REVIEW ARTICLE

Blood pressure variability and arterial stiffness parameters derived from ambulatory blood pressure monitoring

Masahiro Kikuya[1], Kei Asayama[1,2], Takayoshi Ohkubo[1,2]

1 Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
2 Tohoku Institute for Management of Blood Pressure, Sendai, Japan

KEY WORDS
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ABSTRACT
Multiple blood pressure (BP) measurements allow an evaluation of BP variability and BP-derived arterial stiffness indices. Periodic variations in BP are well known, from beat-to-beat BP readings in intra-arterial measurement to seasonal variations in BP. Diurnal BP variation has been investigated in relation to its prognostic value. People with night-to-day BP ratio of 1 or higher, that is, those with a higher nocturnal than daytime BP, were older than those with normal dipping status at baseline and had a greater risk of cardiovascular mortality and morbidity. Short-term BP variability was evaluated using an intraindividual standard deviation or average real variability without any assumption of a periodic fluctuation. The ambulatory arterial stiffness index (AASI), which is derived from ambulatory BP monitoring, is a surrogate measure of arterial stiffness. An increased short-term BP variability and the AASI have been linked to target organ damage and poor prognosis, while short-term BP variability added only 1% or less to the prediction of a cardiovascular event. Although strict BP control at any time of the day is essential, studies are required to clarify how much additional benefit is derived from a treatment considering BP variability or the AASI in patients with hypertension.

Correspondence to:
Masahiro Kikuya, MD, PhD, Department of Hygiene and Public Health, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173–8605, Japan, email: kikuyam@med.teikyo-u.ac.jp
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Introduction There is a considerable amount of research data to support the prognostic significance of blood pressure (BP).[1-3] Even a single set of BP measurements predicts future cardiovascular mortality and morbidity.[1-3] A BP-lowering intervention prevents cardiovascular disease.[4] Multiple BP measurements definitely provide also other benefits. Home BP measurement, for example, enhances the reproducibility of an average BP value,[5] improves the prognostic value by acquiring the reliable point estimates of an average BP,[6] facilitates titration of antihypertensive drugs in clinical practice,[7] improves adherence to antihypertensive treatment,[8,9] and promotes lifestyle modification and personal health management. In relation to ambulatory BP monitoring (ABPM), obtaining multiple BP readings is also beneficial. Blood pressure measurement within a short time frame of the hospital setting does not necessarily represent the total BP load in an individual. Optimal BP values at all times (both in the hospital and home setting) are associated with the best prognosis.[10,11] In addition to these advantages, there is another field of research that focuses on obtaining useful data from serial BP measurements in an individual by information processing of BP readings other than simply calculating the average value. This yields 2 measures derived from ABPM: BP variability and BP-derived arterial stiffness (TABLE 1). In this review, we provide an overview of these indices.

Periodic changes in blood pressure Persistent efforts have been made to identify periodic variations in data from serial BP measurements in an individual.[12-16] Among beat-to-beat BP readings obtained by a direct measurement of intra-arterial BP, the Meyer wave has been known since the 19th century.[12] It is a short-term

TABLE 1 Blood pressure variability and blood pressure–derived arterial stiffness indices by blood pressure measurement (based on Asayama et al[31]; reproduced with permission)

	Intra-arterial BP[a]	ABPM	Home BP[b]	Office BP[c]
Blood pressure variability				
Beat-to-beat	Yes	No	No	No
Mayer wave	Yes	No	No	No
15- to 30-minute changes	Yes	Yes	No	No
Morning–evening difference	Yes	Yes	Yes	No
Diurnal blood pressure variation	Yes	Yes	Possible	No
Morning hypertension	Yes	Yes	Yes	No
Weekly cycle	No	No	Yes	No
Monthly change	No	No	Yes	Possible
Visit-to-visit variability	No	No	Yes	Yes
Seasonal variation	No	No	Yes	Yes
Blood pressure–derived arterial stiffness indices				
Pulse pressure	Yes	Yes	Yes	Yes
AASI and derivatives	Yes	Yes	Yes	No

a Intra-arterial direct blood pressure measurement; **b** Self-measurement of blood pressure at home; **c** Office blood pressure measured in a clinic or examination center

Abbreviations: AASI, ambulatory arterial stiffness index; ABPM, ambulatory blood pressure monitoring; BP, blood pressure

periodic variation in BP, lasting about 10 seconds (0.1 Hz). It is derived from breath and the oscillation of the sympathetic vasomotor tone of arterial blood vessels.[13] There have also been studies on longer-term periodic changes in BP, such as diurnal or seasonal variations in BP.[14,15-17]

Diurnal blood pressure variation Circadian rhythms are observed in various biological activities, and they are related to sleep and feeding patterns. It is also well established that circadian rhythms are present in BP. To investigate the circadian rhythm in BP, a simple model has been developed, known as the cosinor method.[14] It has been used, for example, for a comparison of circadian BP change in a target individual or population[18] or for evaluation of drug efficacy.[19] In the cosinor method, BP readings obtained during 24 or 48 hours are fitted to a cosine curve as follows: BP = MESOR + amplitude × cos {π/12 × (hour of the day – acrophase)}, where MESOR stands for the midline-estimating statistic of rhythm. Thus, the circadian circle of BP can be easily expressed by using 3 parameters: MESOR, amplitude, and acrophase.[14] Then, along with the widespread use of ABPM, which is a noninvasive and intermittent method for BP measurement, more easy-to-use and practical parameters of BP circadian rhythm have been developed and have become standard indices: the degree of nocturnal BP reduction and night-to-day BP ratio.[20]

These parameters are calculated using the following equations: 1) degree of nocturnal BP reduction (%) = [average daytime BP – average nighttime BP] / average daytime BP × 100; and 2) night-to-day BP ratio = average nighttime BP / average daytime BP. The degree of nocturnal BP reduction can be also calculated using the following formula: degree of nocturnal BP reduction (%) = (1 – night-to-day BP ratio) × 100.

The dipping status[20] is a dichotomized indicator of the above indices. Classically, patients with a nocturnal BP reduction of 10% or more (ie, night-to-day BP ratio of less than 0.9) are classified as "dippers." Similarly, individuals with a nocturnal BP reduction of less than 10% (0.9 or more) are considered "nondippers."[21] The key concept is that it is normal for an individual to have lower BP during sleep at night than during daytime, and that a blunted nocturnal decline in BP is an abnormal state.[20] The nondipper status, which is an abnormal circadian BP variation, is observed in patients with secondary hypertension, such as Cushing syndrome.[22] It is also seen in patients on exogenous glucocorticoid therapy.[23] The aldosterone-to-renin ratio as a marker of abnormal aldosterone activity and salt sensitivity was shown to be related to a nondipping pattern of BP, especially in individuals with high sodium intake.[24] Abnormal diurnal variation in BP was associated not only with secondary hypertension or exogenous glucocorticoid therapy but also with more common pathological conditions such as heart or renal failure, autonomic neuropathy, sleep apnea syndrome,[25] anxiety disorder,[26] and cerebrovascular disorders.[7] Shift work and race or ethnicity were reported to be associated with the diurnal rhythm of BP.[27] A diminished nocturnal decline in BP was also associated with arterial stiffness,[28] hypertensive target organ damage,[29] and cardiovascular mortality.[30] In a population-based cohort study in Ohasama, Japan, a higher decline in nocturnal BP was correlated with a greater risk of cardiovascular mortality.[30,31] Among the 7458 patients (mean age, 56.8 years) from Europe, Asia, and Latin America included in the IDACO study (International Database on Ambulatory BP monitoring in relation to Cardiovascular Outcomes),[32] which encompassed prospective cohort studies of a random population sample, the night-to-day BP ratio was associated with cardiovascular death and fatal events combined with nonfatal ones, during a median follow-up of 9.6 years, after adjustment for sex, age, body mass index, smoking and drinking, serum cholesterol levels, history of cardiovascular disease, diabetes mellitus, and antihypertensive treatment. However, after further adjustment for 24-hour BP, the night-to-day BP ratio lost its predictive power for these

outcomes.[32] The IDACO investigators concluded that 24-hour BP rather than the dipping pattern should continue to inform clinical decisions.[33] The night-to-day BP ratio should be interpreted with caution because the ratio is composed of and affected by both nighttime and daytime BP. A high night-to-day ratio is observed not only in patients with high nocturnal BP but also in those with lower BP during the day than at nighttime. This could be caused by physical inactivity during daytime. A short-acting antihypertensive drug taken in the morning could also result in an insufficient duration of the BP-lowering effect and a relatively high nocturnal BP compared with daytime BP.

It should be noted that the high night-to-day BP ratio is not necessarily associated with a shorter life expectancy.[32] In the IDACO study, patients with a night-to-day BP ratio of 1 or higher were about 4 years older and also died at an older age than those with the normal dipping status at baseline.[32]

In summary, the night-to-day BP ratio should be interpreted with caution. Clinical decisions should be made on the basis of 24-hour BP rather than the dipping pattern.[31,33]

Short-term blood pressure variability In the previous section, we focused on periodic changes in BP, namely, abnormalities in diurnal biological rhythm. However, there are also different types of variability that do not show periodic fluctuations. Short-term BP variability usually refers to a BP fluctuation of every few minutes to 30 minutes. It is not characterized by periodic fluctuations, but it also has physiological or pathological implications. Large variability in BP can cause cerebral hypoperfusion via increased shear stress in small vessels. Moreover, it could be a marker of an underlying comorbidity and poor prognosis. Increased variability could result from atherosclerotic lesions in a large artery, damage of medullary vasomotor center, cardiovascular autonomic dysfunction, impaired baroreflex function, exaggerated sympathetic activation, and poor adherence to antihypertensive treatment.[34] In rats, BP variability is a marker of cardiac damage, renal lesions, and aortic hypertrophy independent of BP levels.[35] In rats after sinoaortic denervation, high BP variability was observed compared with sham operation rats, which led to aortic and left ventricular hypertrophy.[36]

To evaluate BP variability, a standard deviation (SD) of BP in an individual is used. Specifically, 48 readings are obtained from 24-hour measurement of ABPM at intervals of 30 minutes. Then, the index of BP variability can be calcualted as the SD of the 48 readings for an individual. However, in practice, the 24-hour SD is usually corrected by the following equation: weighted 24-hour SD = {(daytime SD × hour of daytime) + (nighttime SD × hour of nighttime)} / (hour of daytime + hour of nighttime). This correction is nessesary because durnal change in BP explains most of the interindividual variation in the SD.[37] Daytime and nighttime SDs are also independent from a durnal change in short-term BP variability.

Blood pressure variability was also described by another indicator. While the SD does not consider the temporal order of BP readings, the average real variability considers consecutive BP readings.[38] The average real variability is the average of the absolute differences between consecutive measurements, as calculated by the following equation:

$$\frac{1}{\sum w} \times \sum_{k=1}^{n-1} w \times \left| BP_{k+1} - BP_k \right|,$$

where w is the time interval between BP_k and BP_{k+1}, n is the number of BP readings, and k ranges from 1 to n–1.[38]

Several observational studies have reported large SD in relation to target organ damage and poor prognosis. The Ohasama study group revealed that nighttime SD was associated with carotid plaque after correction by nighttime BP.[29] An SD of systolic BP was shown to be associated with chronic kidney disease progression from stage 1 to stage 5 in 16 546 patients from the Spanish Ambulatory Blood Pressure Monitoring Registry.[39] An increased daytime SD of BP and a reduced daytime SD of heart rate independently predicted cardiovascular mortality.[40] Pringle et al[41] reported that a 5-mm Hg increase in nighttime SD of systolic BP corresponded to an increase of 80% in the risk of stroke in the placebo group of the Systolic Hypertension in Europe (Syst-Eur) trial. Nighttime SD was also reported to be an independent predictor of cardiovascular disease in elderly patients with type 2 diabetes.[42] Palatini et al[43] showed that nighttime SD was an independent predictor of all-cause mortality, cardiovascular mortality, and cardiovascular events in 7112 participants with untreated hypertension from 6 prospective cohort studies. The Second Australian National Blood Pressure Study reported that weighted 24-hour SD of systolic and diastolic BP was significantly associated with increased all-cause and cardiovascular mortality.[44]

Generally, the larger the average value, the larger the variance of the biological variables. This principle applies to BP as well. The correlation coefficient between the BP level and SD of BP is considerably strong. Therefore, in studies investigating the association between BP variability and prognosis, BP levels were recognized as a strong confounding factor. In all the above studies,[29,39-44] the average value of BP was adjusted as an independent variable in a multivariate analysis. After adjustment for the BP level, the associations of BP variability with

the outcome were attenuated despite being significant in most of those studies. For a long time, it was unclear whether BP variability can offer an independent and clinically relevant prognostic value, as studies reported only its statistical significance, increased by a large sample size. The clinical significance of BP variability was first studied by IDACO investigators.[45] Among the 8938 people (mean age, 53 years) from Denmark, Belgium, Sweden, Russian Federation, Japan, China, Uruguay, Czech Republic, Ireland, Italy, and Poland, 1242 deaths and 1049 cardiovascular events were observed during a mean follow-up of 11 years. The average real variability of systolic and diastolic BP was an independent predictor of all-cause mortality and cardiovascular events after adjustment for 24-hour BP levels. However, when the generalized R^2 statistic was applied to assess the risks accounted for by the average real variability in Cox regression,[45] the average real variability added only 1% to the prediction of a cardiovascular event.[46]

Blood pressure fluctuation is a hetero parameter, affected by various external and internal stimuli, including elastic properties of blood vessels, postprandial hypotension, orthostatic hypotension, morning surge,[47] stress hypertension, and noise. Although the independent prognostic significance of BP variability above the 24-hour BP level is small in terms of the generalized R^2 statistic from the results of the IDACO database,[46] after a careful separation of those various factors, there could be a possibility of undiscovered prognostic significance of BP variability. Only a profound understanding of the mechanisms of BP fluctuation in each stimulus can reveal the hidden prognostic potential of BP variability.

Ambulatory arterial stiffness index In 2006, the AASI was projected as a surrogate measure of arterial stiffness. The index was derived from ABPM and defined as one minus regression coefficient of diastolic BP against systolic BP in an individual.[48,49] Mathematically, the regression coefficient is a product of the correlation coefficient and the ratio of an SD of a dependent variable to that of an independent variable. The AASI can be calculated from the following equation: AASI = 1 – r × [(SD of diastolic BP)/(SD of systolic BP)], where r is the correlation coefficient of diastolic BP and systolic BP. This index can be computed from 24-hour BP recordings in an individual and is used to express the dynamic relationship between diastolic and systolic BP. The ratio of the SD of BP indicates that the AASI is linked with BP variability, suggesting that not only a certain number of BP readings but also a wide variability or range of BP is necessary to calculate the AASI. The ratio of diastolic to systolic BP variability is the main component of the AASI. Generally, changes in diastolic BP occur in parallel with those in systolic BP. The lack of parallelism between diastolic and systolic BP variability is the key concept of the AASI. When the mean arterial pressure increases, arterial stiffness increases exponentially.[50] The lack of parallelism was connected with a nonlinear relation between the mean arterial pressure and arterial stiffness. Dolan et al[48] focused on this nonlinear relation with the mean arterial pressure and explained the concept of the AASI as follows: "In subjects with elastic arteries, with variation in mean arterial pressure, changes in systolic and diastolic BPs occur in parallel throughout the BP range. In subjects with less compliant arteries, increases in the distending pressure, above a certain threshold, are associated with a greater increase in systolic pressure than diastolic pressure. In those with very stiff vessels, although systolic pressure sharply rises with each increase in mean arterial pressure, diastolic pressure may even decline."[48]

The AASI correlated with 24-hour pulse pressure,[51] carotid-femoral pulse wave velocity,[51] central and peripheral augmentation indexes,[52] the aortic collagen content, and the ratio of collagen to elastin.[53] The AASI predicted cardiovascular mortality[48,49] over and above pulse pressure. It is a better predictor of stroke than of cardiac disease.[48,54,55] A recent study demonstrated a direct relationship between the AASI and the lower limit of cerebral autoregulation of brain perfusion detected by transcranial Doppler ultrasonography in patients during cardiac surgery.[56]

The suggestion that the AASI may be used as a noninvasive measure of arterial stiffness has raised some controversy. Schillaci et al[57] argued that it was not a specific marker of reduced arterial compliance based on their observation that it was related to left ventricular mass index and carotid-femoral pulse wave velocity only in a univariate alalysis but not in a multivatiate analysis in patients with untreated hypertension.[57] This inconsistency could be partly explained by differences in methodology and characteristics of the study group. In particular, the night to day ratio of the number of BP readings affects the AASI, because it depends on nocturnal BP dipping.[57-60] Therefore, in studies of the AASI, it is necessary to report the number of readings at daytime and nighttime and to adjust for the degree of nocturnal BP reduction. Furthermore, standardization of ABPM protocols is desirable.

Recently, Gavish et al[61,62] proposed a similar index, namely, the pulse stiffening ratio (PSR), which is the ratio of systolic BP variability to diastolic BP variability, calculated as follows: PSR = (SD of systolic BP/SD of diastolic BP).

However, it remains unclear whether the PSR and AASI are useful in clinical practice,[62] and strict BP control still remains the standard of care.

Perspectives Literature on BP fluctuations and the AASI has reported their prognostic implications as well as a relationship with other arterial stiffness indices and target organ damage. However, at the moment, the application of BP variability and the AASI in clinical practice is limited, and they have not been proved useful enough to be included in standard care, with the exception of diurnal BP change. Strict BP control is still a routine strategy in antihypertensive treatment, and it should be applied at any time of the day.[5,7,10,11,30,32] Further studies are needed to clarify how much additional benefit is derived from a treatment considering BP variability or the AASI in hypertensive patients after strict BP control.

ARTICLE INFORMATION

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REFERENCES

1 Lewington S, Clarke R, Qizilbash N, et al; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360: 1903-1913.

2 Fujiyoshi A, Ohkubo T, Miura K, et al. Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women. Hypertens Res. 2012; 35: 947-953.

3 Ikeda N, Saito E, Kondo N, et al. What has made the population of Japan healthy? Lancet. 2011; 378: 1094-1105.

4 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009; 338: b1665.

5 Imai Y, Obara T, Asamaya K, Ohkubo T. The reason why home blood pressure measurements are preferred over clinic or ambulatory blood pressure in Japan. Hypertens Res. 2013; 36: 661-672.

6 Ohkubo T, Asayama K, Kikuya M, et al. How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. J Hypertens. 2004; 22: 1099-1104.

7 Shimamoto K, Ando K, Fujita T, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). Hypertens Res. 2014; 37: 253-392.

8 Van Onzenoort HA, Verberk WJ, Kroon AA, et al. Effect of self-measurement of blood pressure on adherence to treatment in patients with mild-to-moderate hypertension. J Hypertens. 2010; 28: 622-627.

9 Ogedegbe G, Schoenthaler A. A systematic review of the effects of home blood pressure monitoring on medication adherence. J Clin Hypertens (Greenwich). 2006; 8: 174-180.

10 Satoh M, Asayama K, Kikuya M, et al. Long-term stroke risk due to partial white-coat or masked hypertension based on home and ambulatory blood pressure measurements: the Ohasama study. Hypertension. 2016; 67: 48-55.

11 Asayama K, Thijs L, Li Y, et al. Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. Hypertension. 2014; 64: 935-942.

12 Penaz J. Mayer waves: history and methodology. Automedica. 1978; 2: 135-141.

13 Julien C. The enigma of Mayer waves: Facts and models. Cardiovasc Res. 2006; 70: 12-21.

14 Halberg F. Chronobiology. Annu Rev Physiol. 1969; 31: 675-726.

15 Imai Y, Munakata M, Tsuji I, et al. Seasonal variation in blood pressure in normotensive women studied by home measurements. Clin Sci (Lond). 1996; 90: 55-60.

16 Hanazawa T, Asayama K, Watabe D, et al. Association between amplitude of seasonal variation in self-measured home blood pressure and cardiovascular outcomes: HOMED-BP (Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure) study. J Am Heart Assoc. 2018; 7.

17 Modesti PA, Rapi S, Rogolino A, et al. Seasonal blood pressure variation: implications for cardiovascular risk stratification. Hypertens Res. 2018; 41: 475-482.

18 Munakata M, Imai Y, Abe K, et al. Assessment of age-dependent changes in circadian blood pressure rhythm in patients with essential hypertension. J Hypertens. 1991; 9: 407-415.

19 Munakata M, Imai Y, Hashimoto J, et al. The influence of antihypertensive agents on circadian rhythms of blood pressure and heart rate in patients with essential hypertension. Tohoku J Exp Med. 1992; 166: 217-227.

20 O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. Lancet. 1988; 2: 397.

21 O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013; 31: 1731-1768.

22 Imai Y, Abe K, Sasaki S, et al. Altered circadian blood pressure rhythm in patients with Cushing's syndrome. Hypertension. 1988; 12: 11-9.

23 Imai Y, Abe K, Sasaki S, et al. Exogenous glucocorticoid eliminates or reverses circadian blood pressure variations. J Hypertens. 1989; 7: 113-120.

24 Satoh M, Kikuya M, Ohkubo T, et al. Aldosterone-to-renin ratio and nocturnal blood pressure decline in a general population: the Ohasama study. J Hypertens. 2011; 29: 1940-1947.

25 Hla KM, Young T, Finn L, et al. Longitudinal association of sleep-disordered breathing and nondipping of nocturnal blood pressure in the Wisconsin Sleep Cohort Study. Sleep. 2008; 31: 795-800.

26 Kayano H, Koba S, Matsui T, et al. Anxiety disorder is associated with nocturnal and early morning hypertension with or without morning surge. Circ J. 2012; 76: 1670-1677.

27 Yamasaki F, Schwartz JE, Gerber LM, et al. Impact of shift work and race/ethnicity on the diurnal rhythm of blood pressure and catecholamines. Hypertension. 1998; 32: 417-423.

28 Jerrard-Dunne P, Mahmud A, Feely J. Circadian blood pressure variation: relationship between dipper status and measures of arterial stiffness. J Hypertens. 2007; 25: 1233-1239.

29 Shintani Y, Kikuya M, Hara A, et al. Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: The Ohasama study. J Hypertens. 2007; 25: 1704-1710.

30 Ohkubo T, Hozawa A, Yamaguchi J, 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: 2183-2189.

31 Asayama K, Satoh M, Kikuya M. Diurnal blood pressure changes. Hypertens Res. 2018; 41: 669-678.

32 Boggia J, Li Y, Thijs L, et al. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet. 2007; 370: 1219-1229.

33 Stolarz-Skrzypek K, Thijs L, Richart T, et al. Blood pressure variability in relation to outcome in the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome. Hypertens Res. 2010; 33: 757-766.

34 JCS Joint Working Group. Guidelines for the clinical use of 24 hour ambulatory blood pressure monitoring (ABPM) (JCS 2010). Circ J. 2012; 76: 508-519.

35 Miao CY, Xie HH, Zhan LS, Su DF. Blood pressure variability is more important than blood pressure level in determination of end-organ damage in rats. J Hypertens. 2006; 24: 1125-1135.

36 Miao CY, Su DF. The importance of blood pressure variability in rat aortic and left ventricular hypertrophy produced by sinoaortic denervation. J Hypertens. 2002; 20: 1865-1872.

37 Imai Y, Aihara A, Ohkubo T, et al. Factors that affect blood pressure variability. A community-based study in Ohasama, Japan. Am J Hypertens. 1997; 10: 1281-1289.

38 Mena L, Pintos S, Queipo NV, et al. A reliable index for the prognostic significance of blood pressure variability. J Hypertens. 2005; 23: 505-511.

39 Sarafidis PA, Ruilope LM, Loutradis C, et al. Blood pressure variability increases with advancing chronic kidney disease stage. J Hypertens. 2018; 36: 1076-1085.

40 Kikuya M, Hozawa A, Ohkubo T, et al. Prognostic significance of blood pressure and heart rate variabilities the Ohasama study. Hypertension. 2000; 36: 901-906.

41 Pringle E, Phillips C, Thijs L, et al. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. J Hypertens. 2003; 21: 2251-2257.

42 Eguchi K, Ishikawa J, Hoshide S, et al. Night time blood pressure variability is a strong predictor for cardiovascular events in patients with type 2 diabetes. Am J Hypertens. 2009; 22: 46-51.

43 Palatini P, Reboldi G, Beilin LJ, et al. Added predictive value of night-time blood pressure variability for cardiovascular events and mortality. Hypertension. 2014; 64: 487-493.

44 Chowdhury EK, Wing LM, Jennings GL, et al; 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: 1059-1067.

45 Gillespie BW. Use of generalized R-squared in Cox regression. Presented at: the American Public Health Association 134th Annual Meeting and Exposition; November 4-8, 2006; https://apha.confex.com/apha/134am/techprogram/paper_135906.htm. Accessed January 10, 2019.

46 Hansen TW, Thijs L, Li Y, et al. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. Hypertension. 2010; 55: 1049-1057.

47 Metoki H, Ohkubo T, Kikuya M, et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. Hypertension. 2006; 47: 149-154.

48 Dolan E, Thijs L, Li Y, et al. Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study. Hypertension. 2006; 47: 365-370.

49 Dolan E, Li Y, Thijs L, al. Ambulatory arterial stiffness index: rationale and methodology. Blood Press Monit. 2006; 11: 103-105.

50 Mitchell GF. Arterial stiffness and wave reflection in hypertension: pathophysiologic and therapeutic implications. Curr Hypertens Rep. 2004; 6: 436-441.

51 Kollias A, Stergiou GS, Dolan E, O'Brien E. Ambulatory arterial stiffness index: A systematic review and meta-analysis. Atherosclerosis. 2012; 224: 291-301.

52 Li Y, Wang JG, Dolan E, et al. Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. Hypertension. 2006; 47: 359-364.

53 Li ZY, Xu TY, Zhang SL, et al. Telemetric ambulatory arterial stiffness index, a predictor of cardio-cerebro-vascular mortality, is associated with aortic stiffness--determining factors. CNS Neurosci Ther. 2013; 19: 667-674.

54 Hansen TW, Staessen JA, Torp-Pedersen C, et al. Ambulatory arterial stiffness index predicts stroke in a general population. J Hypertens. 2006; 24: 2247-2253.

55 Kikuya M, Staessen JA, Ohkubo T, et al. Ambulatory arterial stiffness index and 24-hour ambulatory pulse pressure as predictors of mortality in Ohasama, Japan. Stroke. 2007; 38: 1161-1166.

56 Obata Y, Barodka V, Berkowitz DE, et al. Relationship between the ambulatory arterial stiffness index and the lower limit of cerebral autoregulation during cardiac surgery. J Am Heart Assoc. 2018; 7: e007816.

57 Schillaci G, Parati G, Pirro M, et al. Ambulatory arterial stiffness index is not a specific marker of reduced arterial compliance. Hypertension. 2007; 49: 986-991.

58 Staessen JA, Bieniaszewski L, O'Brien E, et al. An epidemiological approach to ambulatory blood pressure monitoring: the Belgian Population Study. Blood Press Monit. 1996; 1: 13-26.

59 Dechering DG, Adiyaman A, van der Steen M, Thien T. Interstudy variability in the ambulatory arterial stiffness index. Hypertension. 2007; 50: e65.

60 Adiyaman A, Boggia J, Li Y, et al. Dipping deeper into the ambulatory arterial stiffness index. Hypertension. 2007; 50: e59-e60.

61 Gavish B, Ben-Dov IZ, Kark JD, et al. The association of a simple blood pressure-independent parameter derived from ambulatory blood pressure variability with short-term mortality. Hypertens Res. 2009; 32: 488-495.

62 Gavish B, Izzo JL. Arterial stiffness: going a step beyond. Am J Hypertens. 2016; 29: 1223-1233.