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REVIEW ARTICLE

Review Series-Implication of Blood Pressure Variation

Clinical implication of visit-to-visit blood pressure variability

Satoshi Hoshide[1]

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Abstract

In clinical practice, out-of-office blood pressure (BP) measurements, i.e., ambulatory BP monitoring and home BP measurement, provide superior results, reproducibility, and evaluation of the effect of antihypertensive drugs compared with office BP measurement. However, following a report on the clinical impact of visit-to-visit BP variability, in addition to the results of a clinical trial, office BP measurement has regained prominence in clinical and research settings. Many reports have been published on the association between visit-to-visit BP variability and cardiovascular outcomes. However, other indexes of BP variability besides visit-to-visit BP variability can be evaluated in the office. In addition, methodology has been developed for calculation of visit-to-visit BP variability. Although most studies have shown a positive association between visit-to-visit BP variability and cardiovascular outcomes, this association was not observed in some studies. Further research is still needed for clarification.

Keywords Visit-to-visit blood pressure variability · Methodology · Cardiovascular outcome

Introduction

Office blood pressure (BP) measurement is the gold standard for the management of hypertension [1–3]. Physicians often observe fluctuations of office BP between visits, and these fluctuations are considered "noise," resulting in inaccurate BP values. Therefore, the measurement of out-of-office BP, i.e., ambulatory and home monitored BP, has been recommended in international hypertension guidelines and is widely used in clinical practice because of superior results, reproducibility, and evaluation of the effects of antihypertensive drugs, compared with those based on office BP measurement. As a result, many studies reported that ambulatory BP monitoring or home measurement had prognostic value for cardiovascular morbidity and mortality greater than that based on office BP measurement in the hypertensive population. Thus, until recently, the importance of out-of-office BP measurement has been emphasized for the management of hypertension. However, Rothwell et al. [4] reported the clinical impact of visit-to-visit BP variability in 2010, and the Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that strict control of systolic BP (<120 mmHg) using office-based measurement compared with standard treatment of systolic BP (<140 mmHg) in high-risk populations without diabetes or prior stroke significantly reduced cardiovascular events [5]. The measurement of office BP subsequently regained prominence in clinical and research settings.

✉ Satoshi Hoshide
hoshide@jichi.ac.jp

[1] Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

BP variability observed in the office

Rothwell et al. [4, 6] simultaneously published three interesting reports on visit-to-visit BP variability in 2010. First, the United Kingdom Transient Ischemic Attack Aspirin (UK-TIA) trial reported that the top decile group of visit-to-visit systolic BP (SBP) variability in a population with prior cerebrovascular events was a strong predictor of stroke incidence, independent of mean SBP level, compared with that in the lowest decile group (hazard ratio [HR]: 6.22, 95% confidence interval [CI]: 4.16–9.29, $P < 0.0001$) [4]. In addition, the top decile of maximum SBP during follow-up was also associated with stroke incidence, independent of mean SBP level (HR: 12.08, 95% CI: 7.40–19.72, $P < 0.0001$). The Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) study reported that residual visit-to-visit variability of SBP, i.e., BP variability under antihypertensive treatment, was

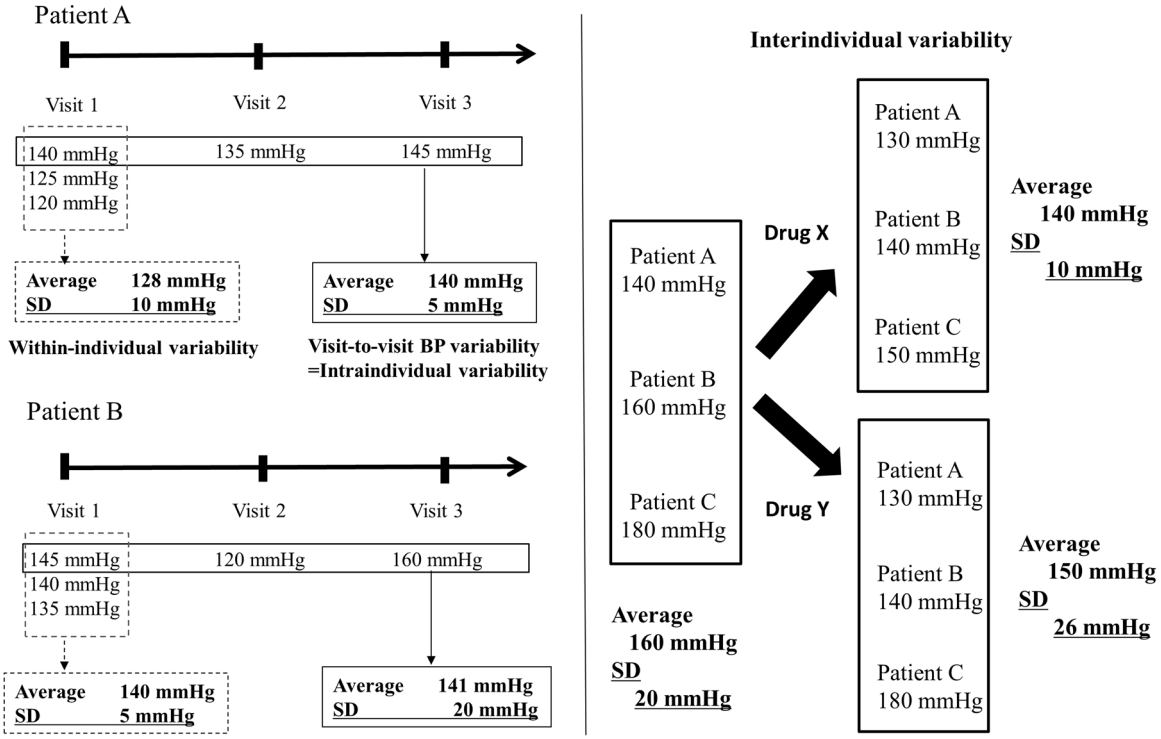

Fig. 1 Concept of three-index blood pressure variability evaluated using office measurement. The left figure shows the concept of within-individual variability and visit-to-visit BP variability (intraindividual variability). If SD is used as the index of BP variability, within-individual variability is defined as SD using multiple BP measurements at one visit (dotted line box). Visit-to-visit BP variability is defined as SD using multiple measurements on multiple visits (solid line box). In this case, within-individual variability in patient A (10 mmHg) is higher than that in patient B (5 mmHg), and visit-to-visit BP variability in patient B (20 mmHg) is higher than that in patient A (5 mmHg). The right figure shows the concept of interindividual variability. Interindividual variability refers to the SD derived from the calculation of average BP in each group. Interindividual variability on drug B (26 mmHg) is greater than that on drug A (10 mmHg), because BP in patient C did not decrease with intervention using drug Y. BP blood pressure, SD standard deviation

associated with stroke incidence. Although ASCOT-BPLA was randomized into amlodipine (plus perindopril) and atenolol (plus bendroflumethiazide) groups for the investigation of class effects of antihypertensive drugs on cardiovascular events in hypertensive patients with more than three cardiovascular risk factors, a second paper by Rothwell et al. [6] reported that within-individual BP variability and visit-to-visit BP variability were lower in the amlodipine group than in the atenolol group in ASCOT-BPLA. That report concluded that the effect of amlodipine-based treatment for the reduction of BP variability compared with atenolol-based treatment was associated with a reduced event rate. In addition, the report demonstrated that the effect of amlodipine-based treatment for reduction of interindividual BP variability was greater than that using atenolol-based treatment alone (Fig. 1). Finally, a third paper reported that the effect of a calcium-channel blocker (CCB) on reduction of interindividual BP variability was greatest among antihypertensive drugs tested, based on the results of a meta-analysis [7]. These three papers introduced three terms used to describe BP variability, i.e., visit-to-visit BP variability, within-individual BP variability, and interindividual BP variability. The authors concluded that interindividual variability was strongly associated with intraindividual variability, leading to some confusion among physicians. The figure demonstrates the concept of BP variability using the three indexes. Thus, interindividual BP variability is significantly different from visit-to-visit BP variability and within-individual BP variability. Interindividual BP variability refers to the variability of response to BP reduction by an antihypertensive drug. For instance, we previously reported a comparison between the effects of amlodipine and valsartan monotherapy for BP reduction using ambulatory BP monitoring in untreated hypertensive patients [8]. That study revealed that both amlodipine and valsartan monotherapy significantly reduced 24-h baseline BP levels through the end of the treatment period of 8 to 16 weeks, but the effect of BP reduction was higher with amlodipine than with valsartan. Interestingly, although amlodipine reduced not only mean 24-h BP values but also standard deviation of mean 24-h BP values, valsartan increased standard deviation of mean 24-h BP values after the follow-up period. The standard deviation value refers to interindividual BP variability under treatment with an

antihypertensive drug. Therefore, we cannot statistically compare differences in interindividual BP variability for two drugs.

Methodology of evaluation of visit-to-visit BP variability

Most methods used for the evaluation of visit-to-visit BP variability use standard deviation (SD) when calculating mean BP values, because it is easier to calculate and probably more practical than other methods. However, higher SD is usually correlated with higher average values. Therefore, the coefficient of variation (CV), calculated dividing the mean value by the SD, has also been used as a standard method for the evaluation of visit-to-visit BP variability. Average real variability (ARV) of BP is calculated by summation of the values obtained for the absolute difference between a BP value and the immediately preceding BP value. If BP measurements are continuously taken at similar time intervals, the ARV may provide more clinically useful data than SD or CV. However, when BP is measured at different intervals, the clinical significance of ARV may be diluted. Another BP measure, i.e., variability independent of the mean (VIM), has been developed by Rothwell et al. [4].

The calculation of VIM is as follows. First, the formula of non-linear regression is made by using standard deviation (SD) of BP [SD_i] and mean of BP [M_i] of each subject as follow.

$SD_i = \beta_0 \times M_i^{\beta_1}, \beta_0 = \text{constant}, \ \beta_1 = \text{power}$ (parameter of regression)

A log-transformed linear regression is also applied instead of a non-linear regression.

$\ln(SD_i) = \beta_0 + \beta_1 \times \ln(M_i), \ \beta_0 = \text{constant}, \ \beta_1 = \text{regression coefficient}$

Then, change the formula above into the following formula

$$\frac{VIM_i}{(\overline{M})^{\beta_1}} = \frac{SD_i}{(M_i)^{\beta_1}}$$

$$VIM_i = (\overline{M})^{\beta_1} \times \frac{SD_i}{(M_i)^{\beta_1}}$$

$$\overline{M} = \text{mean of } M_i$$

VIM has been considered a better index of BP variability than other indexes, because it has no association with average BP level. However, there is a significant difference between VIM and other indexes of BP variability (SD, CV, and ARV). For example, if a patient has values of 10 mmHg, 6%, and 12 mmHg in SD, CV, and ARV, respectively, the values of these indexes never change. However, when a patient is included in a different database set for analysis, VIM varies depending on each database set, because VIM is calculated based on the non-linear regression analysis of each data set. Therefore, clinicians should separate VIM and other indexes of BP variability depending on the situation. When we evaluate BP variability in a more scientific light, VIM may be more useful than other BP indexes. When we evaluate BP variability in a more practical light, BP indexes other than for VIM may be acceptable.

Visit-to-visit BP variability and cardiovascular outcomes

Since Rothwell's report about the association between visit-to-visit BP variability and cardiovascular outcomes, many papers about this association have been published. Because visit-to-visit BP variability was evaluated using only office measurement on multiple visits, it was not difficult to perform retrospective analysis of the association between visit-to-visit BP variability and cardiovascular outcomes in previous clinical trials of antihypertensive drugs. Although there is no doubt that higher average office BP level is associated with worse cardiovascular prognosis, the association with visit-to-visit BP variability is controversial. In the Combination of OLMesartan and a calcium-channel blocker or a diuretic in Japanese elderly hypertensive patients (COLM) trial, which enrolled 4876 hypertensive patients aged 65–84 years with a history of and/or risk factors for cardiovascular disease who were randomized to receive treatment with olmesartan along with either a CCB or a diuretic, the incidence rate of composite cardiovascular morbidity and mortality increased, along with an increase in the SD of SBP in all age and treatment groups [9]. Muntner et al. [10] reported that visit-to-visit BP variability defined as the SD was associated with incremental risk of fatal coronary heart disease or non-fatal myocardial infarction, all-cause mortality, stroke, and heart failure in 25,814 participants aged 55 years or older with one or more additional risk factor for cardiovascular diseases in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). In a special population, Hata et al. [11] reported that visit-to-visit variability of SBP was positively associated with the risk of major macrovascular events, microvascular events, and death in 8811 patients with type 2 diabetes mellitus who were randomized according to controlled BP lowering and blood glucose control in the Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified Release Controlled Evaluation (ADVANCE) trial. In the African American Study of Kidney Disease (AASK) trial, a prospective observational study of 908 participants with hypertensive nephrosclerosis and a glomerular filtration rate of 20–65 ml/min per 1.73 m^2, visit-to-visit variability of SBP was

associated with increased overall mortality as well as cardiovascular mortality [12]. On the other hand, results as to the relation between visit-to-visit BP variability and cardiovascular outcome were inconsistent. In 1521 mildly to moderately hypertensive patients in the European Lacidipine Study on Atherosclerosis (ELSA), visit-to-visit BP variability assessed by SD and CV during treatment was not associated with carotid intima-media thickness and cardiovascular outcomes [13]. Another study, the double-blind Systolic Hypertension in the Elderly (Syst-Eur) trial, which compared the CCB nitrendipine with placebo for the reduction of stroke and cardiovascular complications, demonstrated that visit-to-visit variability of SBP assessed by SD, CV, ARV, and VIM was not associated with a composite cardiovascular end-point (death, stroke, myocardial infarction, and congestive heart failure) [14]. The recent Systolic Blood Pressure Intervention Trial (SPRINT), which randomized a standard BP control group (<140 mmHg in SBP) and a strict BP control group (<120 mmHg in SBP), showed that strict BP control significantly reduced composite cardiovascular outcomes, compared with those in the standard BP control group [5]. In that study, visit-to-visit variability of SBP assessed by CV was not significantly associated with the primary composite end-point of fatal and non-fatal cardiovascular events, or with heart failure or stroke hospitalizations [15]. The results of those studies are summarized in the Table 1. The reason for the inconsistent results among studies showing the association between visit-to-visit BP variability and cardiovascular outcomes is not clear. Although one of the reasons for the absence of an association in patients at low or intermediate cardiovascular risk has been debated [16], two studies without evidence of an association between visit-to-visit BP variability and cardiovascular outcomes included older patients and high-risk populations in the Syst-Eur and SPRINT trials, respectively [13, 14]. Compared with studies showing a positive association between visit-to-visit BP variability and cardiovascular outcomes, the ELSA and Syst-Eur trials showed lower values for visit-to-visit BP variability. In addition, the number of measurements used for visit-to-visit BP variability was smaller: three and four times in the Syst-Eur and ELSA trials, respectively [13, 14]. The SPRINT study also used a lower number of measurements for visit-to-visit BP variability (four times). Moreover, the average SBP level in the SPRINT study was strictly controlled compare with that in other studies. With regard to the clinical impact of visit-to-visit BP variability in a population with lower risk and BP levels in the Coronary Artery Risk Development in Young Adults (CARDIA) study, visit-to-visit BP variability during young adulthood (age and SBP at baseline: 25.6 years and 109.9 mmHg, age and SBP at follow-up: 50.6 years and 116.6 mmHg) assessed using SD and ARV was associated with lower normal tissue volumes in the hippocampus, gray matter, and total brain assessed by magnetic resonance imaging [17]. Thus, even in a younger population with low BP levels, increased visit-to-visit BP variability is a pathophysiological condition. In the SPRINT study, strict BP control reduced cardiovascular events [5]. Strict BP control for hypertensive patients may have changed a high-risk population into a low-risk population, thereby offsetting the impact of visit-to-visit BP variability on cardiovascular events, and resulting in the absence of an association between visit-to-visit BP variability and CV outcomes in the SPRINT study.

Visit-to-visit BP variability and other BP variability

In the diagnosis and treatment of hypertension, physicians should use not only office BP but also home BP measurement, as recommended in international guidelines. Increased day-by-day BP variability assessed using home BP measurement has been associated with cardiovascular events in the general population. Recently, the Japan Morning Surge-Home Blood Pressure (J-HOP) study reported that increased day-by-day home BP variability calculated using average morning and evening home BP for 14 days was associated with cardiovascular events in a population of 4310 subjects with one or more cardiovascular risk factors, independent of surrogate organ damage (urinary albumin creatinine ratio and plasma brain natriuretic peptide) [18]. Thus, day-by-day home BP variability is not simply an epiphenomenon similar to organ damage, but instead a risk factor for cardiovascular events. Although a previous review of BP variability by Parati et al. [19] classified day-by-day home BP variability and visit-to-visit BP variability as mid-term BP variability and long-term BP variability according to the time range of measurements, these two variabilities may be similar. For example, if a patient only measures home BP on the same day as an office visit and the home and office BP measurements coincide, variability would be similar for both office and home BP. The greatest difference between office and home BP may not be whether the reading is measured in the office or home, but rather whether it is self-measured or measured by a professional. In the Dallas Heart Study (DHS), Tientcheu et al. [20] reported that sustained hypertension (high office BP ≥ 140/90 mmHg and high home BP ≥ 135/85 mmHg) had the worst cardiovascular prognosis and that normotension (low office BP < 140/90 mmHg and low home BP < 135/85 mmHg) had the best prognosis; moreover, both white-coat hypertension (high office BP ≥ 140/90 mmHg and normal home BP < 135/85 mmHg) and masked hypertension (normal office BP < 140/90 mmHg and high home BP ≥135/85 mmHg) had similar intermediate risk for cardiovascular prognosis. This result was

Table 1 Recent evidence for the association between visit-to-visit BP variability and cardiovascular events

Paper, year	Study	Population	Mean age	Average (median) SBP	Number of patients	Frequency of measurement	Value of SBP variability, average (median)		Outcome
							SD	CV	
Mancia et al., 2012 [13]	ELSA	Hypertensive patients	56	163 mmHg (baseline)	1521	More than 7 occasions	8.0	5.7	VVV was not associated with progression of intima-media thickness or cardiovascular outcomes during a 4-year follow-up
Hata et al., 2013 [11]	ADVANCE	Diabetes patients	66	137 mmHg	8811	6 occasions	11	7.9	VVV was positively associated with the risk of major macrovascular events, microvascular events, and death
McMullan et al., 2013 [12]	AASK	CKD patients	55	136 mmHg	908	5 occasions	13.6	—	VVV was associated with increased overall mortality as well as cardiovascular mortality
Rakugi et al., 2015 [9]	COLM	Hypertensive patients	70	136 mmHg	2778	8 occasions	9.8	—	With patients divided into quartiles according to the SD of SBP, the incidence rate of the primary end-point (composite of cardiovascular morbidity and mortality) increased along with an increase in the SD of SBP
Muntner et al., 2015 [10]	ALLHAT	Hypertensive patients	66	136 mmHg	25,814	7 occasions	8.7 to 11.0	—	VVV was associated with fatal coronary heart disease or non-fatal myocardial infarction, all-cause mortality, stroke, and heart failure
Chang et al., 2017 [15]	SPRINT	Hypertensive patients	68	128 mmHg	7879	4 occasions	—	7.8	VVV was not significantly associated with the primary composite end-point of fatal and non-fatal cardiovascular events or with heart failure or stroke hospitalization
Hara et al., 2014 [14]	SYST-EUR	Hypertensive patients	70	174 mmHg (baseline)	4695	3 occasions	6.4	3.7	VVV was not associated with the main end-point (death, stroke, myocardial infarction, and congestive heart failure)

BP blood pressure, *SBP* systolic blood pressure, *VVV* visit-to-visit BP variability, *SD* standard deviation, *CV* coefficient of variation, *CKD* chronic kidney disease

inconsistent with previous reports that sustained hypertension and masked hypertension had similar risk for cardiovascular outcomes and that white-coat hypertension and normotension had similar low risk [21]. In the DHS, home BP was obtained by professionals, rather than by self-measurement. As a result, the DHS demonstrated that high BP measured by professionals in both the office and home had the highest risk and that high BP measured in either the office or home by professionals had an intermediate risk; moreover, normal BP measured in both the office and home by professionals had the lowest risk for cardiovascular outcomes. Accordingly, visit-to-visit BP variability evaluated in SPRINT may be comparable to day-by-day home BP variability. Some measurements in SPRINT used a fully automated, oscillometric method to record multiple BP readings with the patient resting quietly, and without health professionals or research staff present. SPRINT failed to show a significant correlation between BP variability and cardiovascular outcomes, which was inconsistent with the results using day-by-day home BP variability; however, BP measurements based on visit-to-visit BP variability were not significantly different from those using home BP measurement.

Conclusion

Increased visit-to-visit BP variability is a common phenomenon that physicians often encounter, and can represent a pathophysiological condition. Visit-to-visit BP variability evaluated using automated office measurement might reflect the characteristics of BP variability observed during visits, because BP measurement in the office is likely to be performed more correctly and may be less affected by environmental effects such as room temperature, in contrast with out-of-office BP measurements. However, its feasibility in clinical practice is challenging. In addition, unsolved problems in the evaluation of visit-to-visit BP variability include more than those mentioned above. For example, how many times should we measure office BP, or how long an interval is acceptable between office visits to enable prediction of cardiovascular outcomes? Although many studies on visit-to-visit BP variability have been reported, further research is needed.

Compliance with ethical standards

Conflict of interest Dr. Hoshide reports receiving speaker fee from Takeda Pharmaceutical Company.

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