

**Review**

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# Blood Pressure Variability and Cognitive Function in the Elderly

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**Key Words**

Elderly people · Cognition · Hypertension · Variability

**Abstract**

With the increase in the aging population, it is important to understand the individual diseases and their interactions which are prevalent and have a great impact on the health status of the elderly. Hypertension is one of the most common diseases in older age and may impact the health status because it is the main risk factor for cardiovascular and cerebrovascular diseases such as heart failure and stroke. Recently, much evidence has been accumulated showing that hypertension plays an important role in the development and progression of cognitive impairment and dementia. Cerebral hypoperfusion secondary to severe atherosclerosis resulting from long-standing hypertension may be a major biological pathway linking high blood pressure (BP) to cognitive decline and dementia. Furthermore, increased BP variability has also been reported to be significantly associated with white matter hyperintensities and brain atrophy, which are predisposing conditions of dementia, depression, and falls in the elderly even after adjusting for BP levels and other confounding variables. Several mechanisms have been shown to be involved in the association between BP variability and cognitive impairment in elderly individuals. In addition to an increased cerebral blood flow fluctuation, neurohumoral activation, endothelial dysfunction, inflammation, and oxidative stress have been suggested to be the underlying mechanisms. However, clinical trials provide limited evidence for a protective effect of antihypertensive therapy against dementia and stroke-related cognitive decline. In this article, we aimed to review the existing evidence of the connection between BP variability and cognitive impairment in elderly people.

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## Introduction

Hypertension and cognitive dysfunction are both common disorders in elderly people. As the age of the population grows, the prevalence of hypertension increases linearly, exceeding 60% for people aged  $\geq 60$  years and 70% in individuals  $\geq 70$  years old [1]. Additionally, the prevalence of dementia is estimated to be around 8% in people aged  $\geq 65$  years [2]. Hypertension, beyond its direct effect on cerebrovascular events, is known to play a role in the development of cognitive impairment and vascular dementia in elderly people [3]. This close relationship between hypertension and cognitive impairment has been widely reported in multiple epidemiological studies [4–6].

However, previous studies mainly focused on the effect of once-measured (casual) blood pressure (BP) rather than on ambulatory BP (ABP) or repeated measurement of BP. ABP can provide an estimate of the mean BP level, the diurnal rhythm of BP, and BP variability, all of which are of potential value in clinical practice [7].

There has been evidence of a relationship between these ABP findings and brain structural changes and cognitive impairment. In addition, higher visit-to-visit variation of BP has been reported to be associated with an increased risk of stroke [8].

In this article, we aimed to review the current evidence of associations between non-dipping, nocturnal hypertension, 24-hour BP variability, and visit-to-visit BP variability and brain structural alteration such as total brain volume and white matter hyperintensities, and to investigate the possible mechanisms linking BP variability to cognitive impairment in elderly people.

## Association between Hypertension and Cognitive Impairment

Hypertension has been reported to be a risk factor for cognitive dysfunction in the elderly, ranging from silent white matter lesions to overt stroke. There are a number of large longitudinal studies which showed the effect of chronic exposure to hypertension for more than 20 years on the later cognitive function.

A study performed in Uppsala, Sweden, reported that the diastolic BP (DBP) measured in midlife is related to global cognitive dysfunction at the age of 70 years [5]. The Honolulu-Asia Aging Study [4] showed an association between high systolic BP (SBP) and following cognitive dysfunction after 25 years. In addition, higher BP and longer exposure to hypertension were associated with poorer subsequent results in neuropsychological tests from the Framingham study [9]. A study conducted in Kuopio and Joensuu, Finland, demonstrated that midlife hypertension and dyslipidemia increased the risk for Alzheimer's disease in later life [10].

However, there is little evidence that hypertension in later life also has the same negative effect on cognition. Indeed, based on some reports concerning the harmful effect of low BP on cognitive function, it seems that in older adults, and particularly in those who are very old, an appropriate BP level may be required to retain cognitive function by maintaining adequate cerebral perfusion [11].

All of these longitudinal studies suggest that high midlife BP is a risk factor for later-life cognitive impairment and dementia, and that a low DBP and a very high SBP in older adults may be associated with subsequent development of dementia. Cerebral hypoperfusion secondary to severe atherosclerosis resulting from long-standing hypertension and low BP may be a major biological pathway linking both high BP in midlife and low BP in later life to cognitive decline and dementia. However, clinical trials provide limited evidence for a protective effect of antihypertensive therapy against dementia and stroke-related cognitive decline.

## Clinical Significance of BP Variability

Previous studies have shown that ABP variability is associated with target organ damage including brain white matter hyperintensities independent of the mean 24-hour BP values [12–19]. In addition, the 24-hour BP standard deviation, which is one of the BP variability indices, has been shown to be related to the progression of organ damage over the years [15, 20]. In the Syst-Eur sub-study, increased nighttime SBP variability was an independent risk factor for stroke even after adjusting for BP level and other confounding variables [21].

Long-term BP variability, usually measured as visit-to-visit BP variability, was once believed a random phenomenon. However, the increasing evidence of the prognostic importance of this variability changed this perception [22]. The mechanisms of this variability associated with poor clinical outcomes have not been well studied, but they may be explained by baroreceptor dysfunction or increased arterial stiffness.

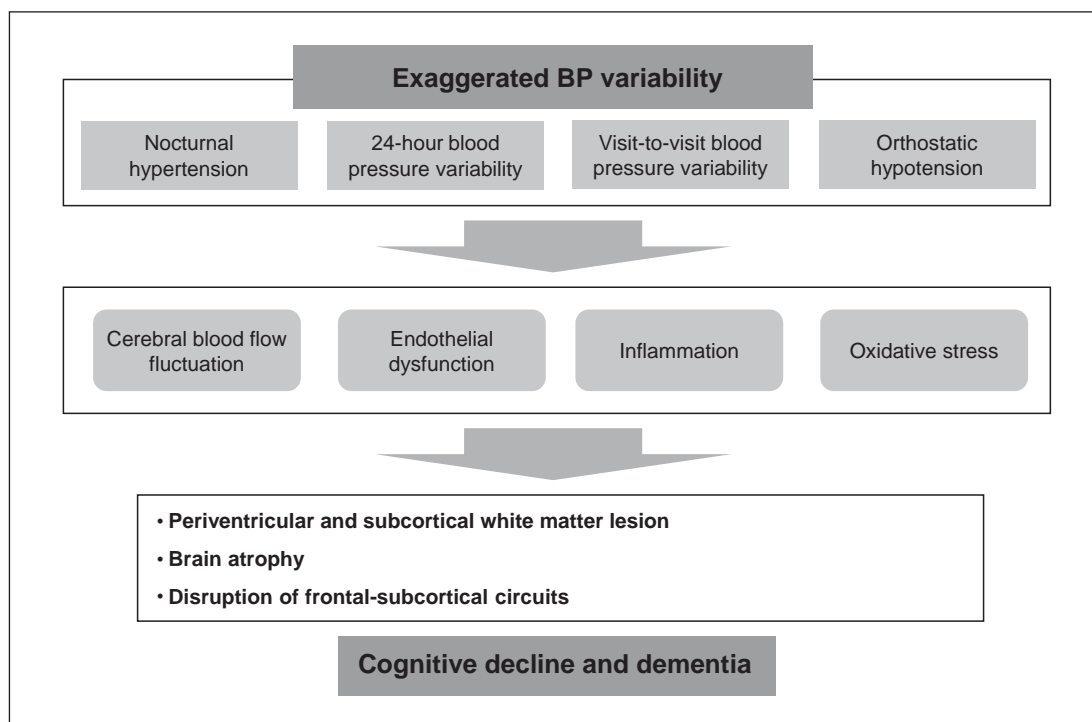
## Relationship between BP Variability and Structural Brain Changes or Cognitive Dysfunction

Although cerebral white matter hyperintensities are known to be a common finding in the elderly, several studies have reported a significant association between hypertension and white matter hyperintensities and the development of cognitive decline [23]. In patients with mild cognitive impairment, white matter hyperintensities have been reported to be related to further cognitive decline [24]. In addition, a positive correlation between the amplitude of dipping (difference between daytime BP and nighttime BP) and the extent of white matter hyperintensities measured by brain MRI has been detected [25]. Puisieux et al. [26] demonstrated that higher leukoaraiosis was associated with a higher SBP and a greater SBP variability during 24 h. Goldstein et al. [27] evaluated the relationship between ABP and brain atrophy in healthy elderly individuals. In this study, greater sleep SBP variability was associated with brain atrophy. A following study by the same authors, which reevaluated brain MRI scans after 5 years, showed that elevated SBP and greater sleep SBP variability were associated with aggravated brain atrophy [28]. Conversely, Nagai et al. [29] showed a positive correlation of nocturnal SBP dipping and total brain volume, although awake and sleep SBP were negatively correlated with total brain volume.

In addition, in the Uppsala cohort study [5], 999 elderly men with ABP and cognitive function tests including Mini-Mental State Examination (MMSE) and Trail-Making Test were analyzed. This study identified lower cognitive scores in non-dippers. However, there was no relation between extreme dippers (daytime SBP – nocturnal SBP  $\geq 20$  mm Hg) as well as participants with high sleep BP variability and cognitive impairment. In addition, Ohya et al. [30] showed that inverted dippers and non-dippers were more frequent among elderly individuals with decreased activity of daily living and impaired cognitive function.

One study demonstrated that exaggerated 24-hour BP variability is associated with cognitive dysfunction in elderly people [31]. Moreover, exaggerated ABP variability was related to cognitive dysfunction in the elderly, especially in the very elderly, and to lower quality of life in the younger elderly [32]. Recently, visit-to-visit BP variability has also been shown to be associated with cognitive function [33], beyond the previously known relationship with cerebral white matter hyperintensities [34].

In summary, a non-dipping pattern and exaggerated BP variability (ambulatory and visit-to-visit variability) are associated with structural brain changes, such as white matter hyperintensities and brain volume atrophy, and cognitive dysfunction in elderly people.



**Fig. 1.** Association between augmented blood pressure variability and cognitive dysfunction in the elderly people.

### Causal Relationship between BP Variability and Cognitive Impairment

As described before, although some discordance exists, there is evidence showing a correlation between nocturnal non-dipping and cognitive impairment. However, due to a lack of studies evaluating ABP and cognitive function longitudinally, the causal relationship between non-dipping and cognitive impairment is hard to tell. Considering autonomic dysregulation as a mechanism of the non-dipping phenomenon, non-dipping can be caused by an underlying disease which can cause both cognitive impairment and autonomic dysregulation. This possible process is supported by studies focusing on lacunar infarct [35] or dementia [36]. Therefore, research to elucidate the causal relationship of non-dipping and cognition is needed.

On the other hand, considering the mechanisms of exaggerated short- and long-term BP variability, i.e. baroreflex dysfunction and arterial stiffness, and the resultant cerebral white matter changes, cognitive dysfunction may be a result rather than a cause of these BP variation.

Usually, white matter lesions occur in watershed areas [37] and may be caused by ischemia due to more-than-physiological BP fluctuation seen in patients with exaggerated short- and long-term BP variability. Therefore, abnormal BP variability might cause cognitive dysfunction. Several mechanisms have been reported to be involved in the association between BP variability and cognitive impairment in elderly people. In addition to an increased cerebral blood flow fluctuation, neurohumoral activation, endothelial dysfunction, increase in inflammation, and oxidative stress have been suggested to be the underlying mechanisms (fig. 1) [38–40].

## Conclusions

Although hypertension and following cognitive functional decline have been well studied in longitudinal studies, the associations between BP variability and cognitive function have only been illuminated relatively recently. However, recent evidence suggests that BP variability, such as nocturnal non-dipping, 24-hour BP variation (short-term variation), and visit-to-visit BP variation (long-term variation), are associated with subsequent cognitive dysfunction and cerebral structural changes including white matter hyperintensities and atrophy. Further research is needed to identify the underlying mechanisms responsible for cognitive dysfunction associated with increased BP variability.

## Disclosure Statement

The authors have no conflicts of interest to declare.

## References

- 1 Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J: Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365:217–223.
- 2 Fratiglioni L, De Ronchi D, Aguero-Torres H: Worldwide prevalence and incidence of dementia. *Drugs Aging* 1999;15:365–375.
- 3 Papademetriou V: Hypertension and cognitive function. Blood pressure regulation and cognitive function: a review of the literature. *Geriatrics* 2005;60:20–22, 24.
- 4 Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ: The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA* 1995;274:1846–1851.
- 5 Kilander L, Nyman H, Boberg M, Hansson L, Lithell H: Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertension* 1998;31:780–786.
- 6 Cacciatore F, Abete P, Ferrara N, Paolisso G, Amato L, Canonico S, Maggi S, Varricchio M, Rengo F: The role of blood pressure in cognitive impairment in an elderly population. *Osservatorio Geriatrico Campano Group. J Hypertens* 1997;15:135–142.
- 7 Pickering TG, Shimbo D, Haas D: Ambulatory blood-pressure monitoring. *N Engl J Med* 2006;354:2368–2374.
- 8 Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR: Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;375:895–905.
- 9 Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR: Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *Am J Epidemiol* 1993;138:353–364.
- 10 Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A: Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001;322:1447–1451.
- 11 Kim KI, Cho YS, Choi DJ, Kim CH: Optimal treatment of hypertension in the elderly: a Korean perspective. *Geriatr Gerontol Int* 2008;8:5–11.
- 12 Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R, Valagussa F, Bombelli M, Giannattasio C, Zanchetti A, Mancia G: Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). *Circulation* 2001;104:1385–1392.
- 13 Eto M, Toba K, Akishita M, Kozaki K, Watanabe T, Kim S, Hashimoto M, Ako J, Iijima K, Sudoh N, Yoshizumi M, Ouchi Y: Impact of blood pressure variability on cardiovascular events in elderly patients with hypertension. *Hypertens Res* 2005;28:1–7.
- 14 Björklund K, Lind L, Zethelius B, Berglund L, Lithell H: Prognostic significance of 24-h ambulatory blood pressure characteristics for cardiovascular morbidity in a population of elderly men. *J Hypertens* 2004;22:1691–1697.
- 15 Mancia G, Parati G: The role of blood pressure variability in end-organ damage. *J Hypertens Suppl* 2003;21:S17–S23.
- 16 Sega R, Corrao G, Bombelli M, Beltrame L, Facchetti R, Grassi G, Ferrario M, Mancia G: Blood pressure variability and organ damage in a general population: results from the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). *Hypertension* 2002;39:710–714.
- 17 Parati G, Mancia G: Blood pressure variability as a risk factor. *Blood Press Monit* 2001;6:341–347.

- 18 Gunstad J, Cohen RA, Tate DF, Paul RH, Poppas A, Hoth K, Macgregor KL, Jefferson AL: Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. *Blood Press* 2005;14:353–358.
- 19 Gomez-Angelats E, de La Sierra A, Sierra C, Parati G, Mancia G, Coca A: Blood pressure variability and silent cerebral damage in essential hypertension. *Am J Hypertens* 2004;17:696–700.
- 20 Zakopoulos NA, Tsiygoulis G, Barlas G, Papamichael C, Spengos K, Manios E, Ikonomidis I, Kotsis V, Spiliopoulou I, Vemmos K, Mavrikakis M, Mouloupoulos SD: Time rate of blood pressure variation is associated with increased common carotid artery intima-media thickness. *Hypertension* 2005;45:505–512.
- 21 Pringle E, Phillips C, Thijs L, Davidson C, Staessen JA, de Leeuw PW, Jaaskivi M, Nachev C, Parati G, O'Brien ET, Tuomilehto J, Webster J, Bulpitt CJ, Fagard RH: Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J Hypertens* 2003;21:2251–2257.
- 22 Rothwell PM: Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 2010;375:938–948.
- 23 de Leeuw FE, Richard F, de Groot JC, van Duijn CM, Hofman A, Van Gijn J, Breteler MM: Interaction between hypertension, apoE, and cerebral white matter lesions. *Stroke* 2004;35:1057–1060.
- 24 Debette S, Bombois S, Bruandet A, Delbeuck X, Lepoittevin S, Delmaire C, Leys D, Pasquier F: Subcortical hyperintensities are associated with cognitive decline in patients with mild cognitive impairment. *Stroke* 2007;38:2924–2930.
- 25 Watanabe N, Imai Y, Nagai K, Tsuji I, Satoh H, Sakuma M, Sakuma H, Kato J, Onodera-Kikuchi N, Yamada M, Abe F, Hisamichi S, Abe K: Nocturnal blood pressure and silent cerebrovascular lesions in elderly Japanese. *Stroke* 1996;27:1319–1327.
- 26 Puisieux F, Monaca P, Deplanque D, Delmaire C, di Pompeo C, Monaca C, Leys D, Pruvo JP, Dewailly P: Relationship between leuko-araiosis and blood pressure variability in the elderly. *Eur Neurol* 2001;46:115–120.
- 27 Goldstein IB, Bartzokis G, Guthrie D, Shapiro D: Ambulatory blood pressure and brain atrophy in the healthy elderly. *Neurology* 2002;59:713–719.
- 28 Goldstein IB, Bartzokis G, Guthrie D, Shapiro D: Ambulatory blood pressure and the brain: a 5-year follow-up. *Neurology* 2005;64:1846–1852.
- 29 Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K: Ambulatory blood pressure as an independent determinant of brain atrophy and cognitive function in elderly hypertension. *J Hypertens* 2008;26:1636–1641.
- 30 Ohya Y, Ohtsubo T, Tsuchihashi T, Eto K, Sadanaga T, Nagao T, Abe I, Fujishima M: Altered diurnal variation of blood pressure in elderly subjects with decreased activity of daily living and impaired cognitive function. *Hypertens Res* 2001;24:655–661.
- 31 Bellelli G, Pezzini A, Bianchetti A, Trabucchi M: Increased blood pressure variability may be associated with cognitive decline in hypertensive elderly subjects with no dementia. *Arch Intern Med* 2002;162:483–484.
- 32 Sakakura K, Ishikawa J, Okuno M, Shimada K, Kario K: Exaggerated ambulatory blood pressure variability is associated with cognitive dysfunction in the very elderly and quality of life in the younger elderly. *Am J Hypertens* 2007;20:720–727.
- 33 Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K: Visit-to-visit blood pressure variations: new independent determinants for cognitive function in the elderly at high risk of cardiovascular disease. *J Hypertens* 2012;30:1556–1563.
- 34 Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, DeCarli C, Brown TR, Mayeux R: Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol* 2010;67:564–569.
- 35 Kario K, Shimada K: Change in diurnal blood pressure rhythm due to small lacunar infarct. *Lancet* 1994;344:200.
- 36 Otsuka A, Mikami H, Katahira K, Nakamoto Y, Minamitani K, Imaoka M, Nishide M, Ogihara T: Absence of nocturnal fall in blood pressure in elderly persons with Alzheimer-type dementia. *J Am Geriatr Soc* 1990;38:973–978.
- 37 Lechner H, Schmidt R, Bertha G, Justich E, Offenbacher H, Schneider G: Nuclear magnetic resonance image white matter lesions and risk factors for stroke in normal individuals. *Stroke* 1988;19:263–265.
- 38 Di Flaviani A, Picconi F, Di Stefano P, Giordani I, Malandrucchio I, Maggio P, Palazzo P, Sgreccia F, Peraldo C, Farina F, Frajese G, Frontoni S: Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients. *Diabetes Care* 2011;34:1605–1609.
- 39 Diaz KM, Veerabadrappa P, Kashem MA, Fearheller DL, Sturgeon KM, Williamson ST, Crabbe DL, Brown MD: Relationship of visit-to-visit and ambulatory blood pressure variability to vascular function in African Americans. *Hypertens Res* 2012;35:55–61.
- 40 Kim KI, Lee JH, Chang HJ, Cho YS, Youn TJ, Chung WY, Chae IH, Choi DJ, Park KU, Kim CH: Association between blood pressure variability and inflammatory marker in hypertensive patients. *Circ J* 2008;72:293–298.