Blood pressure variability and the development of hypertensive organ damage in the general population

Tomonori Sugiura MD, PhD1 | Hiroyuki Takase MD, PhD2 | Masashi Machii MD, PhD2 | Kazusa Hayashi MD2 | Suguru Nakano MD2 | Shin Takayama MD2 | Yoshihiro Seo MD, PhD1 | Yasuaki Dohi MD, PhD3

1Department of Cardiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
2Department of Internal Medicine, Enshu Hospital, Hamamatsu, Japan
3Department of Internal Medicine, Faculty of Rehabilitation Sciences, Nagoya Gakuin University, Nagoya, Japan

Correspondence
Hiroyuki Takase MD, PhD, Department of Internal Medicine, Enshu Hospital, 1-1-1 Chuo, Naka-ku, Hamamatsu 430-0929, Japan.
Email: h-takase.ken@shizuokakouseiren.jp

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Abstract
Increasing blood pressure variability (BPV) has been reported to be a strong predictor of cardiovascular events in patients with hypertension. However, the effects of BPV in the general population have not been intensively studied. The present study was designed to investigate a possible relationship between year-to-year BPV and hypertensive target organ damage (TOD) in a relatively low-risk general population. A total of 5489 consecutive patients (mean age 58.6 ± 10.7 years) who visited our hospital for an annual physical checkup for five consecutive years during 2008–2013 were enrolled in this study. The average systolic and diastolic blood pressures and pulse pressure were calculated, as well as standard deviation, coefficient of variation, and average real variability in blood pressures. Cross-sectional analysis was conducted and subjects without TOD at baseline (n = 3115) were followed up (median 1827 days) with the end-point of TOD, defined as left ventricular hypertrophy on electrocardiogram or declining glomerular filtration rate. At baseline, BPV was closely associated with TOD. During follow-up, left ventricular hypertrophy and declining glomerular filtration rate developed in 189 and 400 subjects, respectively. Although the standard deviation for systolic blood pressure and pulse pressure predicted future development of TOD in a univariate analysis, BPV was not a significant determinant of incident TOD in adjusted Cox hazard models. These results suggest that year-to-year BPV is a marker of the presence of TOD in the general population but does not independently predict future TOD.

KEYWORDS
blood pressure variability, electrocardiogram, glomerular filtration rate, left ventricular hypertrophy, pulse pressure
1 | INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular diseases, such as coronary heart disease, heart failure, and stroke, which seriously affect healthy life expectancy and lifespan.1 Blood pressure levels measured in an appropriate condition and environment show a continuous relationship with future incidence of cardiovascular events, and elevated blood pressure confirmed on several occasions predicts an increased risk of cardiovascular events.1 However, blood pressure is highly variable, and fluctuations in blood pressure are frequently observed in clinical settings. In addition to the blood pressure level, exaggerated visit-to-visit blood pressure variability (BPV) is also a strong predictor of the incidence of stroke in a population with prior cerebrovascular events.2 Recent studies confirmed that cardiovascular events, as well as target organ damage (TOD), are associated with the degree of BPV independent of blood pressure levels,2–10 though the clinical significance of BPV in the general population has not yet been intensively studied.

Most of these studies investigating BPV were conducted in populations with hypertension, a history of stroke, or increased risk of cardiovascular diseases,2–10 and the significance of BPV in relatively low-risk populations has not been intensively studied.11 Most healthy individuals do not have many chances to measure their blood pressure, but those undergoing regular medical checkups (eg, annual physical checkups for employees) measure blood pressure every year, but BPV is not usually assessed. Although visit-to-visit BPV assessed (usually every 2–3 months) in various patient populations has been associated with arterial stiffness and baroreceptor dysfunction,12–16 long-term, that is year-to-year, BPV in the general population may have a different clinical significance. Individuals with increased year-to-year BPV may have hypertensive organ damage and be at increased risk of cardiovascular events even if their average blood pressure from the recent several years is within the normal range. Thus, the present study was designed to investigate whether year-to-year BPV is associated with hypertensive TOD in the general population using cross-sectional and follow-up study designs.

2 | METHODS

2.1 | Study design

The present cohort study was performed in participants in our annual physical checkup program. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Enshu Hospital. All participants provided written informed consent prior to the start of the study and at each study visit.

2.2 | Study participants and procedures

A total of 5542 consecutive individuals who participated in our physical checkup program for five consecutive years from 2008 to 2013 (2008–2012 or 2009–2013) were screened for eligibility in the present study. All participants provided blood pressure readings for the five visits. Participants with a history of cardiovascular diseases (n = 53) were excluded, and the remaining 5489 subjects were included in the present study. First, the average blood pressure, as well as the standard deviation (SD), coefficient of variation (CV), and average real variability (ARV) in blood pressure during the five consecutive visits (screening period) were calculated and used as indices of blood pressure at baseline. ARV was calculated as the average of the absolute difference from the preceding blood pressure value in multiple consecutive measurements. Baseline data other than those mentioned above were obtained at the fifth visit (2012 or 2013), and a possible relationship of the BPV indices with hypertensive TOD at baseline was investigated (cross-sectional study). Among participants in the cross-sectional study, those without TOD at baseline (n = 3115) were followed until 2019 (median 1827 days), and the effect of the BPV
determined during the screening period on the occurrence of TOD during the follow-up period was observed (follow-up study).

Our physical checkup program included a routine physical examination, chest X-ray, electrocardiography, laboratory assessment of cardiovascular risk factors, and a questionnaire about the subject’s health condition. Blood pressure was measured by trained technicians using an automated device (Omron Colin, BP-203RV III C) in the morning in a seated position after an overnight fast. Three consecutive blood pressure measurements were taken at 2-min intervals; the mean of the second and third measurements was recorded as the blood pressure. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive medications. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl and/or HbA1c ≥ 6.5% or the use of antidiabetic medications, and dyslipidemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dl, high-density lipoprotein cholesterol < 40 mg/dl, triglyceride ≥ 150 mg/dl, or the use of antidyshlipemic medications. Left ventricular hypertrophy (LVH) was assessed using Sokolow-Lyon voltage > 3.8 mV and/or Cornell product > 2440 mm ms. The glomerular filtration rate was estimated (eGFR) using the modified Modification of Diet in Renal Disease study formula for the Japanese population; eGFR < 60 ml/min/1.73 m² was defined as a decline in eGFR. Participants reported alcohol consumption as ranging between 0 and 7 times/week, with frequent alcohol consumption defined as 6 or 7 times/week.

### Statistical analysis

All analyses were performed using IBM SPSS statistics 24 (IBM SPSS, Chicago, IL, USA). Data are presented as the mean ± SD or as the number and percentage of participants. In some analyses, participants were divided into four groups according to the quartile of each BPV index. The significance of any difference between two means

### Table 1 Characteristics of cross-sectional study participants

| Characteristic          | Total n = 5489 | Q1 n = 1374 | Q2 n = 1374 | Q3 n = 1370 | Q4 n = 1371 |
|-------------------------|---------------|-------------|-------------|-------------|-------------|
| Age (years)             | 58.6 ± 10.7   | 56.7 ± 10.5 | 57.2 ± 10.8 | 59.1 ± 10.7 | 61.4 ± 10.3 |
| Male (male/female)      | 2672 (47.9%)  | 2892 (64.9%)| 2894 (68.9%)| 2955 (67.5%)| 2962 (70.2%)|
| Body mass index (kg/m²) | 22.7 ± 3.2    | 22.7 ± 3.1  | 22.8 ± 3.2  | 22.8 ± 3.2  | 23.1 ± 3.3  |
| SBP (mm Hg)             | 123.5 ± 14.1  | 121.3 ± 12.4| 122.3 ± 13.1| 123.4 ± 13.7| 127.1 ± 16.2|
| DBP (mm Hg)             | 75.4 ± 9.2    | 74.4 ± 8.7  | 75.3 ± 9.0  | 75.1 ± 9.1  | 76.6 ± 9.8  |
| PP (mm Hg)              | 48.2 ± 9.9    | 46.9 ± 8.7  | 47.0 ± 9.1  | 48.3 ± 9.7  | 50.4 ± 11.6 |
| Pulse rate (bpm)        | 63.2 ± 9.5    | 63.4 ± 9.4  | 62.9 ± 9.3  | 62.9 ± 9.1  | 63.7 ± 10.1 |
| Serum creatinine (mg/dl)| .79 ± .23     | .78 ± .16   | .80 ± .17   | .79 ± .17   | .81 ± .37   |
| eGFR (ml/min/1.73 m²)   | 74.1 ± 13.4   | 75.2 ± 12.3 | 74.1 ± 13.2 | 74.1 ± 13.6 | 72.9 ± 14.4 |
| Uric acid (mg/dl)       | 5.50 ± 1.31   | 5.41 ± 1.31 | 5.45 ± 1.26 | 5.49 ± 1.31 | 5.64 ± 1.34 |
| Fasting plasma glucose  | 98.1 ± 16.3   | 97.0 ± 14.6 | 97.4 ± 15.9 | 97.7 ± 16.6 | 100.5 ± 17.6|
| HbA1c (%)               | 5.23 ± 5.8    | 5.67 ± 5.1  | 5.69 ± 5.6  | 5.74 ± 6.1  | 5.80 ± 6.1  |
| LDL-C (mg/dl)           | 123.4 ± 27.9  | 123.8 ± 28.4| 123.6 ± 27.4| 123.6 ± 27.8| 122.8 ± 27.8|
| HDL-C (mg/dl)           | 60.9 ± 15.5   | 61.3 ± 15.1 | 61.1 ± 15.6 | 61.6 ± 16.0 | 60.0 ± 15.4 |
| Triglyceride (mg/dl)    | 109.0 ± 71.2  | 107.5 ± 71.4| 107.9 ± 62.0| 106.4 ± 71.8| 114.1 ± 78.4|
| Sokolow-Lyon voltage    | 2.27 ± .86    | 2.24 ± .82  | 2.26 ± .84  | 2.28 ± .88  | 2.28 ± .90  |
| Cornell product (mm ms)| 1510 ± 681    | 1496 ± 661  | 1469 ± 606  | 1510 ± 723  | 1566 ± 724  |

aFrequent alcohol consumption
bDecline in eGFR
cLVH

(Continues)
TABLE 1 (Continued)

Indices of blood pressure variability

|                     | Total $n = 5489$ | SD quartile for systolic blood pressure |
|---------------------|------------------|----------------------------------------|
|                     |                   | Q1 $n = 1374$ | Q2 $n = 1374$ | Q3 $n = 1370$ | Q4 $n = 1371$ |
| BPV (mm Hg)         |                  |             |             |             |             |
| SBP-Ave             | 123.8 ± 12.6     | 121.2 ± 12.0 | 122.3 ± 12.1| 123.3 ± 11.8*| 128.3 ± 13.3***
| SBP-SD              | 8.04 ± 3.50      | 1.21 ± .97   | 6.54 ± .57* | 8.68 ± .69***| 12.78 ± 2.78***
| SBP-CV              | 6.50 ± 1.69      | 3.51 ± .88   | 5.40 ± .72* | 7.10 ± .87***| 9.99 ± 2.04***
| SBP-Average real variability (mm Hg) | 9.18 ± 4.42   | 4.99 ± 1.68  | 7.67 ± 1.98*| 10.01 ± 2.61**| 14.09 ± 4.48***
| DBP-Ave             | 76.0 ± 7.8       | 74.9 ± 7.6   | 75.5 ± 7.7  | 75.6 ± 7.3  | 77.8 ± 8.2***
| DBP-SD              | 5.60 ± 2.40      | 4.57 ± 1.92  | 5.07 ± 2.06*| 5.68 ± 2.10**| 7.08 ± 2.69***
| DBP-CV              | 7.41 ± 3.15      | 6.16 ± 2.65  | 6.76 ± 2.79*| 7.58 ± 2.87**| 9.14 ± 3.43***
| DBP-Average real variability (mm Hg) | 6.43 ± 3.11   | 5.36 ± 2.64  | 5.86 ± 2.76*| 6.58 ± 2.89**| 7.93 ± 3.48***
| PP-Ave              | 47.8 ± 7.6       | 46.3 ± 7.0   | 46.8 ± 7.0  | 47.7 ± 7.3***| 50.4 ± 8.5***
| PP-SD               | 6.59 ± 2.86      | 4.91 ± 2.04  | 5.84 ± 2.19*| 6.73 ± 2.43**| 8.87 ± 3.04***
| PP-CV               | 13.8 ± 5.5       | 10.62 ± 4.14 | 12.59 ± 4.60*| 14.20 ± 4.97**| 17.72 ± 5.72***
| PP-Average real variability (mm Hg) | 7.70 ± 3.81   | 5.78 ± 2.78  | 6.96 ± 3.07*| 7.89 ± 3.47**| 10.16 ± 4.33***

Indices of blood pressure variability were calculated using data obtained from five consecutive occasions during the screening period. Data are given as the mean ± SD, n (%).

Q1–4, study participants were divided into four groups according to the quartile of the SD for systolic blood pressure.

nP < .05 versus Q1.

**P < .05 versus Q2.

***P < .05 versus Q3 (ANOVA followed by Scheffe’s test or chi-squared test followed by z analysis with Bonferroni’s correction).

Frequent alcohol consumption was defined as the consumption of alcohol six or seven times per week.

Decline in eGFR was defined as eGFR < 60 ml/min/1.73 m².

Left ventricular hypertrophy (LVH) was assessed using Sokolow-Lyon voltage > 3.8 mV and/or Cornell product > 2440 mm ms.

Abbreviations: Ave, average; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.

with a normal distribution was determined using unpaired t tests. Chi-squared tests were used for comparisons of categorical data. The relationship between BPV indices and TOD was cross-sectionally investigated using data obtained at baseline. In the cross-sectional analysis, participants were categorized into four groups according to systolic BPV because systolic blood pressure is more variable than diastolic blood pressure, and previous studies revealed that systolic BPV is a strong predictor of cardiovascular events.2,4–8 Comparisons among four groups (quartiles) were performed using one-way analysis of variance (ANOVA) followed by Scheffe’s post hoc test or chi-squared test followed by z analysis with Bonferroni’s correction. The impact of baseline BPV on the future development of TOD was investigated using Cox hazard regression analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. In all cases, two-tailed tests were used and P < .05 was considered significant.

3 | RESULTS

3.1 | Cross-sectional study

The baseline characteristics of participants obtained at the end of the screening period (2012 or 2013) are listed in Table 1. Indices of BPV were calculated using data obtained during the screening period (five consecutive annual physical checkups from 2008 to 2013) and taken as the baseline data for BPV. Hypertension was present in 34.5% (n = 1895) of all subjects, 75.9% (n = 1439) of whom were under treatment with antihypertensive medication. The backgrounds of four subgroups of subjects divided according to the quartiles of SD for systolic blood pressure are shown in Table 1. Most of the indices of risk factors showed an increase or worsening across SD quartiles for systolic blood pressure. In line with this observation, Sokolow-Lyon voltage on electrocardiogram and eGFR correlated with most of the indices of BPV. Moreover, the prevalence of LVH or decline in eGFR showed an increase across the quartiles of the Ave systolic blood pressure or most of the indices of variability in systolic blood pressure (Figure 1). Similar results were obtained using pulse pressure or diastolic blood pressure for calculating BPV (data not shown). However, the impact of the average blood pressure, either systolic, diastolic, or pulse pressure, on the TOD was the most prominent blood pressure indices investigated at baseline (Figure 1).
3.2 | Follow-up study

Subjects without LVH or a decline in eGFR (n = 3500) were followed until 2019 with the endpoint being the occurrence of TOD. A total of 3115 subjects were analyzed because 203 subjects were lost to follow-up and data were missing from 182 subjects. The baseline characteristics of participants (n = 3115) are listed in Table 4. The actual follow-up period was 14247 and 14244 person-years and the median follow-up period was 1827 (range, 168–2898) and 1825 (range, 168–2898) days, for the incidence of electrocardiogram-determined LVH and a decline in eGFR, respectively. During the follow-up period, any TOD occurred in 558 participants. The results of the retrospective comparison between participants who did and did not develop hypertensive TOD during the follow-up period are presented in Tables 5 and 6. Although the average blood pressure or pulse pressure was greater in participants with future LVH (Table 5) or a decline in eGFR than those without (Table 6), BPV during the screening period showed minimal influence on future TOD. Univariate regression analysis between BPV indices at baseline and Sokolow-Lyon voltage on electrocardiogram or eGFR at the end of follow-up showed similar results (Tables 5 and 6). Next, the impact of BPV on the future development of TOD was prospectively assessed using Cox hazard regression analysis (Tables 7 and 8). Although some indices of BPV were significantly associated with the future development of TOD in univariate analyses, adjusting for possible factors revealed that indices of BPV, either systolic, diastolic, or pulse pressure, were not associated with future development of electrocardiogram-determined LVH or a decline in GFR. In the next series of analyses, subjects were divided into four groups according to the quartiles of each index of baseline blood pressure variability, either systolic, diastolic, or pulse pressure, were not associated with the future development of TOD (Tables 7 and 8). Although some indices of BPV were significantly associated with the future development of TOD in univariate analyses, adjusting for possible factors revealed that indices of BPV, either systolic, diastolic, or pulse pressure, were not associated with future development of electrocardiogram-determined LVH or a decline in GFR. In the next series of analyses, subjects were divided into four groups according to the quartiles of each index of baseline blood pressure variability. The occurrence of TOD during the follow-up period was not increased across the quartiles of BPV indices at baseline (Figure S1).

4 | DISCUSSION

The present study demonstrates that year-to-year BPV is associated with the presence of hypertensive TOD but an increase in BPV does not necessarily predict future development of hypertensive TOD in the general population. Increased BPV often observed in individuals without hypertension may be the result of latent progression of atherosclerotic changes in the vasculature.

Increased BPV means an increased chance of blood pressure elevation, as well as blood pressure reduction. This concept leads to speculative regression analysis (Tables 7 and 8). Although some indices of BPV were significantly associated with the future development of TOD in univariate analyses, adjusting for possible factors revealed that indices of BPV, either systolic, diastolic, or pulse pressure, were not associated with future development of electrocardiogram-determined LVH or a decline in GFR. In the next series of analyses, subjects were divided into four groups according to the quartiles of each index of baseline blood pressure variability. The occurrence of TOD during the follow-up period was not increased across the quartiles of BPV indices at baseline (Figure S1).
| TABLE 4 | Baseline characteristics of follow-up study participants |
|----------------|-----------------------------------------------|
|               | Total | Q1  | Q2  | Q3  | Q4  |
|               | n = 3115 | n = 775 | n = 778 | n = 778 | n = 784 |
| Age (years)   | 56.8 ± 10.3 | 55.3 ± 9.9 | 55.3 ± 10.2 | 57.1 ± 10.7* | 59.5 ± 10.0**.***.**** |
| Male          | 2087 (67.0%) | 490 (63.2%) | 537 (69.0%)* | 514 (66.1%)* | 546 (69.6%)* |
| Body mass index (kg/m²) | 22.8 ± 3.2 | 22.5 ± 2.9 | 22.8 ± 3.2 | 22.6 ± 3.1 | 23.1 ± 3.3*** |
| SBP (mm Hg)   | 121.8 ± 14.0 | 120.0 ± 12.4 | 120.4 ± 13.1 | 121.4 ± 13.4 | 125.3 ± 16.1**.***.**** |
| DBP (mm Hg)   | 74.8 ± 9.1 | 74.0 ± 8.9 | 74.4 ± 8.9 | 74.4 ± 8.8 | 75.9 ± 9.5***.**** |
| PP (mm Hg)    | 47.1 ± 9.5 | 46.0 ± 8.4 | 46.0 ± 8.7 | 47.1 ± 9.4 | 49.4 ± 10.9**.***.**** |
| Pulse rate (bpm) | 63.2 ± 9.1 | 63.7 ± 9.4 | 62.6 ± 8.7 | 62.9 ± 8.8 | 63.4 ± 9.4 |
| Serum creatinine (mg/dl) | .75 ± .13 | .75 ± .13 | .76 ± .13 | .74 ± .13 | .75 ± .13 |
| eGFR (ml/min/1.73 m²) | 77.9 ± 11.1 | 77.8 ± 10.1 | 77.9 ± 11.2 | 78.4 ± 11.5 | 77.7 ± 11.4 |
| Uric acid (mg/dl) | 5.34 ± 1.28 | 5.28 ± 1.29 | 5.36 ± 1.23 | 5.31 ± 1.31 | 5.41 ± 1.30 |
| Fasting plasma glucose (mg/dl) | 97.7 ± 16.2 | 96.0 ± 14.4 | 97.5 ± 14.2 | 97.2 ± 17.1 | 99.9 ± 18.6***.**** |
| HbA1c (%)     | 5.71 ± .59 | 5.64 ± .50 | 5.68 ± .55 | 5.73 ± .64* | 5.79 ± .63*** |
| LDLC (mg/dl)  | 123.9 ± 28.4 | 123.0 ± 28.3 | 123.8 ± 29.2 | 125.2 ± 27.9 | 123.4 ± 28.4 |
| HDLC (mg/dl)  | 61.0 ± 15.2 | 61.4 ± 15.3 | 60.9 ± 15.1 | 61.4 ± 15.4 | 60.2 ± 14.7 |
| Triglyceride (mg/dl) | 108.2 ± 71.9 | 107.3 ± 74.3 | 108.1 ± 70.9 | 106.4 ± 75.0 | 110.8 ± 67.0 |
| Sokolow-Lyon voltage (mV) | 2.11 ± .73 | 2.13 ± .71 | 2.13 ± .73 | 2.12 ± .74 | 2.08 ± .74 |
| Cornell product (mm ms) | 1347 ± 503 | 1357 ± 485 | 1363 ± 503 | 1334 ± 519 | 1336 ± 507 |
| Current smoking status | 1115 (35.8%) | 276 (35.6%) | 288 (37.0%) | 259 (33.3%) | 292 (37.2%) |
| Family history of hypertension | 673 (21.6%) | 149 (19.2%) | 168 (21.6%) | 185 (23.8%) | 171 (21.8%) |
| Hypertension | 515 (16.5%) | 124 (16.0%) | 120 (15.4%) | 126 (16.2%) | 145 (18.5%) |
| under antihypertensive medication | 810 (26.0%) | 126 (16.3%) | 166 (21.3%)* | 188 (24.2%)* | 330 (42.1%)*.***.**** |
| Diabetes mellitus | 309 (9.9%) | 56 (7.2%) | 68 (8.7%) | 76 (9.8%) | 109 (13.9%)* |
| Dyslipidemia | 1520 (48.8%) | 358 (46.2%) | 355 (45.6%) | 385 (49.5%)* | 422 (53.8%)*.***.**** |

**Indices of blood pressure variability**

| SBP-Ave (mm Hg) | 121.6 ± 12.2 | 119.9 ± 11.9 | 120.3 ± 11.9 | 121.2 ± 11.5 | 125.0 ± 13.0**.***.**** |
| SBP-SD (mm Hg)  | 7.70 ± 3.24 | 4.07 ± .93 | 6.31 ± .55* | 8.34 ± .67** | 12.03 ± 2.47**.***.**** |
| SBP-CV (%)      | 6.35 ± 2.57 | 3.43 ± .87 | 5.30 ± .71* | 6.94 ± .84** | 9.67 ± 1.84***.**** |
| SBP-Average real variability (mm Hg) | 8.82 ± 4.13 | 4.87 ± 1.64 | 7.41 ± 1.92* | 9.62 ± 2.62** | 13.34 ± 4.03**.***.**** |
| DBP-Ave (mm Hg) | 75.1 ± 7.6 | 74.4 ± 7.6 | 74.6 ± 7.6 | 74.8 ± 7.2 | 76.4 ± 7.8***.**** |
| DBP-SD (mm Hg)  | 5.39 ± 2.26 | 4.44 ± 1.87 | 4.89 ± 1.94* | 5.52 ± 2.01** | 6.69 ± 2.48**.***.**** |
| DBP-CV (%)      | 7.22 ± 3.01 | 6.02 ± 2.57 | 6.60 ± 2.68* | 7.43 ± 2.77** | 8.81 ± 3.22***.**** |
| DBP-Average real variability (mm Hg) | 6.23 ± 2.97 | 5.24 ± 2.61 | 5.72 ± 2.62* | 6.39 ± 2.81** | 7.56 ± 3.27*** |
| PP-Ave (mm Hg)  | 46.5 ± 7.2 | 45.4 ± 6.7 | 45.6 ± 6.7 | 46.4 ± 7.0 | 48.6 ± 8.0***.**** |
| PP-SD (mm Hg)   | 6.29 ± 2.71 | 4.75 ± 2.01 | 5.64 ± 2.12* | 6.37 ± 2.33** | 8.36 ± 2.87**.***.**** |
| PP-CV (%)       | 13.54 ± 5.46 | 10.49 ± 4.14 | 12.50 ± 4.66* | 13.83 ± 5.01** | 17.34 ± 5.50**.***.**** |
| PP-Average real variability (mm Hg) | 7.36 ± 3.58 | 5.59 ± 2.72 | 6.75 ± 2.96* | 7.41 ± 3.24** | 9.65 ± 3.96**.***.**** |

Indices of blood pressure variability were calculated using data obtained from five consecutive occasions during the screening period. Data are given as the mean ± SD, n (%).

Q1–4, study participants were divided into four groups according to the quartile of the SD for systolic blood pressure.

*P < .05 versus Q1.

**P < .05 versus Q2.

***P < .05 versus Q3 (ANOVA followed by Scheffe’s test or chi-squared test followed by z analysis with Bonferroni’s correction).

Frequent alcohol consumption was defined as the consumption of alcohol six or seven times per week.

Abbreviations: Ave, average; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.
the retrospective analysis supported this concept. The impact of BPV on LVH was somewhat small compared to the impact on eGFR because kidney damage, but not LVH, showed an increase across the CV quartiles of systolic blood pressure. This may be attributed to the relatively low positive and negative predictive values of electrocardiogram for the detection of echocardiographic LVH.26 These results are compatible with a recent report in which a cross-sectional design demonstrated a close association between long-term variability in systolic blood pressure or pulse pressure and arterial stiffness assessed by brachial-ankle pulse wave velocity in Chinese adults.11 The increased arterial stiffness in the previous study may indicate latent progression of hypertensive or other risk factor-induced vascular damage. However, the close association between BPV and TOD observed in the previous cross-sectional study does not lead to a causal relationship between BPV and TOD. Thus, in the present study, patients without TOD were followed up with the endpoint of electrocardiogram-determined LVH or a decline in eGFR (< 60 ml/min/1.73 m²). In univariate Cox hazard regression analysis, some indices of BPV, such as the SD for pulse pressure in LVH and the SD and ARV for systolic blood pressure in a decline in eGFR, were associated with future development of TOD, but adjusting for important factors mostly eliminated the significance of the relationship of BPV with future LVH or kidney damage. Thus, increased BPV may not be a cause of hypertensive TOD, but a result of latent organ damage caused by cardiovascular risk factors in the general population. In line with this speculation, the average blood pressure was increased, and other cardiovascular risk factors showed an increase or worsening across the quartiles of systolic SD at baseline. Various cardiovascular risk factors, including slightly increased blood pressure, that coexist with increased BPV, but not BPV itself, may play a major role in the future development of TOD.

Recent studies demonstrated that cardiovascular events, as well as TOD, are associated with the degree of BPV independent of blood pressure levels,2–10 which seems to be incompatible with the present results, though some investigators have not observed such an association.27–29 However, most studies investigating the clinical significance of BPV have targeted various patient populations. In one such study, exaggerated visit-to-visit BPV was found to be a strong predictor of the incidence of stroke in a population with prior cerebrovascular events.3 Thus, the significance of BPV in the general population has not been intensively studied. Although a close association between long-term BPV (SD calculated using three points of measurements during 2440 mm ms.11) and other cardiovascular risk factors showed an increase or worsening across the quartiles of systolic SD at baseline. Various cardiovascular risk factors, including slightly increased blood pressure, that coexist with increased BPV, but not BPV itself, may play a major role in the future development of TOD.

### TABLE 5  
Blood pressure variability (BPV) at baseline in participants with (+) and without (−) future left ventricular hypertrophy (LVH) and the relationship of baseline BPV with future Sokolow-Lyon voltage in a retrospective analysis (n = 3115)

| LVH       | Sokolow-Lyon voltage | r  | P value |
|-----------|----------------------|----|---------|
| −; n = 2926 | 121.4 ± 12.2         | .138 | <.001  |
| +; n = 189   | 124.8 ± 12.0         | .018 | .303   |
| SBP-Ave (mm Hg) | 7.70 ± 3.24         | .065 | .035   |
| SBP-CV (%)   | 6.36 ± 2.57          | .019 | .295   |
| SBP-ARV (mm Hg) | 8.84 ± 4.16        | .009 | .611   |
| DBP-Ave (mm Hg) | 75.0 ± 7.6           | .118 | <.001  |
| DBP-SD (mm Hg) | 5.39 ± 2.26         | .009 | .611   |
| DBP-CV (%)   | 7.22 ± 3.01          | .018 | .318   |
| DBP-ARV (mm Hg) | 6.23 ± 2.97         | .033 | .064   |
| PP-Ave (mm Hg) | 46.4 ± 7.2          | .111 | <.001  |
| PP-SD (mm Hg) | 6.26 ± 2.69         | .044 | .015   |
| PP-CV (%)    | 13.52 ± 5.45         | .002 | .922   |
| PP-ARV (mm Hg) | 7.33 ± 3.56         | .049 | .006   |

Indices of blood pressure variability were calculated using data obtained from five consecutive occasions during the screening period. Data are given as mean ± SD.

*P < .01.
**P < .05 compared to absence of LVH (unpaired t test).
*LVH was defined as Sokolow-Lyon voltage > 3.8 mV and/or Cornell product > 2440 mm ms.

Abbreviations: ARV, average real variability; Ave, average; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.

### TABLE 6  
Blood pressure variability (BPV) at baseline in participants with (+) and without (−) future decline in eGFR and the relationship of baseline BPV with future eGFR in a retrospective analysis (n = 3115)

| eGFR        | −; n = 2715 | +; n = 400 | r  | P value |
|-------------|-------------|------------|----|---------|
| SBP-Ave (mm Hg) | 121.2 ± 12.2 | 123.9 ± 12.4 | .059 | .001   |
| SBP-SD (mm Hg) | 7.64 ± 3.18  | 8.13 ± 3.63 | .030 | .097   |
| SBP-CV (%)    | 6.32 ± 2.54  | 6.55 ± 2.76 | .017 | .337   |
| SBP-ARV (mm Hg) | 8.72 ± 4.04  | 9.49 ± 4.65 | .038 | .036   |
| DBP-Ave (mm Hg) | 74.9 ± 7.6   | 76.3 ± 7.5  | .068 | <.001  |
| DBP-SD (mm Hg) | 5.37 ± 2.26  | 5.50 ± 2.19 | .005 | .788   |
| DBP-CV (%)    | 7.22 ± 3.02  | 7.26 ± 2.92 | .010 | .583   |
| DBP-ARV (mm Hg) | 6.20 ± 2.97  | 6.46 ± 2.94 | .020 | .255   |
| PP-Ave (mm Hg) | 46.3 ± 7.1   | 47.6 ± 7.9  | .028 | .112   |
| PP-SD (mm Hg) | 6.26 ± 2.66  | 6.52 ± 2.98 | .014 | .444   |
| PP-CV (%)     | 13.53 ± 5.43 | 13.68 ± 5.66 | .004 | .803   |
| PP-ARV (mm Hg) | 7.32 ± 3.52  | 7.61 ± 3.91 | .005 | .789   |

Indices of blood pressure variability were calculated using data obtained from five consecutive occasions during the screening period. Data are given as mean ± SD.

*P < .05 compared to decline in eGFR (unpaired t test).

†Decline in eGFR was defined as eGFR < 60 ml/min/1.73 m². 

Abbreviations: ARV, average real variability; Ave, average; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.
TABLE 7 Results of Cox hazard regression analysis of each index of baseline blood pressure variability investigating possible associations with future left ventricular hypertrophy (follow-up study, n = 3115)

| Univariate | Model 1 | Model 2 | Model 3 |
|------------|---------|---------|---------|
|            | P       | HR (95% CI) | P       | HR (95% CI) | P       | HR (95% CI) |
| SBP-Ave    | <.001   | 1.020 (1.008–1.032) | .001   | 1.020 (1.008–1.032) | <.001 | 1.030 (1.016–1.044) |
| SBP-SD     | .92     | .998 (0.955–1.042)  | .69    | .991 (0.948–1.036)  | .66   | .990 (0.946–1.036)  |
| SBP-CV     | .34     | .973 (0.920–1.029)  | .24    | .967 (0.914–1.023)  | .17   | .961 (0.908–1.017)  |
| SBP-ARV    | .35     | .983 (0.949–1.019)  | .19    | .976 (0.942–1.012)  | .18   | .975 (0.940–1.012)  |
| DBP-Ave    | <.05    | 1.019 (1.000–1.039) | <.05   | 1.024 (1.005–1.045) | <.001 | 1.040 (1.017–1.063) |
| DBP-SD     | .60     | 1.017 (0.955–1.082) | .63    | 1.016 (0.953–1.083) | .67   | 1.014 (0.951–1.082) |
| DBP-CV     | .84     | 1.005 (0.958–1.054) | .93    | 1.002 (0.955–1.051) | .90   | .997 (0.950–1.046)  |
| DBP-ARV    | .63     | 1.012 (0.965–1.061) | .67    | 1.010 (0.963–1.060) | .66   | 1.011 (0.963–1.062) |
| PP-Ave     | <.001   | 1.035 (1.017–1.055) | <.005  | 1.031 (1.010–1.052) | <.001 | 1.038 (1.016–1.060) |
| PP-SD      | .01     | 1.068 (1.017–1.122) | .021   | 1.061 (1.009–1.115) | <.05  | 1.066 (1.013–1.121) |
| PP-CV      | .27     | 1.015 (0.989–1.041) | .28    | 1.015 (0.989–1.041) | .26   | 1.015 (0.989–1.042) |
| PP-ARV     | .06     | 1.038 (0.999–1.078) | .11    | 1.032 (0.993–1.073) | .09   | 1.035 (0.995–1.076) |

Indices of blood pressure variability were calculated using data obtained from five consecutive occasions during the screening period.
Left ventricular hypertrophy was defined as Sokolow-Lyon voltage > 3.8 mV and/or Cornell product > 2440 mm ms.
Abbreviations: ARV, average real variability; Ave, average; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.
Cox-hazard regression analyses were conducted separately for each index of blood pressure variability:
Model 1, adjusted for age and sex at baseline.
Model 2, further adjusted for family history of hypertension, frequent alcohol consumption (six or seven times per week), current smoking, body mass index, heart rate, serum creatinine, fasting plasma glucose, low-density lipoprotein cholesterol, and triglyceride at baseline.
Model 3, further adjusted for the average of each blood pressure index.

TABLE 8 Results of Cox hazard regression analysis of each index of baseline blood pressure variability investigating possible associations with future decline in eGFR (follow-up study, n = 3115)

| Univariate | Model 1 | Model 2 | Model 3 |
|------------|---------|---------|---------|
|            | P       | HR (95% CI) | P       | HR (95% CI) | P       | HR (95% CI) |
| SBP-Ave    | <.001   | 1.015 (1.007–1.023) | .23    | 1.005 (0.996–1.013) | .74   | 1.002 (0.992–1.011) |
| SBP-SD     | <.05    | 1.036 (1.007–1.065) | .45    | 1.011 (0.983–1.041) | .55   | 1.009 (0.981–1.037) |
| SBP-CV     | .18     | 1.025 (0.988–1.063) | .80    | 1.005 (0.969–1.042) | .73   | 1.006 (0.971–1.043) |
| SBP-ARV    | <.001   | 1.038 (1.015–1.061) | .14    | 1.017 (0.995–1.041) | .09   | 1.020 (0.997–1.043) |
| DBP-Ave    | <.05    | 1.016 (1.003–1.029) | .16    | 1.010 (0.996–1.024) | .68   | 1.003 (0.988–1.019) |
| DBP-SD     | .18     | 1.029 (0.987–1.074) | .96    | .999 (0.957–1.043)  | .13   | .965 (0.923–1.010)  |
| DBP-CV     | .41     | 1.014 (0.982–1.047) | .74    | .994 (0.963–1.027)  | .11   | .973 (0.940–1.007)  |
| DBP-ARV    | <.05    | 1.033 (1.000–1.066) | .47    | 1.012 (0.980–1.046) | .50   | .989 (0.956–1.022)  |
| PP-Ave     | <.001   | 1.026 (1.012–1.040) | .74    | 1.002 (0.988–1.017) | .89   | 1.001 (0.986–1.016) |
| PP-SD      | <.05    | 1.039 (1.003–1.076) | .58    | 1.010 (0.975–1.046) | .95   | .999 (0.965–1.034)  |
| PP-CV      | .41     | 1.008 (0.990–1.026) | .66    | 1.004 (0.986–1.022) | .93   | .999 (0.982–1.017)  |
| PP-ARV     | .06     | 1.026 (0.999–1.054) | .70    | 1.005 (0.978–1.033) | .90   | .998 (0.972–1.026)  |

Indices of blood pressure variability were calculated using data obtained from five consecutive occasions during the screening period.
Decline in eGFR was defined as eGFR < 60 ml/min/1.73 m².
Abbreviations: ARV, average real variability; Ave, average; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.
Cox-hazard regression analyses were conducted separately for each index of blood pressure variability:
Model 1, adjusted for age and sex at baseline.
Model 2, further adjusted for family history of hypertension, frequent alcohol consumption (six or seven times per week), current smoking, body mass index, heart rate, serum creatinine, fasting plasma glucose, low-density lipoprotein cholesterol, and triglyceride at baseline.
Model 3, further adjusted for the average of each blood pressure index.
The interpretation of the present results is limited by the following points. BPV has many indices, such as beat-to-beat, diurnal, day-to-night, day-to-day, month-to-month, and seasonal variability, and the present study only investigated the effects of year-to-year variability on the development of hypertensive TOD. Moreover, we adopted electrocardiogram-determined LVH and decline in eGFR as markers of TOD. Different results may be obtained using different indices of variability or other markers of TOD. Once-a-year assessment of TOD may have resulted in an inaccurate evaluation of the time to onset of damage and the statistical power of the Cox proportional hazard regression analysis may not have been enough for a sufficient discussion. Variability was calculated using blood pressure values obtained on five consecutive occasions and the frequency of measurements may have affected the results. Another important point is a lack of precise information on medication, such as classes of antihypertensive drugs prescribed or adherence to treatment, which may have influenced BPV and the development of TOD. Finally, a follow-up period of 5 years may not be sufficient. Although the large number of participants may partially overcome some of these limitations, a study with more participants and a longer observation period is necessary to draw definitive conclusions.

5 | CONCLUSIONS

Increased year-to-year BPV reflects the presence of hypertensive TOD possibly caused by risk factors other than blood pressure and may not predict future development of TOD in the general population.

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CONFLICT OF INTEREST

No conflict of interest exists.

AUTHOR CONTRIBUTIONS

Tomonori Sugiuira, Hiroyuki Takase and Yasuaki Dohi contributed to the study conception and design. Material preparation and data collection were performed by Hiroyuki Takase, Masashi Machii, Kazusa Hayashi, Suguru Nakano and Shin Takayama. Data analysis was performed by Hiroyuki Takase and Yasuaki Dohi. Interpretation was performed by Tomonori Sugiuira and Yasuaki Dohi. The first draft of the manuscript was written by Hiroyuki Takase and Yasuaki Dohi. Tomonori Sugiuira and Yoshihiro Seo revised the manuscript. All authors revised the manuscript and approved the final version.

ORCID

Hiroyuki Takase MD, PhD @ https://orcid.org/0000-0002-8908-0128

REFERENCES

1. Umemura S, Arima H, Arima S, et al. The Japanese society of hypertension guidelines for the management of hypertension (JSH 2019). Hypertens Res. 2019; 42: 1235-1481.

2. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet. 2010; 375: 895-905.

3. Rothwell PM, Howard SC, Dolan E, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol. 2010; 9: 469-480.

4. Kawai T, Ohishi M, Kamide K, et al. The impact of visit-to-visit variability in blood pressure on renal function. Hypertens Res. 2012; 35: 239-243.

5. Hata J, Arima H, Rothwell PM, et al. Effects ofvisit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with type 2 diabetes mellitus: the ADVANCE trial. Circulation. 2013; 128: 1325-1334.

6. McMullan CJ, Bakris GL, Phillips RA, Forman JP. Association of BP variability with mortality among African Americans with CKD. Clin J Am Soc Nephrol. 2013; 8: 731-738.

7. Rakugi H, Oghara T, Saruta T, et al. Preferable effects of olmesartan/calcium channel blocker to olmesartan/diuretic on blood pressure variability in very elderly hypertension: cQLM study subanalysis. J Hypertens. 2015; 33: 2165-2172.

8. Muntner P, Whittle J, Lynch AI, et al. Visit-to-visit variability of blood pressure and coronary heart disease, stroke, heart failure, and mortality: a cohort study. Ann Intern Med. 2015; 163: 329-338.

9. Nuyujukian DS, Koska J, Bahn G, Reaven PD, Zhou JJ. Blood pressure variability and risk of heart failure in ACCORD and the VADT. Diabetes Care. 2020; 43: 1471-1478.

10. Appiah KO, Nath M, Manning L, et al. Increasing blood pressure variability predicts poor functional outcome following acute stroke. J Stroke Cerebrovasc Dis. 2021; 30: 105466.

11. Zhang Y, Bie L, Li M, et al. Visit-to-visit blood pressure variability is associated with arterial stiffness in Chinese adults: a prospective analysis. J Clin Hypertens. 2021; 23: 802-812.

12. 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.

13. Shimbo D, Shea S, McClelland RL, et al. 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.

14. Zhou TL, Henry RMA, Stehouwer CDA, van Slooten TT, Reesink KD, Kroon AA. Blood pressure variability, arterial stiffness, and arterial remodeling. Hypertension. 2018; 72: 1002-1010.

15. Miyauchi S, Nagai M, Dote K, et al. Visit-to-visit blood pressure variability and arterial stiffness: which came first: the chicken or the egg? Curr Pharm Des. 2019; 25: 685-692.

16. Kikuya M, Asayama K, Ohkubo T. Blood pressure variability and arterial stiffness parameters derived from ambulatory blood pressure monitoring. Kardiol Pol. 2019; 77: 509-514.

17. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, Seino Y, Nanjo K, Tajima N, et al. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig. 2010; 1: 212-228.

18. Teramoto T, Sasaki J, Ueshima H, et al. JAS Committee for Epidemiology and Clinical Management of Atherosclerosis. Diagnostic criteria for dyslipidemia. Executive summary of Japanese Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. J Atheroscler Thromb. 2007; 14: 155-158.

19. Okin PM, Devereux RB, Jern S, et al. LIFE Study Investigators. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. JAMA. 2004; 292: 2343-2349.

20. Hawkins NM, Wang D, McMurray JJ, et al. CHARM Investigators and Committees. Prevalence and prognostic implications of
electrocardiographic left ventricular hypertrophy in heart failure: evidence from the CHARM programme. Heart. 2007; 93: 59-64.

21. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J. 1949; 37: 161-186.

22. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage duration product. J Am Coll Cardiol. 1992; 20: 1180-1186.

23. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of increased left ventricular mass by simple voltage duration products. J Am Coll Cardiol. 1995; 25: 417-423.

24. Dahlöf B, Devereux RB, Kjeldsen SE, et al. LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE); a randomised trial against atenolol. Lancet. 2002; 359: 995-1003.

25. Matsuo S, Imai E, Horio M, et al. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009; 53: 982-992.

26. Okin PM, Devereux RB, Jern S, Julius S, Kjeldsen SE, Dahlöf B. Relation of echocardiographic left ventricular mass and hypertrophy to persistent electrocardiographic left ventricular hypertrophy in hypertensive patients: the LIFE study. Am J Hypertens. 2001; 14: 775-782.

27. 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.

28. Hara A, Thijs L, Asayama K, Jacobs L, Wang JG, Staessen JA. Randomised double-blind comparison of placebo and active drugs for effects on risks associated with blood pressure variability in the Systolic Hypertension in Europe trial. PLoS One. 2014; 9: e103169.

29. Chang TI, Reboussin DM, Chertow GM, et al. Visit-to-visit office blood pressure variability and cardiovascular outcomes in SPRINT (Systolic Blood Pressure Intervention Trial). Hypertension. 2017; 70: 751-758.

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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