Visit-to-Visit Blood Pressure Variability, Silent Cerebral Injury, and Risk of Stroke

Michiaki Nagai[1] and Kazuomi Kario[1]

Apart from the well-known role of hypertension in cerebrovascular disease, visit-to-visit blood pressure (BP) variability is emerging as an independent risk factor for stroke. Although the underlying mechanism is not fully understood, artery remodeling is thought to be closely involved in the relationship between visit-to-visit BP variability and stroke. This review article summarizes the recent literature on these topics. Silent cerebral injury is considered to serve as a common pathophysiology in the relationship of visit-to-visit BP variability with cognitive impairment and stroke. Here we review visit-to-visit BP variability, some comparisons of the effects of antihypertensive agents on visit-to-visit BP variability, and an issue regarding the impact of these agents on stroke.

Keywords: blood pressure; blood pressure variability; stroke; silent cerebral injury; cognitive impairment.

doi:10.1093/ajh/hpt167

Vascular disease of the brain is a major cause of death and disability.[1] Hypertension is the most potent risk factor for cardiovascular disease, including stroke and coronary artery disease.

Blood pressure (BP) fluctuates around average values over both the short and long terms. Its fluctuation is suggested to be caused by a complex interaction between external environmental stimuli and the response of cardiovascular control mechanisms. Diurnal and minute-to-minute BP variability through 24-hour ambulatory BP monitoring (ABPM) have both been recognized as important cardiovascular risk markers.[2,3] Aside from short-term BP variability, a substantial variation in BP exists when a subject is observed over months with repeated clinical visits.

Up to now, visit-to-visit BP variability had been mostly dismissed as "background noise" that dilutes the prognostic effects of average BP measurement or as a so-called "regression dilution bias," which must be neutralized by appropriate statistical techniques to appreciate the "true" associations with the usual BP measurement in patients with disease.[4,5] The demonstration that visit-to-visit BP variability carries independent prognostic information for stroke has the potential of modifying our current understanding of the importance of BP.[6] In addition, visit-to-visit BP variability has been shown to increase with the number of visits[7] and to have high reproducibility.[8]

It is thus apparent that the relationship between visit-to-visit BP variability and stroke could have clinical relevance. The goal of this review is to thoroughly elucidate the association of visit-to-visit BP variability with stroke. To set the stage, we summarize current insights into this relationship, and we propose an updated explanation of the pathophysiology of the link between visit-to-visit BP variability and stroke.

References for this review were identified through searches of PubMed as of July 2013, using the search terms "visit-to-visit blood pressure variability," "blood pressure variability," "meta-analysis," "antihypertensive," and/or "stroke." We reviewed the articles identified from these searches and relevant references cited in those articles. Articles were also identified through searches of our own files and literature databases. The final reference list was generated on the basis of originality and relevance to the topic of this review.

VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY AND STROKE

The clinical significance of ambulatory BP variability has been demonstrated.[9] Increased nighttime systolic BP variability was shown to be an independent risk factor for stroke in subjects with isolated systolic hypertension.[10] A more recent study failed to show a positive relationship between ambulatory BP variability and cardiovascular events.[11]

Hata *et al.*[12] analyzed the relationship between visit-to-visit BP variability and cerebral infarction risk in an elderly population being treated with antihypertensive therapy. Sex- and age-matched control patients were registered for each case patient. The coefficients of variation (CV) in systolic BP (SBP) and diastolic BP (DBP) were each significantly higher in the cerebral infarction group than in the control group. Higher visit-to-visit variability in SBP and DBP were associated with a higher risk of cerebral infarction after adjustment for the average BP level and other confounding factors.

Correspondence: Kazuomi Kario (kkario@jichi.ac.jp).

Initially submitted May 7, 2013; date of first revision August 11, 2013; accepted for publication August 12, 2013; online publication September 30, 2013.

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

In a large cohort of patients with a history of transient ischemic attacks (TIAs; the UK-TIA Aspirin Trials) and in a broad population of patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA), Rothwell *et al.*[6] reported that visit-to-visit SBP variability and maximum SBP were strong predictors of stroke independently of average SBP.

In the Third National Health And Nutrition Examination Survey (NHANES III) trial,[13] 3 consecutive BP readings were taken during 3 separate study visits from 1988 to 1994 from 956 US adults aged ≥20 years. Mortality was assessed through a median follow-up period of 14 years. After multivariable adjustment, it was observed that the factors of older age, female sex, history of myocardial infarction, higher mean SBP and pulse pressure, and use of angiotensin-converting enzyme inhibitors were associated with higher SD in SBP. The SD and CV values in SBP were associated with significantly high hazard ratios for all-cause mortality after multivariable adjustment.

In the Women's Health Initiative, Shimbo *et al.*[14] examined the association between visit-to-visit BP variability and stroke in 58,228 postmenopausal women. Visit-to-visit BP variability was defined as the SD across visits. Over a median follow-up of 5.4 years, 997 strokes occurred. In an adjusted model including average SBP over time, the hazard ratios of stroke for the higher quartiles of SD SBP compared with the lowest quartile (referent) were 1.39 (95% confidential interval (CI) = 1.03–1.89) for the second quartile, 1.52 (95% CI = 1.13–2.03) for the third quartile, and 1.72 (95% CI = 1.28–2.32) for the fourth quartile. The associations did not differ by stroke type (ischemic vs. hemorrhagic). In postmenopausal women, greater visit-to-visit SBP variability was associated with an increased risk of stroke.

On the other hand, in a family-based random population sample representative of the general population, Schutte *et al.*[15] assessed the prognostic significance of visit-to-visit BP variability on health outcomes in 2,944 middle-aged subjects. The within-subject overall of 10 consecutive BP readings, the visit-to-visit BP variability, and the difference between maximum and minimum BP (delta in BP) were measured. Over a median follow-up of 12 years, 401 deaths occurred and 311 participants experienced a fatal or nonfatal cardiovascular event. In multivariable-adjusted analyses, visit-to-visit BP variability as well as delta in BP did not predict the total or cardiovascular mortality or the composite of any fatal plus nonfatal cardiovascular endpoint. In the European Lacidipine Study on Atherosclerosis (ELSA),[16] a randomized, double-blind, 4-year trial, visit-to-visit BP variability was not significantly associated with cardiovascular outcomes in treated mildly to moderately hypertensive patients.

Visit-to-visit BP variability was shown to be associated with cardiovascular disease including stroke, although the degree of association between visit-to-visit BP variability and stroke incidence might differ among study populations. In the UK-TIA, ASCOT, and Medical Research Council (MRC) elderly trials,[6] the patients' ages were higher and they were at higher risk of developing cardiovascular disease compared with the patients in other studies.[15,16] Thus it was speculated that the clinical importance of visit-to-visit BP variability might depend on the level of total cardiovascular risk.

Concerning DBP, the clinical implications of the BP level and variability for stroke might be slightly different from those of SBP. In the NHANES III trial, no association was revealed between visit-to-visit variability in DBP and all-cause mortality.[13] This is consistent with previous research. For example, in the Honolulu Heart Program, variance of DBP across 4 visits was not associated with the subsequent incidence of coronary heart disease.[17] Additionally, in the UK-TIA study, the visit-to-visit variability in DBP was not associated with stroke, and an association was present only in the highest deciles in the ASCOT-BPLA.[6] In light of these findings, the visit-to-visit variability in SBP might be a better indicator for stroke than that in DBP.

Rothwell *et al.* found that visit-to-visit variability in SBP was more predictive of ischemic than hemorrhagic strokes in treated hypertensive participants enrolled in the ASCOT-BPLA.[6] In contrast, Shimbo *et al.*[14] found that the relationship between visit-to-visit variability in SBP and stroke did not differ by subtype such as ischemic and hemorrhagic stroke. The reasons for these divergent results are unclear. The different populations examined and the substantially smaller percentage of hemorrhagic vs. ischemic strokes in either sample may be possible explanatory factors.[14]

MEASUREMENT OF VISIT-TO-VISIT BP VARIABILITY

Table 1 summarizes the measurements of visit-to-visit BP variability obtained in 8 relevant studies. In most of the studies, SD and CV were used as measures in visit-to-visit BP variability. Delta and maximum BP were measured in several studies. CV was estimated from the equation: SD/ average BP value over 12 visits × 100 [%]. Delta BP was estimated from the equation: maximum BP – minimum BP level. However, the number of BP measurements and the BP follow-up period were not consistent among the studies. Until now, there has been no standardization for the measurement of visit-to-visit BP variability. Future studies are needed to determine the number of visits required to obtain reproducible and valid estimates of visit-to-visit BP variability and the optimal interval between visits.[14]

VISIT-TO-VISIT VS. AMBULATORY BP VARIABILITY

Ambulatory BP variability is influenced by various daily activities, such as diet, exercise, rest, change in temperature, sleep, and mental stress, and it reflects the dynamic changes of BP during daily life.[18] Because clinic BP is measured under relatively controlled conditions, the mechanism underlying the fluctuation of these values is likely to be completely different from that underlying the changes in ambulatory BP. Variations in BP at clinic visits reflect many factors, such as the subject's emotional state, posture during BP measurement, respiratory cycle, diet, salt intake, alcohol ingestion, physical activity, and the amount of rest the subject had gotten, as well as the time of day and room temperature during the measurement and the potential presence of other nonstandardized conditions for BP measurements.[19,20]

Numerous BP readings obtained from a single 24-hour ABPM allow the calculation of ambulatory BP variability in daily life, but the generalizability of the results beyond the single

Table 1. Visit-to-visit blood pressure variability measurement

Study	Subjects and age	Number of BP measurements	BP follow- up period	BP measurement at each visit	Visit-to-visit blood pressure variability measurement
Hata *et al.*[12]	138 patients with cerebral infarction and 350 controls; aged ≥ 60 y	12 times	1 mo	2 times, average of the 2 readings	Coefficient of variation (CV)/ delta in blood pressure (BP)
UK-TIA: Rothwell *et al.*[6]	2,006 patients with a recent transient ischemic attack; mean age of 60.3 y	Median 10 times	4 mo	Single blood pressure measurement	SD/CV/ Variation independent of mean C (SD/ mean$^{1.67}$)/ Maximum BP
ASCOT-BPLA: Rothwell *et al.*[6]	18,530 patients with hypertension with >3 other risks; aged 40–79 y	Median 10 times	6 mo	3 times, average of the 2nd and 3rd readings	SD/CV/ Variation independent of mean BP (SD/ mean$^{1.78}$)/ Maximum BP
3SCO: Nagai *et al.*[36]	201 high-risk elderly patients; mean aged of 79.9 y	12 times	1 mo	3 times, average of the 2nd and 3rd readings	SD/CV/ Delta in BP/ Maximum BP
NHANES III: Muntner *et al.*[13]	956 adults; aged ≥ 20 y	3 times from 1988 to 1994	—	3 times, average of the 2nd and 3rd readings	SD/CV
Eguchi *et al.*[18]	457 hypertensives, mean aged of 67 y	Mean 36.5 times	1 mo	3 times, average of the 2nd and 3rd readings	SD
ELSA: Mancia *et al.*[16]	1,521 mild to moderate hypertensives; aged 45–75 y	>7 times	6 mo	3 times, average of the 3 readings	SD/CV
WHI: Shimbo *et al.*[14]	58,228 postmenopausal women, aged 50–79 y	Mean 7.9 times	1 y	2 times, average of the 2 readings	SD and that about the participant's regression line with BP regressed across visits

day being measured is unclear, and ABPM requires special equipment.[18] Visit-to-visit BP variability has an advantage in that it provides data without any special device, but it requires time to collect sufficient readings to calculate BP variability.[18]

The ASCOT-BPLA ABPM study demonstrated that daytime SBP variability on ABPM correlated with visit-to-visit SBP variability, indicating a contribution from fluctuations in the underlying BP.[6] That study also showed that variability in BP on ABPM was a weaker predictor of vascular events than was visit-to-visit variability, suggesting that average variability from minute-to-minute could not capture elements of variability that are associated with the risk of stroke.[6] In addition, Muntner *et al.*[21] reported that the visit-to-visit BP variability and BP variability from ABPM are weakly correlated and not interchangeable in untreated normotensive participants.

VISIT-TO-VISIT BP VARIABILITY, SILENT CEREBRAL INJURY, AND COGNITIVE FUNCTION

Magnetic resonance imaging has revealed that silent cerebral injury such as white matter lesions are common in the elderly.[22] White matter hyperintensity (WMH) has been shown to be associated with stroke.[23] Hypertension is a well-known risk for WMH.[24,25]

In the Washington Heights–Inwood Columbia Aging Project,[26] a total of 686 nondemented elderly who had BP measurements during 3 study visits at 24-month intervals and underwent structural magnetic resonance imaging were studied. The WMH volume increased across the 4 groups in a linear manner, with the lowest WMH volume in the lowest mean/lowest SD group and the highest WMH volume in the highest mean/highest SD group. Compared with individuals with low BP and low SD, the risk of WMH increased with high BP and high BP SD.[26] However, it was not clear whether the relationship between visit-to-visit BP variability and WMH was independent of the average BP level.

In contrast, in the Honolulu–Asia Aging Study,[27] midlife BP measurements at 3 clinical visits in the period 1965–1974 and brain magnetic resonance imaging in the period 1994–1996 were performed on a subset of 575 Japanese American men (average age = 82 years). WMH and brain atrophy were observed and quantified. The study's logistic regression analysis controlling for age, apolipoprotein E4 status, dementia diagnosis, and history of stroke revealed that there were significant 2-fold increased risks for WMH and brain atrophy among the subjects, with the highest quintile of visit-to-visit SBP variability compared with the lowest quintile, independent of the average SBP level.[27]

In the CASISP (Cilostazol vs. Aspirin for Secondary Ischemic Stroke Prevention) study, Liu *et al.*[28] investigated the relationship between visit-to-visit BP variability and the progression of cerebral small vessel diseases. Of 720 patients recruited, 500 and 584 had follow-up results for cerebral microbleeds (CMBs) and WMH, and 13.2% and 48.1% of the patients showed CMBs and WMH progression over a median of 14 months, respectively. Patients with CMBs had higher average, maximum values, SD, CV, and successive variation in BP. Visit-to-visit SBP variability was an

independent risk factor for deep and infratentorial CMBs progression, whereas visit-to-visit DBP variability was independently associated with CMB development in deep regions. However, visit-to-visit SBP variability was not significantly associated with WMH progression.[28]

Although hypertension is a risk factor for vascular dementia,[29,30] trials of BP-lowering drugs have not shown a consistent reduction in the risk of dementia.[31–33] Most of the studies have been focused on absolute BP levels in relation to cognitive dysfunction or dementia. However, in the Kungsholmen Project, a greater decline in SBP occurring 3–6 years before diagnosis was associated with an increased risk of dementia in the elderly.[34] In the Honolulu Heart Program/Honolulu–Asia Aging Study, which had a 32-year follow-up period, the subjects who developed dementia had a greater SBP increase that was followed by a greater SBP decrease compared with those who did not.[30]

In the HiroShima–Shobara–Soryo Cohort (3SCO) study,[35] we investigated the relationship between visit-to-visit BP variations and cognitive function among 201 elderly patients at high risk of cardiovascular disease (aged 79.9 ± 6.4 years; 75% female; 71% antihypertensive medication use). Exaggerated long-term visit-to-visit BP fluctuations were significantly associated with lower Mini-Mental State Examination scores (Figure 1), higher Geriatric Deterioration Scale scores, and cognitive impairment independently of average BP. Specifically, the CV SBP and delta SBP values were significantly positively associated with cognitive impairment in multiple regression models.

MECHANISMS UNDERLYING THE INCREASED VISIT-TO-VISIT BP VARIABILITY IN RELATION TO ARTERY REMODELING

Although higher visit-to-visit BP variability is associated with increased cardiovascular disease in the high-risk population, the physiological basis of visit-to-visit BP variability for stroke is incompletely understood.

We recently found that visit-to-visit BP variability was a significant indicator for carotid artery atherosclerosis and stiffness in the elderly at high risk of cardiovascular disease (Figure 2).[36] Okada *et al.*[37] measured BP once a month during a 1-year period in 422 consecutive patients with type 2 diabetes. The CV SBP positively correlated with pulse wave velocity, whereas CV SBP inversely correlated with ankle brachial index. Multiple regression analysis demonstrated

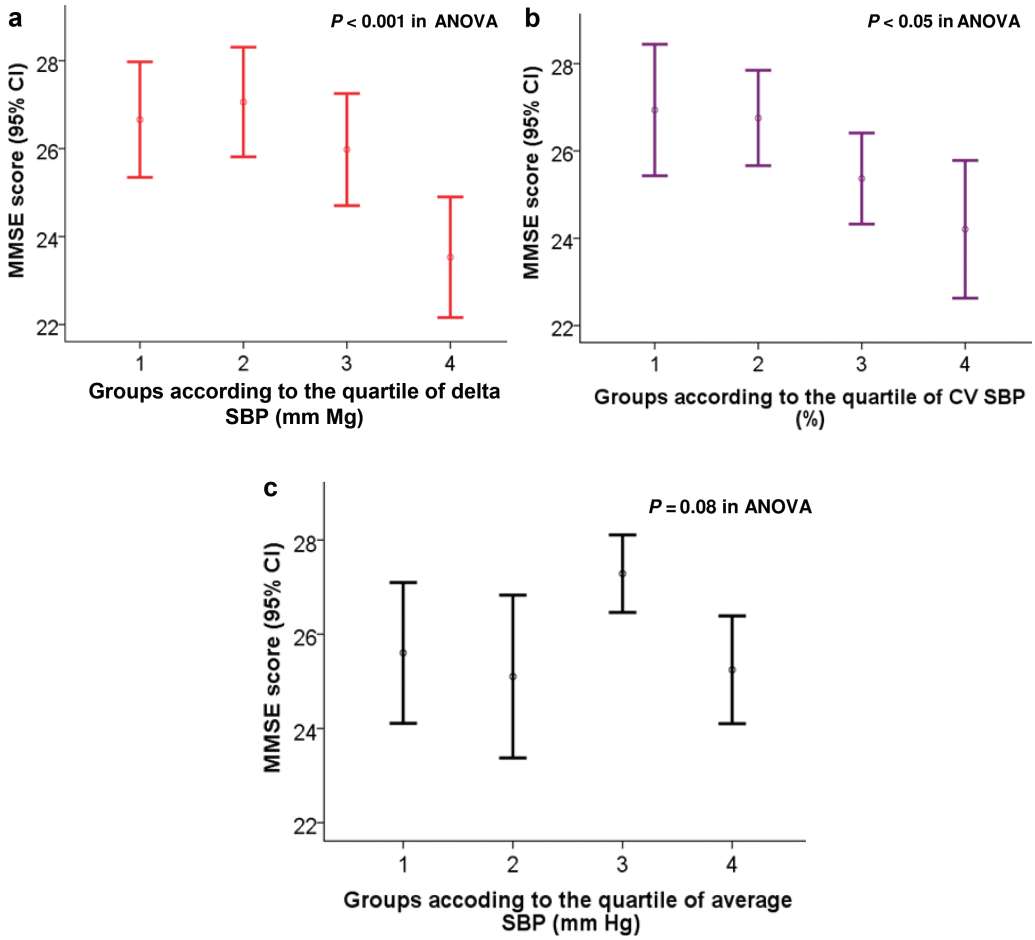

Figure 1. Visit-to-visit blood pressure variations and Mini-Mental State Examination (MMSE) scores. The mean MMSE scores are presented according to the quartiles of delta systolic blood pressure (SBP) (**a**), coefficient of variation (CV) SBP (**b**), and average SBP (**c**). An analysis of variance (ANOVA) was used to determine the differences among the 4 groups. Abbreviation: CI, confidence interval. Reconstructed from Nagai *et al.*[35]

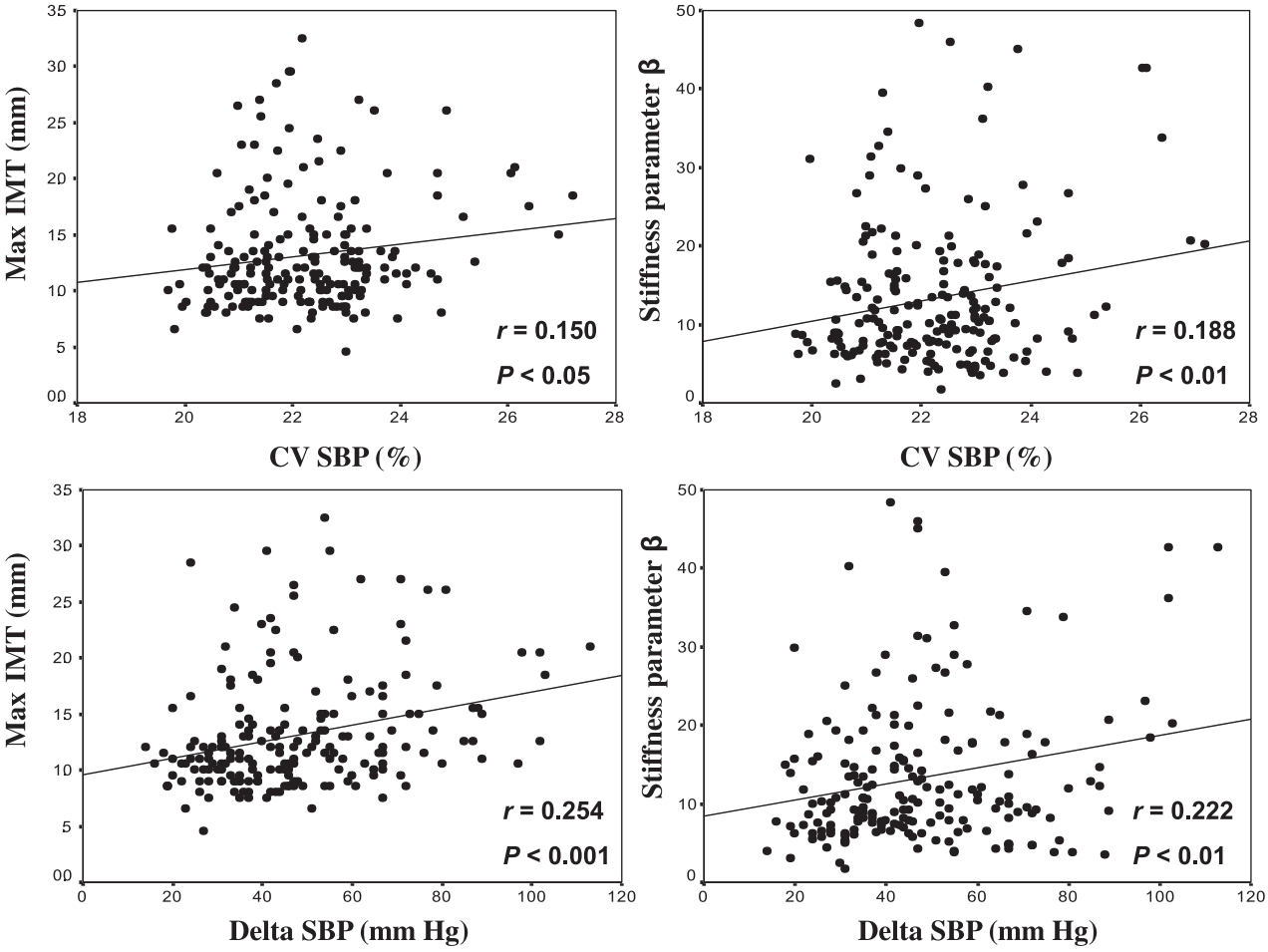

Figure 2. Scatterplots of coefficient of variation (CV) and delta systolic blood pressure (BP) with common carotid artery measures. The CV SBP and delta SBP were positively significantly correlated with maximum intima-media thickness (Max IMT) and stiffness parameter β. From Nagai *et al.*[36]

that the CV SBP was independently correlated with pulse wave velocity and ankle brachial index.

Simbo *et al.*[38] examined the associations of aortic distensibility and artery elasticity indices with visit-to-visit BP variability in 2,640 and 4,560 participants, respectively, from the Multi-Ethnic Study of Atherosclerosis. The SD SBP was inversely associated with aortic distensibility after adjustment for demographics, cardiovascular risk factors, average SBP, and antihypertensive medication use. These results suggest that increased visit-to-visit BP variability is associated with atherosclerosis and increased arterial stiffness.

Although the causes of abnormal BP variability are still debated, autonomic factors, including sympathetic nervous system overactivity and blunted arterial baroreflex function, are likely to be involved.[39] It has also been suggested that hypothalamo-pituitary-adrenal axis dysregulation is associated with sympathovagal imbalance due to factors such as internal emotional stress, external environmental stress, and sleep deprivation.[40–42] In fact, insomnia and long sleep duration were associated with exaggerated visit-to-visit BP variability.[43] Figure 3 illustrates the pathophysiology of visit-to-visit BP variability for silent cerebral injury and stroke.

One major determinant of BP variability depends on the sensitivity of baroreceptor function.[44] Vascular structural changes may reduce baroreceptor sensitivity in hypertension. Reduced large arterial compliance appears to contribute to the depressed baroreceptor sensitivity in hypertensive individuals.[45] Arterial stiffness might be a crucial factor underlying the relationship between BP variability and cerebral damage by reduced dampening of BP changes in response to changes in stroke volume and by contributing to baroreflex impairment. These flows may be associated with silent cerebral injury such as WMH and CMB and with the incidence of stroke.

MANAGEMENT OF BLOOD PRESSURE VARIABILITY FOR PREVENTION OF STROKE

Antihypertensive treatment and stroke prevention

In the UK's National Institute of Health and Clinical Excellence guidelines,[46] the treatment algorithm has been changed, with a greater emphasis on using calcium channel blockers (CCBs) for those aged >55 years and for patients of African or Caribbean descent.

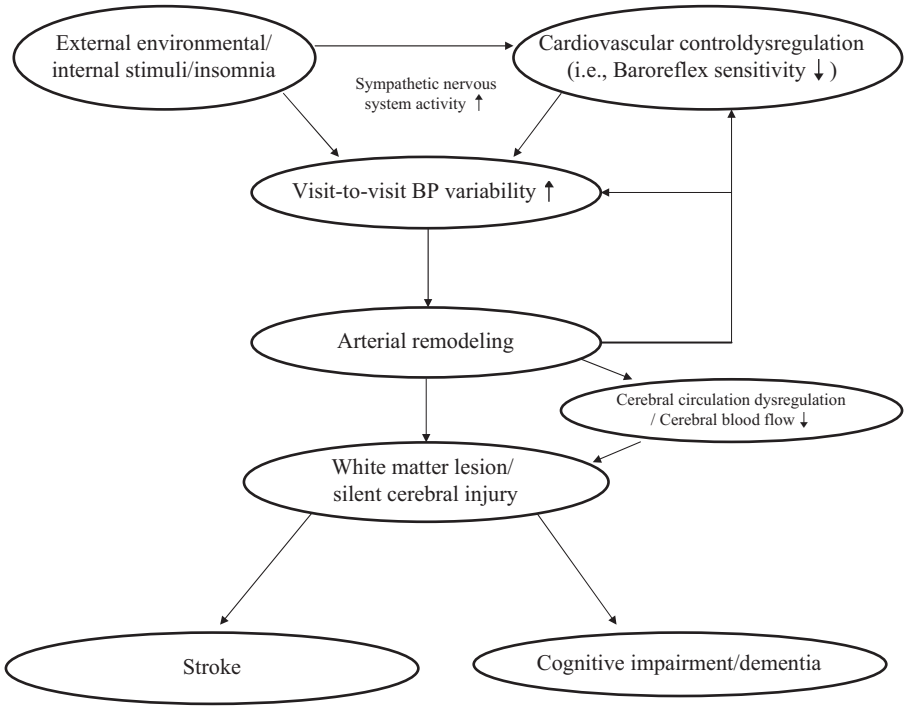

Figure 3. The pathophysiology of visit-to-visit blood pressure (BP) variability for silent cerebral injury and stroke. Visit-to-visit BP variability is associated with artery remodeling. This relationship is suggested as a risk factor for silent cerebral injury, leading to both stroke and cognitive impairment.

Costanzo *et al.*[47] assessed the effect of CCB treatment on stroke in a meta-analysis of 27 randomized controlled trials with 175,634 patients. They reported that CCBs decreased the risk of fatal or nonfatal stroke (odds ratio (OR) = 0.86; 95% CI = 0.82–0.90) and also did so compared with angiotensin-converting enzyme inhibitors (OR = 0.87; 95% CI = 0.78–0.97).

In a quantitative overview of 12 trials with 94,338 patients, Wang *et al.*[48] showed that amlodipine provided more protection against stroke than other antihypertensive drugs, including angiotensis receptor blockers and placebo. The meta-regression analysis correlating ORs with BP differences showed a negative relationship, which reached statistical significance for stroke in the trials involving an amlodipine group. Similarly, Takagi *et al.*[49] conducted reanalyses to determine the relative contribution of BP-dependent and -independent mechanisms to the reduction in the risk of stroke produced by amlodipine. The magnitude of the risk reduction achieved for stroke was positively associated with the size of BP reduction. In the meta-regression analysis, for stroke, amlodipine conferred additional protection beyond that conferred by BP reduction alone. At zero BP reduction, the estimated relative risk reduction for stroke was 10.3% (95% CI = 2.9–17.2). In particular, there was clear evidence of protection against stroke with amlodipine even in the absence of any reduction in BP, in what is called the "beyond blood pressure–lowering effect."[49]

Antihypertensive treatment and reduction in blood pressure variability

In the ASCOT-BPLA,[50] the group SBP SD was lower in the amlodipine group than in the atenolol group at all follow-up visits. The ABPM variability in SBP was also lower in the amlodipine group than in the atenolol group. The lower risk of stroke in the amlodipine group was partly attenuated by adjusting for average SBP during the follow-up, but it was abolished by also adjusting for within-individual SD in SBP. In the ABPM substudy, reduced variability in daytime SBP in the amlodipine group partly accounted for the reduced risk of vascular events, but reduced visit-to-visit variability in SBP had a greater effect. In the MRC trial,[50] the group SD SBP and within-individual visit-to-visit variability in SBP were increased in the atenolol group compared with both the placebo group and the diuretic group during the initial follow-up. Subsequent temporal trends in variability in BP during follow-up in the atenolol group correlated with trends in stroke risk.

In a systematic review, Webb *et al.*[51] assessed the effect of treatment on interindividual variance in BP, a surrogate for within-individual visit-to-visit BP variability, and they found that interindividual variance in BP was related to effects on clinical outcomes in a random-effects meta-analysis. Mean SD SBP at follow-up was reported in 389 of 1,372 eligible trials. Compared with other drugs, the interindividual variation in SBP was reduced by CCBs and nonloop diuretics and increased by angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers. Compared with placebo only, interindividual variation in SBP was reduced the most by CCBs. Across all trials, the effects of treatment on interindividual variation in SBP and on average SBP accounted for the effects on stroke risk. In light of these points, CCBs are the most effective drug class for reducing BP variability.

However, there was no significant association between interindividual variation in SBP and the risk of myocardial

infarction, heart failure, or cardiovascular mortality in this meta-analysis.[51] The smaller benefit from amlodipine for coronary events than for stroke might be because of the opposite effects on heart rate, although neither mean heart rate nor its variability had prognostic value in the ASCOT-BPLA.[6] Alternatively, mean SBP is a stronger risk factor for stroke than for coronary heart disease. This might also be the case for visit-to-visit BP variability.

Although it has been hypothesized that high visit-to-visit SBP variability may be the result of poor antihypertensive medication adherence, only a small proportion of visit-to-visit SBP variability was explained by low antihypertensive medication adherence.[52]

CCB use might be effective for preventing stroke, and this might be due to the reduction in BP variability as well as the absolute BP level.

CONCLUSION

The recent literature confirms that visit-to-visit BP variability is associated with stroke. In addition, arterial remodeling has been found to be closely related to the relationship between visit-to-visit BP variability and stroke. Silent cerebral injury is thought to serve as a common pathophysiology in the relationship of visit-to-visit BP variability with cognitive impairment and stroke. Strict BP control based on CCB use may be useful to prevent the progression of cognitive impairment and stroke in light of the reduction in visit-to-visit BP variability.

ACKNOWLEDGMENT

This work was supported by a Research Grant for Geriatrics and Gerontology (22–5) from the Ministry of Health, Labor, and Welfare, Japan.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. American Heart Association. Heart Disease and Stroke Statistics: 2005 Update. Dallas, TX: American Heart Association; 2005.
2. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008; 51:55–61.
3. Schillaci G, Parati G. Determinants of blood pressure variability in youth: at the roots of hypertension. *J Hypertens* 2010; 28:660–664.
4. MacMahon S, Peto R, Cutler J, Colins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335:765–774.
5. Schillaci G, Pucci G. The importance of instability and visit-to-visit variability of blood pressure. *Expert Rev Cardiovasc Ther* 2010; 8:1095–1097.
6. 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; 375:938–948.
7. Levitan EB, Kaciroti N, Oparil S, Julius S, Muntner P. Blood pressure measurement device, number and timing of visits, and intra-individual visit-to-visit variability of blood pressure. *J Clin Hypertens* 2012; 14:744–750.
8. Muntner P, Joyce C, Levitan EB, Holt E, Shimbo D, Webber LS, Oparil S, Re R, Krousel-Wood M. Reproducibility of visit-to-visit variability of blood pressure measures as part of routine clinical care. *J Hypertens* 2011; 29:2332–2338.
9. Tatasciore A, Renda G, Zimarino M, Soccio M, Bilo G, Parati G, Schillaci G, De Caterina R. Awake systolic blood pressure variability correlates with target-organ damage in hypertensive subjects. *Hypertension* 2007; 50:325–332.
10. 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; Syst-Eur investigators. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J Hypertens* 2003; 21:2251–2257.
11. Khattar RS, Swales JD, Banfield A, Dore C, Senior R, Lahiri A. Prediction of coronary and cerebrovascular morbidity and mortality by direct continuous ambulatory blood pressure monitoring in essential hypertension. *Circulation* 1999; 100:1071–1076.
12. Hata Y, Kimura Y, Muratani H, Fukiyama K, Kawano Y, Ashida T, Yokouchi M, Imai Y, Ozawa T, Fujii J, Omae T. Office blood pressure variability as a predictor of brain infarction in elderly hypertensive patients. *Hypertens Res* 2000; 23:553–560.
13. Muntner P, Shimbo D, Tonelli M, Reynolds K, Arnett DK, Oparil S. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: findings from NHANES III, 1988 to 1994. *Hypertension* 2011; 57:160–166.
14. Shimbo D, Newman JD, Aragaki AK, LaMonte MJ, Bavry AA, Allison M, Manson JE, Wassertheil-Smoller S. Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: data from the Women's Health Initiative. *Hypertension* 2012; 60:625–630.
15. Schutte R, Thijs L, Liu YP, Asayama K, Jin Y, Odili A, Gu YM, Kuznetsova T, Jacobs L, Staessen JA. Within-subject blood pressure level-not variability-predicts fatal and nonfatal outcome in a general population. *Hypertension* 2012; 60:1136–1147.
16. Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability, carotid atherosclerosis and cardiovascular events in the European Lacidipine Study on Atherosclerosis. *Circulation* 2012; 126:569–578.
17. Grove JS, Reed DM, Yano K, Hwang LJ. Variability in systolic blood pressure-a risk factor for coronary heart disease? *Am J Epidemiol* 1997; 145:771–776.
18. Eguchi K, Hoshide S, Schwartz JE, Shimada K, Kario K, Visit-to-visit and ambulatory blood pressure variability as predictors of incident cardiovascular events in patients with hypertension. *Am J Hypertens* 2012; 25:962–968.
19. Mancia G, Omboni S, Parati G. The importance of blood pressure variability in hypertension. *Blood Press Monit* 2000; 5:S9–S15.
20. Nadour W, Biederman RW. Is left ventricular hypertrophy regression important? Does the tool used to detect it matter? *J Clin Hypertens (Greenwich)* 2009; 11:441–447.
21. Muntner P, Shimbo D, Diaz KM, Newman J, Sloan RP, Schwartz JE, Low correlation between visit-to-visit variability and 24-h variability of blood pressure. *Hypertens Res* 2013; in press.
22. Liao D, Cooper L, Cai J, Toole J, Bryan N, Burke G, Shahar E, Nieto J, Mosley T, Heiss G. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. *Neuroepidemiology* 1997; 16:149–162.
23. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke* 2003; 34:1126–1129.
24. Chimowitz MI, Estes ML, Furlan AJ, Awad IA. Further observations on the pathology of subcortical lesions identified on magnetic resonance imaging. *Arch Neurol* 1992; 49:747–752.

25. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: the Cardiovascular Health Study. *Stroke* 1996; 27:1274–1282.
26. 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.
27. Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ, Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: the Honolulu–Asia Aging study. *Stroke* 2002; 33:26–30.
28. Liu W, Liu R, Sun W, Peng Q, Zhang W, Xu E, Cheng Y, Ding M, Li Y, Hong Z, Wu J, Zeng J, Yao C, Huang Y; CASISP study group. Different impacts of blood pressure variability on the progression of cerebral microbleeds and white matter lesions. *Stroke* 2012; 43:2916–2922.
29. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Oden A, Svanborg A. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996; 347:1141–1145.
30. Stewart R, Xue QL, Masaki K, Petrovitch H, Ross GW, White LR, Launer LJ. Change in blood pressure and incident dementia: a 32-year prospective study. *Hypertension* 2009; 54:233–240.
31. McGuinness B, Todd S, Passmore P, Bullock R. The effects of blood pressure lowering on development of cognitive impairment and dementia in patients without apparent prior cerebrovascular disease. *Cochrane Database Syst Rev* 2006; 2:CD004034.
32. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton A, Poulter R, Ma S, Comsa M, Burch L, Fletcher A, Bulpitt C; HYVET investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol* 2008; 7:683–689.
33. Fournier A, Oprisiu-Fournier R, Serot JM, Godefroy O, Achard JM, Faure S, Mazouz H, Temmer M, Albu A, Bordet R, Hanon O, Gueyffier F, Wang J, Black S, Sato N. Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. *Expert Rev Neurother* 2009; 9:1413–1431.
34. Qiu C, von Strauss E, Winblad B, Fratiglioni L. Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. *Stroke* 2004; 35:1810–1805.
35. 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.
36. Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K. Visit-to-visit blood pressure variations: New independent determinants for carotid artery measures in the elderly at high risk of cardiovascular disease. *J Am Soc Hypertens* 2011; 5:184–192.
37. Okada H, Fukui M, Tanaka M, Inada S, Mineoka Y, Nakanishi N, Senmaru T, Sakabe K, Ushigome E, Asano M, Yamazaki M, Hasegawa G, Nakamura N. Visit-to-visit variability in systolic blood pressure is correlated with diabetic nephropathy and atherosclerosis in patients with type 2 diabetes. *Atherosclerosis* 2012; 220:155–159.
38. Simbo D, Shea S, McClelland RL, Viera AJ, Mann D, Newman J, Lima J, Polak JF, Psaty BM, Muntner P. Associations of aortic distensibility and arterial elasticity with long-term visit-to-visit blood pressure variability: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Hypertens* 2013; 26:896–902.
39. Mancia G, DiRienzo M, Parati G, Grassi G. Sympathetic activity, blood pressure variability and end organ damage in hypertension. *J Hum Hypertens* 1997; 11:S3–S8.
40. Spiegel K, Leproult R, Van Cauter E. Impact of sleep dept on metabolic and endocrine function. *Lancet* 1999; 354: 1435–1439.
41. Nagai K, Nagai N, Shimizu K, Chun S, Nakagawa H, Niijima A. SCN output drives the autonomic nervous system: with special reference to the autonomic function related to the regulation of glucose metabolism. *Prog Brain Res* 1996; 111:253–272.
42. Rothwell PM. Limitation of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 2010; 375:938–948.
43. Nagai M, Hoshide S, Nishikawa M, Shimada K, Kario K. Sleep duration and insomnia in the elderly: association with blood pressure variability and carotid artery remodeling. *Am J Hypertens* 2013; 26:981–989.
44. Omboni S, Parati G, Di Rienzo M, Wieling W, Mancia G. Blood pressure and heart rate variability in autonomic disorders: a critical review. *Clin Auton Res* 1996; 6:171–182.
45. Kingwell BA, Cameron JD, Gillies KJ, Jennings GL, Dart AM. Arterial compliance may influence baroreflex function in athletes and hypertensives. *Am J Physiol* 1995; 268:H411–H418.
46. National Institute of Health and Clinical Excellence. *Hypertension: Clinical Management of Primary Hypertension in Adults. NICE Clinical Guideline 127*. NICE: London, 2011.
47. Costanzo P, Perrone-Filardi P, Petretta M, Marciano C, Vassallo E, Gargiulo P, Paolillo S, Petretta A, Chiariello M. Calcium channel blockers and cardiovascular outcomes: a meta-analysis of 175,634 patients. *J Hypertens* 2009; 27:1136–1151.
48. Wang JG, Li Y, Franklin SS, Safer M. Prevention of stroke and myocardial infarction by amlodipine and angiotensin receptor blockers: a quantitative overview. *Hypertension* 2007; 50:181–188.
49. Takagi H, Umemoto T. Revisiting evidence of blood pressure-dependent and independent effects of amlodipine on the risk of stroke. *J Clin Hypertens* 2011; 13:781–782.
50. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Poulter NR, Sever PS, on behalf of the ASCOT-BPLA and MRC Trial investigators. Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol* 2010; 9:469–480.
51. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010; 375:906–915.
52. Muntner P, Levitan EB, Joyce C, Holt E, Mann D, Oparil S, Krousel-Wood M. Association between antihypertensive medication adherence and visit-to-visit variability of blood pressure. *J Clin Hypertension* 2013; 15:112–117.