reflected and retrograde waves are generated in various locations, such as peripheral bifurcations of conducting arteries and smaller muscular arteries. Due to wave reflections, the pressure wave is progressively amplified; the amplitude of the pressure wave is higher in peripheral arteries than central arteries. Thus it is inaccurate to use brachial pulse pressure as a surrogate for aortic pulse pressure.

In young adults with distensible arteries and low PWV, the reflected wave arrives in early diastole, causing an increase in ascending aortic pressure, which has a boosting effect on coronary perfusion. However in old adults with increased arterial stiffness, the reflected wave travels more rapidly along the arterial tree, thus the reflected wave arrives in early systole, which increases systolic pressures in the ascending aorta, causing increased pressure load and myocardial oxygen consumption, and decreases the diastolic pressure, causing decreased coronary perfusion.¹⁰ These effects are

detrimental, causing left ventricular hypertrophy, low left ventricular stroke volume, and coronary heart disease. A recent meta-analysis of 17 longitudinal studies with a total of 15,877 subjects and a mean of 7.7 years' follow-up confirmed that aortic PWV is a strong predictor of future CVD events and all-cause mortality.¹¹

PULSE WAVE VELOCITY AND COGNITIVE FUNCTION

Recent studies have begun to show that PWV is associated with cognitive function and may predict cognitive decline and dementia. In the Baltimore Longitudinal Study of Ageing, higher PWV was associated with faster decline of cognitive function in 582 participants (at baseline) followed-up for an average of 3.7 years, after adjusting for multiple conventional CVD risk factors including age, sex, education, cholesterol, smoking, alcohol use, and CVD comorbidities.¹² Similar results were found in another population-based study that PWV at baseline was associated with greater decline in several cognition domains.¹³

In a study with 873 nursing home residents older than 80 years, aortic PWV was also associated with the Mini-Mental State Examination (MMSE) decline.¹⁴ However, in the Rotterdam study, a population-based longitudinal study (n=3714), PWV was not associated with cognitive decline or diagnosis of incident dementia after adjusting for multiple CVD risk factors.¹⁵ Over-adjustment might be the reason for the null findings because the carotid intima-media thickness, a marker of atherosclerosis was adjusted in the study. Increased arterial stiffness may induce arterial remodeling, resulting in increased wall thickness,^{16,17} thus further adjusting for the intima-media thickness might be over-adjusting for the analysis with pulse wave velocity. Another population-based study was cross-sectional, including 409 participants aged 24 to 92 free of dementia and stroke. In this study, PWV interacted with age in a multiplicative way to have a negative influence on cognitive performance after adjusting for multiple traditional CVD risk factors including age, sex, education, weight, mean arterial pressure, anti-hypertensive treatment.¹⁸

The following table (**Table 1**) summarized the studies of aortic arterial stiffness measured by the carotid-femoral PWV in association with cognitive function. It can be seen that the studies of PWV and cognitive function emerged in recent years. The number of studies has been limited, and most studies were small cross-sectional, patient-based studies, with a few population-based studies (which have been talked in the last paragraph).^{12,13,15} Most of the studies measured the PWV using the Complior device, while other methods such as ultrasound and electrocardiography (ECG) have also been used. Except for a few studies,¹⁹⁻²¹ most studies found some associations between PWV and cognitive function. The reported effect size of the association was generally small however, especially among population-based studies in apparently “healthy” populations. For example, in one cross-sectional study, a 5 m/s increment in PWV (about 1.8 SD increment in PWV) was related to a 0.23 SD decrement in the tracking and scanning composite cognition score.¹⁸ In a

longitudinal study, 1 SD increase in PWV was associated with -0.11 SD change in global function, -0.09 SD change in psychomotor speed, and -0.12 SD change in perceptual speed.¹³ These may be because the cognitive decline was

subtle among the apparent “healthy” population, and survival bias might also dilute the association between arterial stiffness and cognitive decline.

Table 1. Studies on the association of carotid-femoral PWV and cognitive functions.

| Study | Design | Measures | Results |
|---|--|---|---|
| Scuteri, et al, 2005 ³³ | Cross-sectional; patients with memory problems, n=84, mean age: 78 yrs | PWV by Complior; Cognitive function test: MMSE | PWV was associated with MMSE after multiple adjustments, beta: -0.3, p<.01. |
| Scuteri, et al, 2007 ³⁴ | Longitudinal; patients with memory loss, n=102, mean age: 79 yrs, 1 yr follow-up | PWV by Complior; Cognitive function test: MMSE | PWV was the single strongest predictor of cognitive decline after multiple adjustments, beta: -0.7, p<.001. |
| Hannon, et al, 2007 ³⁵ | Cross-sectional; patients with memory loss, n=308, mean age: 78 yrs | PWV by Complior; Cognitive function test: multiple | PWV was associated with MMSE (beta: -0.09, p<.001) and cognitive deficiency score (beta: -0.03, p<.001) after multiple adjustments. |
| Muller, et al, 2007 ²⁰ | Cross-sectional; men, volunteers, n= 400, age: 40-80 yrs | PWV by SphygmoCor; Cognitive function test: multiple | No statistical significant associations were found. |
| Triantafyllidi, et al, 2009 ³⁶ | Cross-sectional; patients with hypertension n=110, age: 40-80 yrs | PWV by Complior; Cognitive function test: MMSE | PWV was associated with MMSE after multiple adjustments (beta: -0.3, p=.03). |
| Elias, et al, 2009 ¹⁸ | Cross-sectional; adults no dementia and stroke, n=409, age: 24 to 92 yrs | PWV by SphygmoCor; Cognitive function test: multiple | The interaction between PWV and age was significant with the cognition domains after multiple adjustments. |
| Poels, et al, 2007 ¹⁵ | Longitudinal; n=3714, mean age: 72 yrs, follow-up: 4.4 yrs | PWV by Complior; Cognitive function test: multiple | PWV was associated with poorer Stroop test score at baseline. No significant association was found in longitudinal analyses. |
| Dhoat et al, 2008 ²¹ | Cross-sectional, patients and volunteer controls, n=55, mean age: 77-80 yrs | PWV by Complior; Cognitive function test: VAD, AD diagnosis | No significant association was found. |
| Waldstein, et al, 2008 ¹² | Longitudinal; n=582, mean age: 54 yrs; follow-up: 8 yrs | PWV by Doppler; Cognitive function test: multiple | PWV was associated with accelerated decline in multiple tests including memory and concentration. |
| Abbatecola, et al, 2008 ³⁷ | Longitudinal; patients with IGT, age: 70-85 yrs, follow-up: 1 yr | PWV by ECG; Cognitive function test: multiple | PWV associated with MMSE and executive function in microalbuminuric patients (n=80) at baseline. |
| Benotos, et al, 2010 ¹⁴ | Longitudinal; nursing home residents, n=873, mean age: 87 yrs, follow-up: 1 yr | PWV by PulsePen; Cognitive function test: MMSE | The third tertile of PWV was associated about -0.8 (p<.03) more decline in MMSE score compared to the first tertile. |
| Triantafyllidi, et al, 2010 ¹⁹ | Cross-sectional; untreated hypertensive patients, n=168, mean age: 53 yrs | PWV by Complior; Cognitive function test: MMSE | No association was found. |
| Watson, et al, 2011 ¹³ | Longitudinal; n=552, mean age: 73 yrs, follow-up: 6 yrs | PWV by Doppler; Cognitive function test: multiple | PWV at baseline was associated with greater decline in several cognition domains. |

In previous studies, most included the MMSE in the cognitive function test, and some studies had only the MMSE test to measure cognitive function. Because the MMSE is designed as a screening test for dementia, and measures general cognitive function, future studies should focus on multiple cognition tests measuring different aspects of cognitive function to understand whether arterial stiffness is particularly related to some specific cognition domains and specific types of dementia,²¹ and whether some cognition domains are more susceptible to the effects of arterial ageing, and decline earlier or faster than other cognition domains. Such studies can help understanding the complicated biological mechanism of vascular disorders in association with cognitive function.

There have been a few other studies focused on the brachial-ankle PWV mostly in Japan and Korea, which were not included in this table, and had yielded similar findings of the association with cognitive function.^{22,23} In summary, current studies suggested that there is some evidence of the association of PWV and cognitive function, but the evidence from longitudinal studies with large sample size has been limited, and more studies are needed to better evaluate this association.

There may be several mechanisms of the association between arterial stiffness and cognitive function. First, as discussed before, increased arterial stiffness has detrimental effects on the cardiovascular system, and cardiovascular disease contributes to stroke and dementia,^{1,24} thus arterial stiffness may be associated with cognitive decline and dementia indirectly through its association with other cardiovascular risk factors. As a direct measurement of artery wall property, arterial stiffness may be a synthetic marker of vasculature health, reflecting the effects of various traditional CVD risk factors. Hence the association between PWV and cognitive function remained significant after adjusting for multiple conventional CVD risk factors in the previous studies. Secondly, high pulse wave velocity may directly contribute to cognitive impairment and dementia due to the high pulsatility. With increased arterial stiffness, the high pulsation cannot be absorbed well in the large elastic arteries, and extends to the distal small and micro vessels, and damages those vessels.²⁵ Brain and kidney are the two most vulnerable organs because the blood vessel leading down to the capillary circulation are more dilated than elsewhere, and would more readily transmit the high pulsation to the smallest vessels and cause damage.^{25,26} In addition, high pulsatility from the arterial tree may cause damage to the integrity of the blood-brain barrier,¹² which may increase the brain's vulnerability to vicious factors, such as inflammation. Recent MRI studies found that PWV of large arteries was an independent predictor of white matter brain atrophy, cerebral microbleeds and lacunar brain infarcts after adjusting for conventional CVD risk factors.^{27,28} The concept of "pulse-wave encephalopathy" has been proposed recently, which refers to the association of high pulsatility from the arterial tree and pathological change in the brain and subsequent dysfunction.²⁹

Fortunately, unlike age and genes, arterial stiffness can be modified through pharmacological treatment and intervention of cardiovascular risk factors, such as physical exercise, weight loss, and dietary changes.⁷ Habitual exercise may improve vascular endothelial function, increase NO bioavailability, and reduce oxidative stress, thus slow down arterial ageing.³⁰ Treatments including anti-hypertensive and anti-diabetic medicines may decrease PWV independent of blood pressure reduction.^{7,31} Use of statins may also reduce arterial stiffness although the evidence has been few and inconclusive.³² Therefore, clinical trials and intervention studies of PWV may also have cognitive benefits in addition to the prevention of cardiovascular events. Up to now, there have been no intervention studies on the cognitive benefits of reducing arterial stiffness. In the future, assessment of cognitive function in intervention studies of PWV may further help to understand the link between cardiovascular disorders and dementia, and may provide evidence for prevention of cognitive decline and dementia in ageing population.

SUMMARY

In summary, aortic PWV, a measurement of arterial stiffness, is not only a predictor of CVD events, but also may predict cognitive decline and dementia. Epidemiological evidence from cross-sectional studies and some longitudinal cohort studies has been reported. But the number of studies has been limited, especially of studies with large sample size, and intervention studies have not been found; more studies are needed. Studies on the association of arterial stiffness and cognitive function may help to untangle the complex link between cardiovascular disorders and cognitive decline, and provide evidence for possible prevention of dementia in the future.

CONFLICT OF INTEREST

None.

REFERENCES

1. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American heart association/American stroke association. *Stroke*. 2011;42(9):2672-2713.
2. Pinkston JB, Alekseeva N, Gonzalez TE. Stroke and dementia. *Neurol Res*. 2009;31(8):824-831.
3. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2009;(4):CD004034.
4. Areosa SA, Grimley EV. Effect of the treatment of Type II diabetes mellitus on the development of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2002;(4):CD003804.
5. Laurent S, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. *Hypertension*. 2005;45(6):1050-1055.
6. Pannier BM, Avolio AP, Hoeks A, Mancia G, Takazawa K. Methods and devices for measuring arterial compliance in humans. *Am J Hypertens*. 2002;15(8):743-753.
7. Laurent S, Cockcroft J, Van BL, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27(21):2588-2605.
8. Mancia G, De BG, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007;25(6):1105-1187.
9. Laogun AA, Gosling RG. In vivo arterial compliance in man. *Clin Phys Physiol Meas*. 1982;3(3):201-212.

10. London GM, Marchais SJ, Guerin AP, Pannier B. Arterial stiffness: pathophysiology and clinical impact. *Clin Exp Hypertens*. 2004;26(7-8):689-699.
11. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318-1327.
12. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. *Hypertension*. 2008;51(1):99-104.
13. Watson NL, Sutton-Tyrrell K, Rosano C et al. Arterial Stiffness and Cognitive Decline in Well-Functioning Older Adults. *J Gerontol A Biol Sci Med Sci*. 2011. 66(12):1336-1342.
14. Benetos A, Watfa G, Hanon O, et al. Pulse Wave Velocity is Associated With 1-Year Cognitive Decline in the Elderly Older than 80 Years: the PARTAGE Study. *J Am Med Dir Assoc*. 2010 Oct 20. [Epub ahead of print]
15. Poels MM, van OM, Mattace-Raso FU, et al. Arterial stiffness, cognitive decline, and risk of dementia: the Rotterdam study. *Stroke*. 2007;38(3):888-892.
16. Witteman JC, Grobbee DE, Valkenburg HA, et al. J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet*. 1994;343(8896):504-507.
17. Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT. Distribution of circumferential stress in ruptured and stable atherosclerotic lesions. A structural analysis with histopathological correlation. *Circulation*. 1993;87(4):1179-1187.
18. Elias MF, Robbins MA, Budge MM, Abhayaratna WP, Dore GA, Elias PK. Arterial pulse wave velocity and cognition with advancing age. *Hypertension*. 2009;53(4):668-673.
19. Triantafyllidi H, Tzortzis S, Lekakis J, et al. Association of target organ damage with three arterial stiffness indexes according to blood pressure dipping status in untreated hypertensive patients. *Am J Hypertens*. 2010;23(12):1265-1272.
20. Muller M, Grobbee DE, Aleman A, Bots M, van der Schouw YT. Cardiovascular disease and cognitive performance in middle-aged and elderly men. *Atherosclerosis*. 2007;190(1):143-149.
21. Dhoat S, Ali K, Bulpitt CJ, Rajkumar C. Vascular compliance is reduced in vascular dementia and not in Alzheimer's disease. *Age Ageing*. 2008;37(6):653-659.
22. Fujiwara Y, Chaves PH, Takahashi R, et al. Arterial pulse wave velocity as a marker of poor cognitive function in an elderly community-dwelling population. *J Gerontol A Biol Sci Med Sci*. 2005;60(5):607-612.
23. Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. *Neuron*. 2009;63(3):287-303.
24. Purnell C, Gao S, Callahan CM, Hendrie HC. Cardiovascular risk factors and incident Alzheimer disease: a systematic review of the literature. *Alzheimer Dis Assoc Disord*. 2009;23(1):1-10.
25. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension*. 2005;46(1):200-204.
26. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol*. 2007;50(1):1-13.
27. van Elderen SG, Brandts A, Westenberg JJ, et al. Aortic stiffness is associated with cardiac function and cerebral small vessel disease in patients with type 1 diabetes mellitus: assessment by magnetic resonance imaging. *Eur Radiol*. 2010;20(5):1132-1138.
28. Ohmine T, Miwa Y, Yao H, et al. Association between arterial stiffness and cerebral white matter lesions in community-dwelling elderly subjects. *Hypertens Res*. 2008;31(1):75-81.
29. Henry-Feugeas MC. Intracranial MR dynamics in clinically diagnosed Alzheimer's disease: the emerging concept of "pulse wave encephalopathy". *Curr Alzheimer Res*. 2009;6(6):488-502.
30. Seals DR, Walker AE, Pierce GL, Lesniewski LA. Habitual exercise and vascular ageing. *J Physiol*. 2009;587(Pt 23):5541-5549.
31. Asmar R. Effect of antihypertensive agents on arterial stiffness as evaluated by pulse wave velocity: clinical implications. *Am J Cardiovasc Drugs*. 2001;1(5):387-397.
32. Rizos EC, Agouridis AP, Elisaf MS. The effect of statin therapy on arterial stiffness by measuring pulse wave velocity: a systematic review. *Curr Vasc Pharmacol*. 2010;8(5):638-644.
33. Scuteri A, Brancati AM, Gianni W, Assisi A, Volpe M. Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a pilot study. *J Hypertens*. 2005;23(6):1211-1216.
34. Scuteri A, Tesaro M, Appolloni S, Preziosi F, Brancati AM, Volpe M. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. *J Hypertens*. 2007;25(5):1035-1040.
35. Hanon O, Haulon S, Lenoir H, et al. Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. *Stroke*. 2005;36(10):2193-2197.
36. Triantafyllidi H, Arvaniti C, Lekakis J, et al. Cognitive impairment is related to increased arterial stiffness and microvascular damage in patients with never-treated essential hypertension. *Am J Hypertens*. 2009;22(5):525-530.
37. Abbatecola AM, Barbieri M, Rizzo MR, et al. Arterial stiffness and cognition in elderly persons with impaired glucose tolerance and microalbuminuria. *J Gerontol A Biol Sci Med Sci*. 2008;63(9):991-996.