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REVIEW ARTICLE

Review Series-Implication of Blood Pressure Variation

Implications of blood pressure variations in older populations

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Abstract
Special characteristics of blood pressure (BP) variability have been noted in older people. As some specific types of BP variability related to hypertension or hypotension might be associated with higher mortality or geriatric syndromes, such as dementia and frailty, doctors or medical providers should obtain precise knowledge about BP variations in older people and closely monitor these changes in various situations. In this review article, the proposed mechanisms of BP variability in older people and common and clinically important types of BP variability are explained and discussed using recent studies.

Keywords older people · blood pressure variability · mortality · geriatric syndromes

Introduction

The prevalence of hypertension is increasing with aging. The systolic blood pressure (SBP) of the general population increases in a linear manner with aging, and diastolic BP (DBP) is also increased until the individual reaches 50–60 years, but DBP is mainly decreased after middle age because of increased aortic stiffness induced by aging and atherosclerotic changes. Therefore, pulse pressure increases with aging, and isolated systolic hypertension is common in older populations. In addition, aging influences various other physiological regulatory systems. Therefore, these pathophysiological alterations may contribute to or are associated with elevated BP in aging. The main pathophysiologic alterations induced by aging are increased arterial stiffness (atherosclerotic changes), decreased baroreceptor sensitivity, increased/reduced sympathetic nervous system activity, decreased α- and β-adrenergic responsiveness, decreased endothelial relaxing factor function, elevated sodium sensitivity (decreased glomerular filtration rate), low plasma renin activity (due to elevated salt sensitivity) and insulin resistance [1]. These aging-induced alterations cause short- and long-term BP variations in older individuals; additionally, some special situations, such as posture changes or eating meals, also induced BP variations in this population. We need to understand the implications of these BP variations, particularly in older people, for the treatment of hypertension in older patients in the clinic. The Japanese guideline JSH2014 provides detail explanations of the characteristics of patients with elderly hypertension (Table 1) [2]. JSH2014 emphasizes the necessity of individual treatment strategies for the older person with hypertension because of the various characteristics of aged people, including their BP variations. An understanding of BP variations in older populations is very important for those reasons. Therefore, we are discussing the implications of BP variations in older populations in this review article.

Mechanisms of BP variations in older persons

Aging promotes vascular remodeling and the progression of atherosclerosis that are commonly observed in older people [3]. Homma S et al. reported a physiological effect of aging that corresponds to diffuse intimal thickening using duplex ultrasonography of the carotid artery, particularly in very old persons [3]. Older people without any risks of atherosclerosis may present diffuse intimal thickening, vascular hypertrophy and increasing systemic vascular stiffness during aging. This vascular remodeling induced by aging exponentially increases vascular resistance and the hypersensitivity to vasoconstrictive responses, such as activation of sympathetic nerve systems (SNS) [4]. Consequently, BP is readily increased even by a low level

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Table 1 Precautions in the diagnosis of hypertension in the old population (JSH2014) [2]

Characteristics of hypertension in old peoples
● Increased fluctuation of blood pressure.
● Increase in systolic hypertension.
● Increase in white coat hypertension.
● Increase in orthostatic hypotension or postprandial blood pressure reduction.
● Increase in the non-dipper-type nighttime blood pressure.
● Increase in the incidence of patients with a morning surge.
● Decreases in the vital organ perfusion and reserve.
● Impairment of autoregulation of vital organ perfusion.
Comprehensive evaluation of the blood pressure level
● Blood pressure is repeatedly measured.
● Home or 24-h blood pressure measurement in concomitantly performed.
● Blood pressure in a standing position is measured before and after the start of drug therapy, after switching the regimen, or at the appearance of dizziness (if systolic blood pressure decreases by 20 mmHg or more 3 min after standing up, a diagnosis of orthostatic hypotension is made).[839]
● Conditions for measurement should be considered (after meals, after taking drugs and so on).
● If symptoms of diet-associated blood pressure reduction (such as dizziness) are present, 24-h or postprandial blood pressure measurement should be performed (if systolic blood pressure in a sitting position decreases by 20 mmHg or more 1 h after meals, a diagnosis of postprandial blood pressure reduction in made).[839]

This table is cited from reference [2] as a modified form

stimulation of the SNS (Fig. 1). This hypersensitivity to the vasoconstrictive response is thought to contribute to BP variations in older persons. Thus, white coat hypertension, the white coat effect on patients with hypertension and a morning surge of BP are more common in older populations than young and middle aged populations [4]. Another important mechanism would be reduced responses of the aorta and carotid arteries to baroreceptors caused by vascular stiffness mediated by diffuse intimal thickening or atherosclerosis in older persons [5]. As mentioned above, decreased SNS activities and α-/β-adrenergic responsiveness are often both manifested in older people. These changes are postulated to be main cause of orthostatic hypotension or postprandial hypotension commonly observed in older persons. In addition, a reduced glomerular filtration rate (GFR) induced by aging-related nephrosclerosis or renal dysfunction of any other origin and higher salt sensitivity in older people might result in abnormal BP variations characterized by a high BP at night and a non-dipping pattern in ambulatory BP monitoring (ABPM) [6]. Sleep disturbances were recently suggested to be a common complication in older persons that increases BP during sleep and the non-dipper BP pattern in older populations [7]. Nocturnal polyuria is also very common in older people and is associated with hypertension [8]. Nocturnal polyuria is predicted to be one cause of sleep disturbances. Therefore, nocturnal polyuria may cause nocturnal hypertension or result from salt-sensitive hypertension. Nevertheless, nocturnal polyuria is associated with hypertension in older peoples [8].

Finally, the prevalence of chronic and paroxysmal atrial fibrillation (AF) is increasing with aging [9]. Two-thirds of patients with AF are aged over 75 years. AF is one of causes of beat by beat BP variations. This change in BP characterized by pauses defined as long intervals between beats occurs in patients with AF and may result in syncope and pre-syncope in older people.

Common types of BP variations in older populations

Common types of BP variations in older populations and the proposed underlying mechanisms are summarized in JSH2104 (Table 1).

Diurnal BP variability

In older populations, some abnormal diurnal BP variations are commonly observed. As stated above, the non-dipper type BP variation is a characteristic of hypertension in elderly individuals because of reduced renal function, increased salt sensitivity and sleep disturbance [7]. The non-dipping pattern of hypertension is strongly correlated with

cardiovascular events [10]. The main cause of the non-dipping pattern of hypertension in older people is postulated to be reduced renal function and increased salt sensitivity [11]. Since >50% of older people aged ≥75 years will be diagnosed with stage G3 or higher chronic kidney diseases (CKD), according to the Japanese definition [12], the non-dipping pattern of hypertension will be very common in older people with hypertension. Regarding the relationship between aging-induced sleep disturbances and the non-dipper pattern of hypertension, melatonin may play an important role in older patients with hypertension. The secretion of melatonin from the pituitary gland generally decreases during aging [13], and this reduced melatonin level in the brain may be related to sleep disturbances in older people. Thus, a melatonin receptor agonist is a useful treatment for sleep disturbances [14]. The reduced systemic melatonin level observed in aged people may influence the non-dipper type of BP in elderly patients with hypertension. As reported in the study by Obayashi et al., urinary melatonin secretion is significantly decreased in elderly patients with the non-dipper pattern of hypertension [15].

Another common diurnal BP variability observed in older people is a morning surge in BP. A morning surge in BP and morning hypertension are major causes of masked hypertension. As the main cause of the morning surge in BP is thought to be hyper-reactivity of the SNS [16], the morning surge in BP commonly occurs in older people with remodeled vascular walls that increase vascular resistance, as described above. The morning surge in BP is closely related to the occurrence of cardiovascular diseases (CVDs) in older patients with hypertension [17, 18]. Two types of a morning surge in BP have been identified: an elevated BP in early morning and a high nocturnal BP (non-dipper pattern) plus an exaggerated elevation in BP in the early morning. As mentioned above, a high nocturnal BP is commonly observed in older people, a morning surge in BP poses a greater risk of CVD in these patients than in patients with the dipper pattern of hypertension.

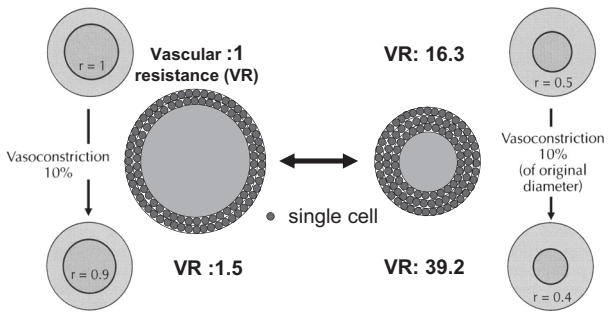

Fig. 1 Vascular remodeling induced by aging The thickness of the vascular wall increases with age, which is known as 'vascular remodeling.' Vascular resistance is exponentially increased by remodeled and hypertrophied blood vessels, and vasoconstrictive stimuli, such as sympathetic nervous activation, may exaggerate the increase in vascular resistance

BP variabilities in daily activities

(a) Orthostatic hypotension

Orthostatic hypotension (OH) is a common disorder leading to dizziness, falls, syncope, and even fatal cardiovascular accidents in older people [19]. The incidence of syncope increases with age and may cause physical injury and a decrease in quality of life. OH is defined as an abnormal decrease in BP upon standing (systolic BP of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 min of standing up [20]). The prevalence of OH ranges from 4 to 33%, depending on the characteristics of the population [21, 22]. In older people with diseases such as diabetes and Parkinson's disease, the prevalence was reported to be 10–30% [23]. Poon et al. reported a prevalence of OH of 55% in the older veteran population with a mean age of 82 years; this population includes many frail people taking multiple medications for various diseases [24]. These conditions cause baroreflex failure with the resulting combination of OH, supine hypertension, and loss of the diurnal BP variations [25]. The presence of OH is also associated with various clinical conditions, e.g., stroke, heart failure, coronary heart disease, and device implantation. Several epidemiological studies have reported significant associations between OH and the risk of future CVDs or mortality [26]. OH is a first symptom of an underlying CVD. On the other hand, OH is also associated with autonomic failure [27] Clinicians should determine whether OH has a neurogenic etiology, i.e., due to a neurological cause and not due to hypovolemia or venous pooling [25].

OH occurs when the mechanisms regulating orthostatic BP fail. During aging, the prevalence of OH increases because of increased vascular stiffness, diminished baroreflex sensitivity (BRS), and decreased β-adrenoreceptor-mediated responses. In consequence, the normal response to standing is reduced, resulting in an increased susceptibility to OH. In addition, aging is associated with an increased number of risk factors for OH, including acute illness, the number of medications, some types of medications, hypertension, diabetes, smoking, carotid artery stenosis/remodeling, and neurological diseases [26].

The practical goal is to improve standing BP to minimize symptoms and improve standing time such that individuals can perform orthostatic activities of daily living without excessive supine hypertension [25]. Three basic methods to treat chronic OH have been reported: mechanical maneuvers, volume expanders, and pharmacological agents. Mechanical maneuvers include elevation of the head while

resting, wearing a lower body compression garment, and exercises, such as calf-muscle flexing. Patients should be taught to rise slowly and to remain as mobile as much as possible. Volume expanders include a high-salt diet and fluorocortisone acetate, which causes a uniform expansion of plasma volume, although elevations in BP in supine and sitting positions should be cautiously monitored. Several pharmacologic agents are used either alone or in sequence to treat OH [28].

Patients must understand what factors aggravate and improve standing BP and. For instance, OH might be worse immediately upon rising in the morning, after a meal, or on a hot day. Patients must learn to recognize subtle symptoms and obtain knowledge about techniques to improve OH, such as a bolus or water, countermaneuvers, or venous compression. The goal of OH treatment is to avoid the severe effects of OH, including the risk of falls, and inform the patients about the cause of their OH and management of the cause [25].

(b) Postprandial hypotension

Postprandial hypotension (PPH) has been traditionally defined as a decrease in systolic BP of >20 mmHg or a decrease to 90 mmHg when the preprandial BP is 100 mmHg, within 2 h of a meal. PPH occurs commonly in older people and represents a major cause of morbidity, as reported in a recent systematic review [29]. Jansen et al. were the first to reported that PPH may be an important causative factor in elderly patients with unexplained syncope [30]. The authors assessed older patients with syncope who displayed PPH due to a failure to maintain systemic vascular resistance, probably because of splanchnic blood pooling without a compensatory increase in peripheral vascular resistance [30]. Kohara et al. first clarified that PPH is a potential independent risk factor for silent lacunae stroke, as evaluated by MRI, and not via non-dipper hypertension in older Japanese patients with hypertension [31]. A higher prevalence of PPH is also observed in patients with neurological diseases, such as Parkinson's disease, Alzheimer's disease, multiple system atrophy, and diabetes [32]. The pathophysiology of PPH remains poorly defined, and diverse factors, including impairments in sympathetic and baroreflex function, the release of vasodilatory peptides, such as insulin and somatostatin, the rate of small intestinal nutrient delivery, gastric distension, and splanchnic blood pooling, are predicted to be important [29]. Carbohydrate intake is a more frequent contributor to the occurrence of PPH than protein and lipid intake. Although a detailed analysis of the prevalence of PPH in old peoples is unavailable, PPH is postulated to be common in older people, particularly in the very elderly. All physicians and medical care-giving staff caring for older patients should be aware of the hypotensive effects of various types of food and should consider PPH in the evaluation of syncope, falls, dizziness, and other cerebral ischemic symptoms [33]. Regarding the prevention of PPH, more frequent small meals rather than three regular sized meals could reduce the occurrence of PPH. A reduction in carbohydrate intakes might also prevent PPH. Acarbose is an effective treatment for preventing PPH in older patients with diabetes [34].

BP variabilities in medical settings

(a) White coat hypertension

As mentioned, white coat hypertension (WCH) or the white coat effect (WCE) on hypertension is more common in older people [4]. The mechanisms of WCH/WCE are mainly due to increased activation of the autonomic nervous system [35] and mental stress [36]. As the aging-induced vascular remodeling in older people exponentially increases vascular resistance and hypersensitivity to the vasoconstrictive response, such as activation of SNS [4], BP is readily increased even by a low level stimulation of the SNS, such as mental stress. Thus, WCH/WCE would be common in older people. The impacts of WCH/WCE on the onset of CVD are still controversial. Although WCH/WCE was not thought to exert a substantial effect on the onset of CVD for many years [2], a recent paper indicates that WCH/WCE is an overt risk factor for CVD [37] and target organ damage, such as microalbuminuria [38]. Home BP self-measurements are very important for detecting and monitoring WCH/WCE in older populations.

(b) Visit-to-visit variability in the outpatient clinic

Visit-to-visit office BP variability (VVV) in the outpatient clinic is strongly correlated with CVD events and prognosis in patients with hypertension [39]. According to a previous report from our group, VVV in patients with hypertension poses a risk of CVD events and CVD-induced death in a Japanese population [40]. In older populations, VVV is common because of various characteristics of BP responses, including progressive arterial stiffness, hyperresponsiveness to vasoconstrictive stimuli (Fig. 1), increased/reduced sympathetic nervous system activity and reduced renal function, as mentioned in this review. Chronic kidney disease [41] and diabetes [42], which are common complications in older populations, are risk factors for VVV in patients with hypertension. A significant association of VVV with dementia (Alzheimer's disease) or cognitive decline has been observed in older people with hypertension [43]. VVV may induce microvascular injuries in the brain and dysregulated cerebral circulation;

consequently, pathological changes in Alzheimer's disease (AD) will progress [43]. However, VVV exerted limited effects on the onset of AD and VVV associated with cognitive decline in a recent study [44]. A Japanese study confirmed this result in very old subjects with an average age of 83–84 years [45]. The prevention of cognitive decline is very desirable in older populations. Thus, medical providers should focus on VVV, particularly in older patients with hypertension. Is VVV or diurnal BP variability a stronger predictor of CVD in older populations? Chowdhury recently reported that ambulatory diurnal BP variability is associated with CVD-induced death, with stronger effect than long-term VVV, in older people with hypertension [46]. Greater daily variations in systolic BP measured using home, self-monitored BP was strongly associated with the future onset of all-cause dementia in the study by Hisayama [47]. These findings indicate the importance of home and ambulatory BP monitoring for older people, along with office BP measurements in the outpatient clinic. Finally, although VVV is associated with CVD and some other complications of hypertension, clinical BP control will be more important for preventing CVD onset than VVV, based on the results of a post hoc analysis in SPRINT [48]. Therefore, according to the guideline, BP control is definitely important and medical providers carefully assess VVV in the outpatient clinic.

Perspectives and conclusions

As mentioned in this review article, several types of BP variations lead to hypertension or hypotension, and these BP variations are closely associated with the onset of CVDs and their mortality in older populations. Therefore, doctors or medical providers should obtain precise knowledge about BP variations in older people and closely monitor them in various situations. For the detection of BP variability and prevention of its complications in daily life in older people, BP measurements performed in the clinic in response to postural changes as sitting, supine and standing and home BP measurements (HBPM) recorded during various daily activities not only at morning and nigh time but also after eating meals are important. Furthermore, ambulatory BP monitoring (ABPM) would be useful for detecting BP variations during sleep. HBPM is recommended as a necessary daily practice, and ABPM should be examined once before starting medication and every time antihypertensive drug dose is changed or added, whenever possible. However, HBPM using an electric automated BP measuring device in very elderly populations has not yet been completely validated. This validation is definitely necessary. For treatments of clinically important BP variations in older people, appropriate maneuvers and some medications for their specific types of BP variations described in this review should be considered. Finally, the numbers of non-agenarians and centenarians are increasing rapidly, particularly in Japan. Although hypertension is commonly present in these very old generations, the appropriate treatment strategy for hypertension in these generations is still not fully established. According to our epidemiological study of older people, including non-agenarians and centenarians, known as the 'SONIC study', the BP of these individuals is much lower than the BP in octogenarians, and the average BP in centenarians does not meet the criteria for hypertension [49]. SBP has recently been shown to decrease in subjects aged >80 years, and a low SBP was strongly correlated with higher mortality and frailty rates in a non-randomized observation study [50]. Thus, additional discussions and investigations of the treatment BP levels and treatment strategies for very old populations are needed.

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Compliance with ethical standards

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References

1. Cassel CK, Cohen HJ, Larson EB, Meier DE, Resnick NM, Rubenstein LZ et al. Geriatric Medicine. Third edition. (Springer-Verlag, New York 1996).
2. Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M et al. Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). Hypertens Res. 2014;37:253–390.
3. Homma S, Hirose N, Ishida H, Ishii T, Araki G. Carotid plaque and intima-media thickness assessed by b-mode ultrasonography in subjects ranging from young adults to centenarians. Stroke. 2001;32:830–5.
4. Rakugi H. Hypertension/Hypotension in old peoples (Japanese) Geriatric Medicine text book. p.214–219. Edited by: Japanese Geriatric Society, Nishimura shoten, Tokyo 2013.
5. Ohuchi Y. Changes in Cardiovascular systems by aging (Japanese) Geriatric Medicine text book. p.128–130. Edited by: Japanese Geriatric Society, Nishimura shoten, Tokyo 2013.
6. Asayama K, Satoh M, Kikuya M. Diurnal blood pressure changes. Hypertens Res. 2018;41:669–78.
7. Zhao S, Fu S, Ren J, Luo L. Poor sleep is responsible for the impaired nocturnal blood pressure dipping in elderly hypertensive: a cross-sectional study of elderly. Clin Exp Hypertens. 2018;40:582–8.
8. McKeigue PM, Reynard JM. Relation of nocturnal polyuria of the elderly to essential hypertension. Lancet. 2000;355:486–8.

9. da Silva RM. Atrial fibrillation: epidemiology and peculiarities in the elderly. Cardiovasc Hematol Agents Med Chem. 2015;13:72–77.
10. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. J Hypertens. 2002;20: 2183–9.
11. Kimura G, Dohi Y, Fukuda M. Salt sensitivity and circadian rhythm of blood pressure: the keys to connect CKD with cardiovascular events. Hypertens Res. 2010;33:515–20.
12. Itabashi M. CKD management in elderly patients. (Japanese) Nihon Ronen Igakkai Zasshi. 2018;55:345–51.
13. Hattori A. Melatonin and aging. (Japanese) Hikaku Seiri Seikagaku. 2017;34:2–11.
14. Xie Z, Chen F, Li WA, Geng X, Li C, Meng X et al. A review of sleep disorders and melatonin. Neurol Res. 2017;39: 559–65.
15. Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S et al. Nocturnal urinary melatonin excretion is associated with non-dipper pattern in elderly hypertensives. Hypertens Res. 2013;36:736–40.
16. Lambert EA1, Chatzivlastou K, Schlaich M, Lambert G, Head GA. Morning surge in blood pressure is associated with reactivity of the sympathetic nervous system. Am J Hypertens. 2014;27:783–92.
17. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation. 2003;107:1401–6.
18. Pierdomenico SD, Pierdomenico AM, Cuccurullo F. Morning blood pressure surge, dipping, and risk of ischemic stroke in elderly patients treated for hypertension. Am J Hypertens. 2014;27:564–70.
19. Finucane C, O'Connell MD, Donoghue O, Richardson K, Savva GM, Kenny RA. Impaired orthostatic blood pressure recovery is associated with unexplained and injurious falls. J Am Geriatr Soc. 2017;65:474–82.
20. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy.. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology. 1996;46:1470.
21. Mader SL, Josephson KR, Rubenstein LZ. Low prevalence of postural hypotension among community-dwelling elderly. JAMA. 1987;258:1511–4.
22. Mader SL. Orthostatic hypotension. Med Clin North Am. 1989;73:1337–49.
23. Low PA, Singer W. Management of neurogenic orthostatic hypotension: an update. Lancet Neurol. 2008;7:451–8.
24. Poon IO, Braun U. High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. J Clin Pharm Ther. 2005;30:173–8.
25. Low PA, Tomalia VA. Orthostatic hypotension: mechanisms, causes, management. J Clin Neurol. 2015;11:220–6.
26. Benvenuto LJ, Krakoff LR. Morbidity and mortality of orthostatic hypotension: implications for management of cardiovascular disease. Am J Hypertens. 2011;24:135–44.
27. Roosendaal EJ, Moeskops SJ, Germans T, Ruiter JH, RWMM Jansen. Different patterns of orthostatic hypotension in older patients with unexplained falls or syncope: orthostatic hypotension patterns in older people. Eur Geriatr Med. 2018;9:485–92.
28. Russell FHRaC. The Encyclopedia of aging and the elderly. NY, USA: Facts On File, Inc; 1992.
29. Trahair LG, Horowitz M, Jones KL. Postprandial hypotension: a systematic review. J Am Med Dir Assoc. 2014;15:394–409.
30. Jansen RW, Connelly CM, Kelley-Gagnon MM, Parker JA, Lipsitz LA. Postprandial hypotension in elderly patients with unexplained syncope. Arch Intern Med. 1995;155: 945–52.
31. Kohara K, Jiang Y, Igase M, Takata Y, Fukuoka T, Okura T et al. Postprandial hypotension is associated with asymptomatic cerebrovascular damage in essential hypertensive patients. Hypertension. 1999;33(1 Pt 2):565–8.
32. Pavelic A, Magdalena Krbot Skoric MK, Luka Crnos̆ija LC, Habek M. Postprandial hypotension in neurological disorders: systematic review and meta-analysis. Clin Auton Res. 2017;27:263–71.
33. Jansen RW1, Lipsitz LA. Postprandial hypotension: epidemiology, pathophysiology, and clinical management. Ann Intern Med. 1995;122:286–95.
34. Madden KM, Harris DE, Meneilly GS. Attenuation of postprandial hypotension with acarbose in older adults with type 2 diabetes mellitus. J Am Geriatr Soc. 2015;63:1484–6.
35. Neumann SA, Jennings JR, Muldoon MF, Manuck SB. White-coat hypertension and autonomic nervous system dysregulation. Am J Hypertens. 2005;18(5 Pt 1):584–8.
36. Saito II, Takeshita E, Murata K, Kawabe H, Saruta T. Serum cortisol in the white-coat phenomenon. Blood Press Monit. 1996;1:381–3.
37. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z et al. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. J Hypertens. 2017;35:677–88.
38. Hata J, Fukuhara M, Sakata S, Arima H, Hirakawa Y, Yonemoto K et al. White-coat and masked hypertension are associated with albuminuria in a general population: the Hisayama Study. Hypertens Res. 2017;40:937–43.
39. Tai C, Sun Y, Dai N, Xu D, Chen W, Wang J et al. Prognostic significance of visit-to-visit systolic blood pressure variability: a meta-analysis of 77,299 patients. J Clin Hypertens. 2015;17:107–15.
40. Kawai T, Ohishi M, Ito N, Onishi M, Takeya Y, Yamamoto K et al. Alteration of vascular function is an important factor in the correlation between visit-to-visit blood pressure variability and cardiovascular disease. J Hypertens. 2013;31:1387–9.
41. Jeffers BW, Zhou D. Relationship between visit-to-visit blood pressure variability (BPV) and kidney function in patients with hypertension. Kidney Blood Press Res. 2017;42: 697–707.
42. Okada R, Yasuda Y, Tsushita K, Wakai K, Hamajima N, Matsuo S. Within-visit blood pressure variability is associated with prediabetes and diabetes. Sci Rep. 2015;5:7964.
43. Lattanzi S, Brigo F, Vernieri F, Silvestrini M. Visit-to-visit variability in blood pressure and Alzheimer's disease. J Clin Hypertens. 2018;20:918–24.
44. van Middelaar T, van Dalen JW, van Gool WA, van den Born BH, van Vught LA, Moll van Charante EP et al. Visit-to-visit blood pressure variability and the risk of dementia in older people. J Alzheimers Dis. 2018;62:727–35.
45. Fujiwara T, Hoshide S, Kanegae H, Eguchi K, Kario K. Exaggerated blood pressure variability is associated with memory impairment in very elderly patients. J Clin Hypertens. 2018;20:637–44.
46. Chowdhury EK, LMH Wing, GLR Jennings, Beilin LJ, Reid CM. ANBP2 Management Committee. Visit-to-visit (long-term) and ambulatory (short-term) blood pressure variability to predict mortality in an elderly hypertensive population. J Hypertens. 2018;36:1059–67.
47. Oishi E, Ohara T, Sakata S, Fukuhara M, Hata J, Yoshida D et al. Day-to-day blood pressure variability and risk of dementia in a general japanese elderly population: the Hisayama study. Circulation. 2017;136:516–25.

48. Chang TI, Reboussin DM, Chertow GM, Cheung AK, Cushman WC, Kostis WJ. et al.SPRINT Research Group. Visit-to-visit office blood pressure variability and cardiovascular outcomes in SPRINT (Systolic Blood Pressure Intervention Trial). Hypertension. 2017;70:751–8.
49. Kamide K, Kabayama M. Blood pressure in centenarian. (Japanese) Ronen Shakaikagaku. 2017;39:38–43.
50. Ravindrarajah R, Hazra NC, Hamada S, Charlton J, SHD Jackson, Dregan A et al. Systolic blood pressure trajectory, frailty, and all-cause mortality >80 years of age: cohort study using electronic health records. Circulation. 2017;135:2357–68.