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Impact of Variability in Blood Pressure and Heart Rate on Beta-Blocker Adherence

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ABSTRACT

Adherence to antihypertensive medications is essential for blood pressure (BP) control, influencing long-term outcomes in hypertensive patients. This study examines the association between visit-to-visit variability in BP and heart rate (HR) and its effect on adherence to beta-blocker therapy among outpatients. Conducted across 160 hospitals in China from January 1, 2011, to December 31, 2011, this study included 9225 hypertensive outpatients prescribed metoprolol succinate. BP and HR variability were assessed over three visits (baseline, 1-month, and 2-month follow-up) using standard deviation (SD) and mean-independent parameters. Nonadherence was defined as medication discontinuation or treatment regimen changes by the 2-month follow-up. Among the 9037 patients analyzed, the mean age was 58.85 years (±12.54), and 52.9% were male. Visit-to-visit variability in the rate–pressure product (RPP; SBP×HR) was a significant predictor of nonadherence, with an odds ratio (OR) of 1.26 (95% confidence interval [CI]: 1.04–1.53, $p < 0.05$) for the top-decile SD of RPP, independent of mean RPP. Variability in diastolic blood pressure (DBP) and pulse pressure (PP) were also associated with nonadherence, with ORs of 1.65 (95% CI: 1.35–2.00, $p < 0.001$) for DBP and 1.66 (95% CI: 1.39–1.99, $p < 0.001$) for PP, independent of their mean values. Patients with fluctuations in PP or HR had a higher risk of nonadherence compared to those with consistent reductions in these measures. Visit-to-visit variability in RPP, DBP, and PP is a significant predictor of nonadherence to beta-blockers, regardless of mean levels. Addressing this variability is critical for improving adherence to antihypertensive treatments and optimizing patient outcomes.

1 | Introduction

According to the latest European Society of Hypertension (ESH) guidelines, beta-blockers are recommended as first-line agents in the management of hypertension [1]. Although this recommendation remains debated, beta-blockers continue to play a crucial role in the clinical treatment of hypertensive patients. As is well established, an elevated heart rate (HR) is an independent risk factor for hypertension [2]. In hypertensive patients, an increased resting HR leads to several adverse cardiovascular effects, including higher cardiac workload, increased myocardial oxygen demand, elevated arterial wall stress, reduced arterial distensibility, and an increased risk of coronary plaque disruption [2]. In this context, beta-blockers are the preferred first-line choice for reducing cardiovascular risk associated with elevated HR, particularly in hypertensive patients with high resting HRs.

A previous study found that different classes of antihypertensive medications can influence visit-to-visit variability in blood pressure (BP). Specifically, patients treated with beta-blockers and calcium channel blockers showed the lowest systolic blood pressure (SBP) variability following treatment initiation [3]. Visit-

to-visit BP variability is a key factor in assessing the effectiveness of antihypertensive therapy. Not only does it impact the efficacy of blood-pressure-lowering treatments, but it may also be linked to patient adherence or compliance [4–6]. Poor medication adherence has been recognized as a predictor of increased long-term cardiovascular events [7–9]. Despite its importance, there are few studies investigating how visit-to-visit BP variability affects adherence to antihypertensive therapy.

Additionally, HR serves as a valuable marker of adherence to beta-blocker treatment in hypertension [10]. However, previous studies have provided limited insights into the combined effects of BP and HR variability on beta-blocker adherence. The aim of our study was to assess the joint impact of visit-to-visit variability in BP and HR on adherence to beta-blocker therapy.

2 | Methods

2.1 | Multicenter Cohort Study

We conducted a *post hoc* analysis using data from a prospective multicenter study involving 9225 outpatients receiving beta-blocker therapy at 160 hospitals across China between January and November 2011. After excluding 188 patients treated with metoprolol tartrate, the final analysis included 9037 patients who were prescribed metoprolol succinate. Sitting BP was measured at baseline, as well as at 1- and 2-month follow-up visits, using a mercury sphygmomanometer operated by trained physicians at each participating center. At baseline, we collected demographic information (age and sex), as well as clinical data, including systolic and diastolic blood pressure (DBP), pulse pressure (PP), resting HR, comorbidities, New York Heart Association (NYHA) classification, echocardiographic findings, and medication details. During follow-up, data on BP, HR, and medications were gathered through telephone interviews at 1-month and 2-month visits. Informed consent was obtained from all participants, and the study was approved by the Institutional Review Board of Beijing Anzhen Hospital, Capital Medical University.

2.2 | Antihypertensive Medication Adherence

Adherence to antihypertensive medication was assessed by a study clinician at both the 1-month and 2-month visits at each center. In addition, participants were contacted through telephone follow-ups, during which they were asked about their medication adherence. These included inquiries about whether they were taking the prescribed antihypertensive medications (e.g., drug name and dosage) and whether there had been any changes to their medication regimen since the baseline survey. If any changes had occurred, participants were asked to provide the names and dosages of any newly prescribed or adjusted medications. Although adherence status varied between the 1-month and 2-month visits, the primary focus of the study was on the impact of visit-to-visit variability on the final adherence status. Nonadherence to beta-blocker therapy was therefore defined as either discontinuation of the medication or any change to the medication regimen at the 2-month visit.

2.3 | Variability of BP and HR Across Visits

Visit-to-visit variability in BP and HR was quantified using several metrics, including the standard deviation (SD) and the coefficient of variation (CV), with the latter being the ratio of SD to the mean. Additionally, we assessed variability independent of the mean (VIM) using the formula: $\mathrm{VIM} = \frac{\mathrm{SD}}{\mathrm{mean}^{\chi}}$, where χ was derived through curve fitting [4]. We also employed average successive variability (ASV), defined as the average absolute difference between successive values, to capture variation in BP and HR that is less influenced by dynamic trends [11]. Furthermore, to evaluate the combined variability of BP and HR across visits, we calculated the rate-pressure product (RPP), which reflects the heart's workload by multiplying SBP by HR. Finally, to explore the potential impact of variability direction in BP and HR across the three visits on medication adherence, participants were classified into four groups based on their dynamic patterns over the baseline, 1-month, and 2-month visits: (1) continuously decreasing, (2) initially decreasing then increasing, (3) initially increasing then decreasing, and (4) continuously increasing.

2.4 | Covariates at Baseline

Data imputation was performed using the mice package in R software. After imputation, baseline continuous covariates were categorized into distinct groups as follows: age groups: < 34, 35–44, 45–54, 55–64, 65–74, and ≥ 75 years; BP categories: SBP < 120 mmHg and DBP < 80 mmHg, SBP 120–139 mmHg or DBP 80–89 mmHg, SBP 140–159 mmHg or DBP 90–99 mmHg, and SBP ≥ 160 mmHg or DBP ≥ 100 mmHg; HR: < 80 beats/min and ≥ 80 beats/min; left ventricular ejection fraction (LVEF): < 40%, 40%–49%, and ≥ 50%; NYHA classification of heart function: Class I, II, III, and IV. Comorbidities, including coronary heart disease (CHD), hyperlipidemia, diabetes, left ventricular hypertrophy (LVH), atrioventricular block, tachyarrhythmia, stroke or transient ischemic attack, congestive heart failure, and renal insufficiency, were categorized as either "Yes" or "No."

2.5 | Statistical Analysis

Visit-to-visit variability in BP and HR metrics—specifically SD, CV, VIM, and ASV—were categorized into deciles based on their distribution within the study population. We used repeated measures in a general linear model to analyze trends in the variation of mean SBP, DBP, HR, and RPP across the three visits. Logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between visit-to-visit variability metrics and medication adherence. Mean values of SBP, DBP, PP, and mean RPP were included as covariates for adjustment, with the lowest deciles serving as the reference group. For the analysis of variability patterns or directions and medication adherence, the "continuously decreasing" pattern was used as the reference group. A sensitivity analysis was performed on a subset of 8796 patients, excluding 221 patients receiving combination therapy with bisoprolol, 7 patients on sotalol hydrochloride, and 13 patients on carvedilol. Statistical significance was defined as a p value of < 0.05. All statistical analyses were conducted using R version 4.3.3 and SPSS version 22.

3 | Results

A total of 9037 outpatients receiving long-acting beta-blocker therapy (metoprolol succinate) were included in the study. The mean age was 58.85 ± 12.54 years, and 52.9% of the participants were male. Among them, 78.2% were aged 45 to 74 years. The mean SBP was 152.24 ± 17.86 mmHg, and the mean DBP was 92.20 ± 13.28 mmHg. The average HR was 81.17 ± 10.51 beats per minute. The main comorbidities included hyperlipidemia in 1825 participants (20.2%), CHD in 1216 (13.5%), diabetes in 904 (10.0%), LVH in 653 (7.2%), and tachyarrhythmia in 508 (5.6%). Regarding NYHA classification, 33.3%, 15.1%, 1.8%, and 0.4% of participants were classified as NYHA class I, class II, class III, and class IV, respectively (eTable 1).

3.1 | Dynamic Trends in BP and HR Across Visits

We observed significant decreasing trends in both BP and HR across various subgroups based on baseline characteristics, including age, genders, BP categories, HR categories (< 80 beats/min vs. ≥80 beats/min), NYHA heart functional classes, LVEF categories (< 40%, 40–49%, and ≥ 50%), and the presence or absence of comorbidities. Discrepancies in measurements across the three visits (baseline, 1-month, and 2-month) were statistically significant ($p < 0.001$) for most subgroups. However, the trends in SBP among participants with baseline SBP between 120 and 139 mmHg or DBP between 80 and 89 mmHg were not significant ($p = 0.13$). Similarly, DBP trends in participants with baseline NYHA class IV did not show significant changes ($p = 0.40$).

A notable finding was that both SBP and DBP significantly decreased at the 1-month visit, but no further significant changes were observed at the 2-month visit. In contrast, HR showed a consistent downward trend across all three visits, with significant reduction observed between both the baseline and 1-month visits, as well as between the 1-month and 2-month visits (Table 1).

3.2 | Effect of Visit-to-Visit Variability in BP and HR on Adherence to Beta-Blocker Therapy

Visit-to-visit variability in DBP and PP was a significant predictor of beta-blocker nonadherence. Specifically, for SD of DBP, individuals in the highest decile had an OR of 1.65 (95% CI: 1.35–2.00, $p < 0.001$), and for SD of PP, the OR was 1.66 (95% CI: 1.39–1.99, $p < 0.001$) (see Table 2 and Figure 1). Similar associations were observed for other measures of variability, including ASV, CV, and VIM. For DBP, the OR for ASV was 1.90 (95% CI: 1.58–2.30, $p < 0.001$), for CV it was 1.40 (95% CI: 1.16–1.69, $p < 0.01$), and for VIM it was 1.59 (95% CI: 1.31–1.92, $p < 0.001$). For PP, the OR for ASV was 2.40 (95% CI: 1.98–2.92, $p < 0.001$), for CV it was 1.69 (95% CI: 1.40–2.05, $p < 0.001$), and for VIM it was 1.60 (95% CI: 1.32–1.93, $p < 0.001$) (see Table 2, Figure 2, and eFigures 1 and 2). These associations remained statistically significant after adjusting for mean DBP or mean PP.

In contrast, visit-to-visit variability in SBP did not significantly predict beta-blocker nonadherence. However, when SBP and HR were combined into a single metric of RPP, visit-to-visit variability in RPP emerged as a predictor of beta-blocker nonadherence after adjusting for mean RPP. Specifically, for SD of RPP, the individuals in the top decile had an OR of 1.26 (95% CI: 1.04–1.53, $p < 0.05$). For ASV of RPP, the OR was 1.48 (95% CI: 1.21–1.80, $p < 0.001$) (see Table 2, Figures 1 and 2). However, no statistically significant associations were found for CV or VIM for RPP in the highest decile (see Table 2, eFigures 1 and 2).

Patients exhibiting an "initially decreasing then increasing" SBP pattern demonstrated significantly higher nonadherence to beta-blockers compared to those with a "continuously decreasing" SBP pattern, with an OR of 1.19 (95% CI: 1.08–1.30, $p < 0.001$), after adjusting for mean SBP. Similarly, patients with certain PP patterns, including "initially decreasing then increasing," "initially increasing then decreasing," or "continuously increasing," also had a higher risk of nonadherence to beta-blockers. The ORs for these patterns were as follows: OR = 2.03 (95% CI: 1.81–2.26, $p < 0.001$) for "initially decreasing then increasing," OR = 1.37 (95% CI: 1.23–1.54, $p < 0.001$) for "initially increasing then decreasing," and OR = 1.64 (95% CI: 1.40–1.93, $p < 0.001$) for "continuously increasing," after adjusting for mean PP. In contrast, compared to patients with a "continuously decreasing" DBP pattern, those with a "continuously increasing" DBP pattern showed higher adherence to beta-blockers, with an OR of 0.81 (95% CI: 0.71–0.92, $p < 0.01$), after adjusting for mean DBP. Additionally, compared to participants with a "continuously deceasing" HR pattern, those with HR pattern of "initially decreasing then increasing" or "initially increasing then decreasing" showed a higher risk of nonadherence to beta-blockers. The ORs for these HR patterns were as follows: OR = 13.28 (95% CI: 8.14–21.68, $p < 0.001$) for "initially decreasing then increasing" and OR = 2.72 (95% CI: 1.69–4.35, $p < 0.001$) for "initially increasing then decreasing," after adjusting for mean HR (eFigure 3).

3.3 | Sensitivity Analysis

We performed a sensitivity analysis after excluding 241 patients receiving combination therapy with bisoprolol, sotalol hydrochloride, or carvedilol. The results were similar to the main findings above (data not shown).

4 | Discussion

We found that visit-to-visit variability in DBP, PP, and the product of SBP and HR is associated with nonadherence to beta-blocker therapy, independent of mean BP or mean product of BP and HR. Additionally, dynamic patterns of SBP, PP, and HR across three visits also predict nonadherence to beta-blocker therapy. Specifically, compared to outpatients receiving metoprolol succinate whose BP or HR consistently decrease, patients with fluctuating BP or HR (e.g., SBP initially decreasing then increasing; PP fluctuating between increasing and decreasing, or continuously increasing; HR fluctuating between increasing and decreasing) are at higher risk of nonadherence to beta-blockers.

Some guidelines have downgraded beta-blockers from their previous position as first-line treatment for hypertension. However, this shift may not be entirely supported by available evidence, which indicates that hypertension is frequently accompanied by activation of the sympathetic nervous system throughout

TABLE 1 | Blood pressure levels, heart rate, and rate-pressure product at baseline, 1-month visit, and 2-month visit according to baseline characteristics in hypertensive outpatients treated with beta-blockers.

	Metoprolol succinate											
Baseline characteristics	**SBP/DBP at baseline**	**SBP/DBP at 1-month visit**	**SBP/DBP at 2-month visit**	P_{trend}	**HR at baseline**	**HR at 1-month visit**	**HR at 2-month visit**	P_{trend}	**RPP at baseline**	**RPP at 1-month visit**	**RPP at 2-month visit**	P_{trend}
Age group (years)												
18–34	149.45 ± 20.87	130.62 ± 15.91	129.53 ± 15.11	<0.001	84.73 ± 12.69	78.29 ± 11.96	72.99 ± 11.87	<0.001	12671.81 ± 2616.38	10218.42 ± 1980.92	9446.61 ± 1871.17	<0.001
	96.00 ± 14.93	81.43 ± 10.08	80.62 ± 9.76	<0.001								
35–44	152.30 ± 18.15	129.33 ± 15.74	128.68 ± 14.97	<0.001	82.84 ± 11.18	76.57 ± 10.48	71.23 ± 10.57	<0.001	12646.65 ± 2461.99	9903.39 ± 1822.49	9156.80 ± 1687.23	<0.001
	95.66 ± 13.45	81.56 ± 10.82	80.70 ± 10.44	<0.001								
45–54	153.05 ± 17.84	129.99 ± 15.93	129.33 ± 15.82	<0.001	82.24 ± 10.46	76.20 ± 10.17	70.77 ± 10.29	<0.001	12620.62 ± 2404.42	9906.52 ± 1820.62	9154.46 ± 1774.55	<0.001
	94.79 ± 13.11	81.18 ± 10.99	81.10 ± 10.85	<0.001								
55–64	151.94 ± 17.38	129.85 ± 15.99	129.14 ± 15.67	<0.001	80.76 ± 9.86	74.49 ± 9.70	69.12 ± 9.78	<0.001	12293.93 ± 2209.13	9673.90 ± 1748.81	8927.16 ± 1681.12	<0.001
	92.56 ± 12.93	80.90 ± 11.19	80.97 ± 10.98	<0.001								
65–74	152.22 ± 17.60	129.74 ± 15.77	129.15 ± 15.37	<0.001	80.14 ± 10.38	74.00 ± 10.24	68.36 ± 10.22	<0.001	12230.20 ± 2321.08	9598.56 ± 1755.94	8826.29 ± 1681.13	<0.001
	89.78 ± 12.62	80.54 ± 10.79	81.09 ± 10.72	<0.001								
75–99	152.48 ± 18.43	129.32 ± 15.61	129.01 ± 15.27	<0.001	79.86 ± 10.60	73.72 ± 10.17	67.97 ± 10.41	<0.001	12209.77 ± 2359.48	9540.04 ± 1815.48	8769.51 ± 1723.93	<0.001
	86.94 ± 12.89	79.80 ± 10.73	80.58 ± 10.56	<0.001								
Gender												
Female	152.06 ± 17.68	129.64 ± 15.92	128.86 ± 15.60	<0.001	80.97 ± 10.40	74.76 ± 10.17	69.28 ± 10.17	<0.001	12335.12 ± 2292.63	9688.60 ± 1760.06	8919.66 ± 1664.33	<0.001
	91.21 ± 12.76	80.53 ± 10.85	80.65 ± 10.77	<0.001								
Male	152.39 ± 18.01	129.91 ± 15.80	129.40 ± 15.40	<0.001	81.35 ± 10.61	75.20 ± 10.28	69.71 ± 10.42	<0.001	12429.80 ± 2384.15	9772.45 ± 1825.56	9024.39 ± 1768.88	<0.001
	93.08 ± 13.67	81.12 ± 10.99	81.24 ± 10.72	<0.001								
SBP/DBP (mmHg)												
<120 and <80	108.39 ± 6.84	131.43 ± 15.51	129.86 ± 14.57	<0.001	76.99 ± 13.55	70.44 ± 11.73	64.99 ± 12.19	<0.001	8337.45 ± 1501.96	9283.22 ± 2043.05	8461.22 ± 1983.19	<0.001
	68.16 ± 5.48	79.46 ± 10.56	79.57 ± 10.20	<0.001								
120–139 or 80–89	129.80 ± 5.72	128.80 ± 15.32	128.65 ± 15.04	0.13	77.77 ± 10.04	71.70 ± 9.70	65.97 ± 9.64	<0.001	10097.13 ± 1394.26	9231.23 ± 1629.86	8477.65 ± 1524.81	<0.001
	82.04 ± 2.89	80.39 ± 10.77	80.83 ± 10.92	0.001								
140–159 or 90–99	146.57 ± 5.36	130.24 ± 16.03	129.18 ± 15.67	<0.001	80.55 ± 9.18	74.39 ± 9.10	68.85 ± 9.13	<0.001	11804.98 ± 1410.77	9688.88 ± 1697.12	8893.61 ± 1612.64	<0.001
	92.37 ± 2.81	80.64 ± 10.77	80.91 ± 10.46	<0.001								
≥ 160 or ≥ 100	172.60 ± 14.20	130.34 ± 16.03	129.14 ± 15.56	<0.001	84.36 ± 11.38	78.09 ± 10.97	72.88 ± 11.06	<0.001	14568.94 ± 2393.71	10180.12 ± 1936.55	9417.54 ± 1877.07	<0.001
	109.49 ± 11.47	81.59 ± 11.15	81.45 ± 10.88	<0.001								

(Continues)

TABLE 1 | (Continued)

Baseline characteristics	Metoprolol succinate											
	SBP/DBP at baseline	SBP/DBP at 1-month visit	SBP/DBP at 2-month visit	P_{trend}	HR at baseline	HR at 1-month visit	HR at 2-month visit	P_{trend}	RPP at baseline	RPP at 1-month visit	RPP at 2-month visit	P_{trend}
HR (beats/min)												
<80	149.51 ± 17.75	129.81 ± 15.91	129.41 ± 15.53	<0.001	71.93 ± 5.20	66.21 ± 5.69	60.67 ± 5.59	<0.001	10757.77 ± 1513.21	8594.39 ± 1287.25	7851.39 ± 1193.52	<0.001
	89.73 ± 13.05	80.81 ± 10.93	81.19 ± 10.72	<0.001								
≥ 80	154.22 ± 17.67	129.76 ± 15.81	128.95 ± 15.47	<0.001	87.89 ± 8.00	81.38 ± 7.75	75.93 ± 7.92	<0.001	13569.86 ± 2116.25	10561.76 ± 1653.31	9793.03 ± 1579.17	<0.001
	94.00 ± 13.16	80.87 ± 10.93	80.80 ± 10.77	<0.001								
Functional class												
NYHA I	152.07 ± 17.79	129.19 ± 15.20	128.27 ± 14.84	<0.001	81.02 ± 10.21	74.77 ± 10.10	69.56 ± 10.21	<0.001	12352.27 ± 2316.77	9663.56 ± 1767.91	8923.11 ± 1684.10	<0.001
	91.83 ± 12.93	80.57 ± 10.74	80.63 ± 10.48	<0.001								
NYHA II	153.61 ± 19.28	130.40 ± 16.51	129.85 ± 16.43	<0.001	83.39 ± 11.51	77.14 ± 11.20	71.71 ± 11.22	<0.001	12860.23 ± 2690.21	10057.63 ± 1946.62	9315.04 ± 1920.01	<0.001
	92.97 ± 14.99	81.05 ± 11.12	81.00 ± 10.77	<0.001								
NYHA III	152.69 ± 22.66	131.59 ± 15.93	129.73 ± 14.60	<0.001	83.28 ± 15.31	75.93 ± 13.77	70.74 ± 13.95	<0.001	12710.36 ± 2958.04	9973.81 ± 2090.80	9165.52 ± 2030.92	<0.001
	90.60 ± 15.92	80.88 ± 10.37	81.36 ± 10.38	<0.001								
NYHA IV	144.51 ± 24.15	127.43 ± 16.65	125.54 ± 13.29	<0.001	84.22 ± 15.54	77.22 ± 15.95	71.00 ± 15.38	<0.001	12300.35 ± 3557.41	9847.11 ± 2528.57	8970.46 ± 2486.22	<0.001
	85.27 ± 19.31	81.68 ± 11.14	81.89 ± 10.56	0.40								
LVEF (%)												
<40	151.02 ± 18.95	129.29 ± 15.08	129.79 ± 15.48	<0.001	82.63 ± 10.12	76.86 ± 10.12	71.70 ± 10.23	<0.001	12531.05 ± 2458.26	9934.44 ± 1731.36	9301.84 ± 1709.35	<0.001
	92.56 ± 13.94	79.76 ± 10.90	80.10 ± 10.74	<0.001								
≥ 40 and <50	151.26 ± 18.82	130.53 ± 16.07	129.64 ± 15.97	<0.001	82.85 ± 11.57	76.82 ± 11.23	71.53 ± 11.42	<0.001	12568.01 ± 2559.22	10033.01 ± 1968.91	9269.04 ± 1867.47	<0.001
	92.63 ± 14.65	80.73 ± 11.03	80.66 ± 10.76	<0.001								
≥ 50	152.36 ± 17.73	129.79 ± 15.90	129.08 ± 15.48	<0.001	80.99 ± 10.47	74.78 ± 10.17	69.26 ± 10.23	<0.001	12367.13 ± 2323.12	9705.86 ± 1789.65	8939.73 ± 1711.71	<0.001
	92.16 ± 13.17	80.92 ± 10.93	81.03 ± 10.75	<0.001								
Comorbidities												
No	151.16 ± 17.26	129.67 ± 15.85	129.34 ± 15.52	<0.001	80.70 ± 9.91	74.57 ± 9.77	68.99 ± 9.79	<0.001	12227.05 ± 2240.32	9667.49 ± 1725.42	8921.09 ± 1654.95	<0.001
	92.05 ± 12.72	81.05 ± 11.01	81.19 ± 10.94	<0.001								
Yes	153.47 ± 18.44	129.91 ± 15.86	128.92 ± 15.47	<0.001	81.70 ± 11.14	75.48 ± 10.71	70.09 ± 10.84	<0.001	12567.13 ± 2441.07	9808.29 ± 1870.04	9037.17 ± 1792.45	<0.001
	92.37 ± 13.90	80.61 ± 10.84	80.69 ± 10.52	<0.001								

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; RPP, rate-pressure product; SBP, systolic blood pressure.

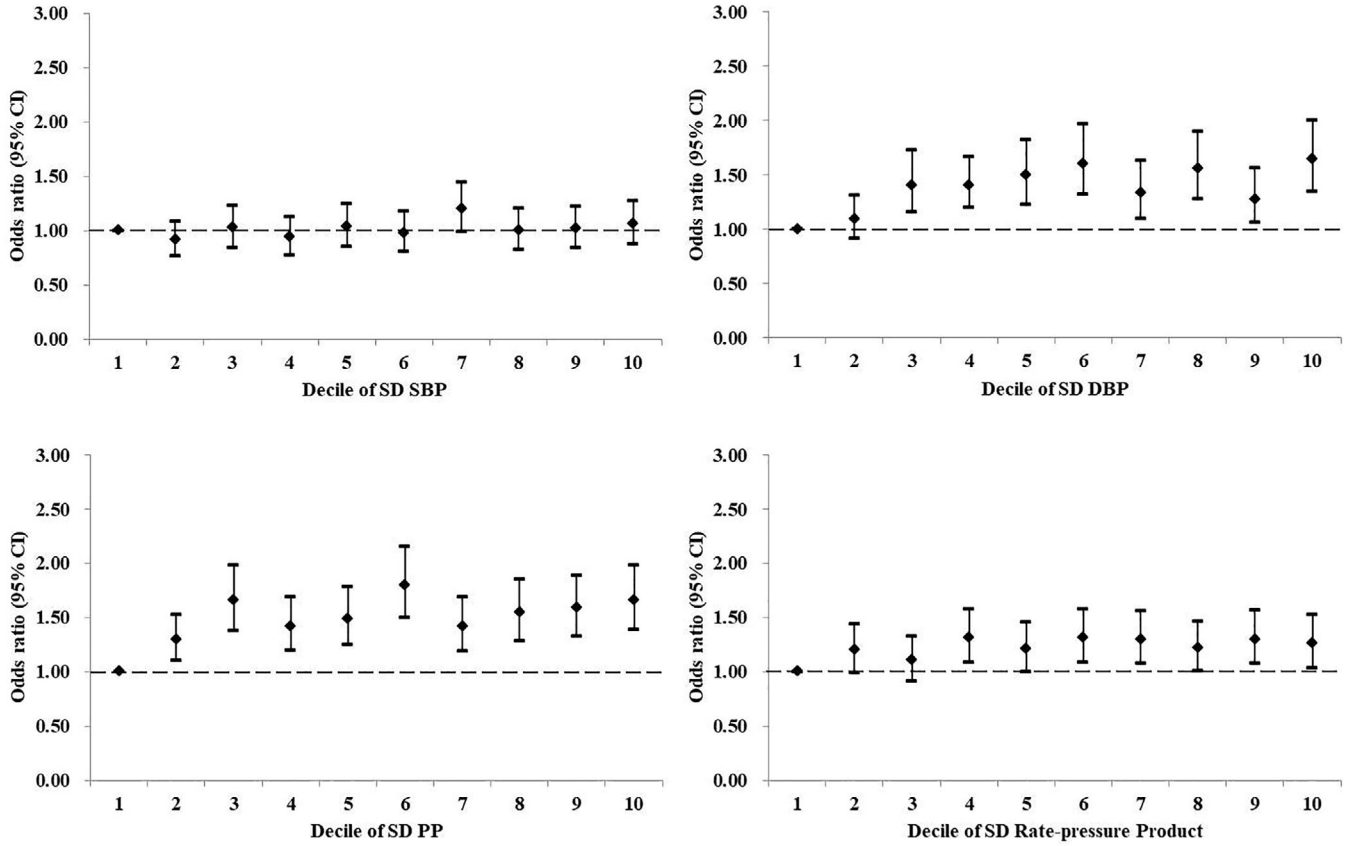

FIGURE 1 | Odds ratios for the risk of nonadherence to beta-blocker therapy by deciles of SD for SBP, DBP, PP, and RPP. DBP, diastolic blood pressure; PP, pulse pressure; RPP, rate-pressure product; SBP, systolic blood pressure; SD, standard deviation.

both its early and late stages, thereby making beta-blockers pathophysiologically appropriate for its management [12, 13]. Elevated resting HR values are common in hypertensive patients, especially in young or middle-aged individuals with mild to moderate hypertension [13, 14]. Moreover, elevated resting HR is associated with organ damage, increased cardiovascular morbidity, mortality and all-cause mortality in hypertensive patients [2, 15]. In terms of therapeutic intervention, despite the lack of direct evidence from randomized clinical trials, the ESC/ESH guidelines recommend that beta-blockers can be a favorable treatment option for hypertensive patients with resting HR values >80 beats/min. These guidelines acknowledge the clinical importance of reducing elevated HR in this group of patients to mitigate cardiac sympathetic overdrive and the related increase in cardiovascular risk [1, 16]. The results of our study show that beta-blocker can consistently and reliably reduce HR over a 2-month follow-up period from the initiation of therapy.

Nonadherence to antihypertensive treatment is a common issue in cardiovascular prevention and can significantly impact patient outcomes [8]. Previous studies have examined the relationship between medication adherence and visit-to-visit variability in BP. These studies suggest that low adherence to antihypertensive medications may contribute to a small proportion of visit-to-visit variability in SBP [17]. Furthermore, improving medication adherence has been shown to reduce visit-to-visit BP variability [6]. It is well recognized that BP varies over time within individuals [18]. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) provides robust evidence that visit-to-visit variability in BP is a significant predictor of cardiovascular outcomes in hypertensive patients, particularly among those with well-controlled BP but high variability [5]. Building on previous research exploring the impact of medication adherence on BP variability, the current study investigates how visit-to-visit BP variability affects adherence to antihypertensive therapy. The findings indicate that higher visit-to-visit variability in DBP and PP is associated with higher nonadherence to beta-blocker therapy, while no similar association was found with variability in SBP.

HR is a useful marker for assessing adherence to beta-blocker treatment in hypertension [10]. In our study, although neither SBP nor HR variability was associated with adherence to beta-blocker therapy, we discovered that higher visit-to-visit variability in RPP—the product of SBP and HR—was linked to a higher risk of nonadherence to beta-blocker therapy. The potential physiological mechanism underlying this observation can be explained as follows: short-term BP variability, including within-visit and 24-h ambulatory blood pressure monitoring (ABPM) variability in SBP [19], is influenced by factors such as sympathetic nervous system activity and baroreflex sensitivity [20]. In contrast, long-term BP variability, such as visit-to-visit SBP variability, is also associated with additional factors like arterial stiffness and aortic distensibility [21], which do not appear to be directly modulated by metoprolol [22]. Metoprolol, as a selective beta-1 blocker, directly reduces HR by blocking beta-1 receptors in the sinoatrial node, thereby lowering myocardial oxygen demand [23]. Additionally, metoprolol may reduce levels of markers of inflammation and

TABLE 2 | Blood pressure and heart rate parameters and their predictive values (Odds ratios and 95% confidence intervals for risk of nonadherence among hypertensive outpatients treated with beta-blockers in the top vs. bottom decile of each measure).

	Metoprolol succinate
Number of cases	9037
Mean (SD) baseline SBP	152.24 (17.86)
Mean (SD) baseline DBP	92.20 (13.28)
Mean (SD) baseline Heart rate	81.17 (10.51)
Mean (SD) baseline Rate-pressure product	12385.22 (2341.85)
Mean (SD) visit-to-visit variability in SBP	
SD	16.55 (10.27)
CV	12.12 (7.45)
VIM	1.17 (0.72)
ASV	16.38 (10.28)
Mean (SD) visit-to-visit variability in DBP	
SD	9.98 (7.03)
CV	11.91 (8.34)
VIM	3.48 (2.43)
ASV	10.38 (7.28)
Mean (SD) visit-to-visit variability in PP	
SD	13.06 (8.89)
CV	25.95 (19.08)
VIM	4.47 (3.03)
ASV	13.97 (10.09)
Mean (SD) visit-to-visit variability in Rate-pressure product	
SD	1930.03 (961.62)
CV	18.67 (8.59)
VIM	0.24 (0.11)
ASV	1887.50 (892.79)
OR (95% CI) for nonconderence adjusted for mean SBP	
SD SBP	1.06 (0.88–1.28)
CV SBP	1.01 (0.83–1.21)
VIM SBP	1.05 (0.87–1.26)
ASV SBP	1.39 (1.14–1.69)
OR (95% CI) for nonconderence adjusted for mean DBP	
SD DBP	1.65 (1.35–2.00)
CV DBP	1.40 (1.16–1.69)
VIM DBP	1.59 (1.31–1.92)
ASV DBP	1.90 (1.58–2.30)
OR (95% CI) for nonconderence adjusted for mean PP	
SD PP	1.66 (1.39–1.99)
CV PP	1.69 (1.40–2.05)
VIM PP	1.60 (1.32–1.93)
ASV PP	2.40 (1.98–2.92)
OR (95% CI) for nonconderence adjusted for mean Rate-pressure product	
SD Rate-pressure product	1.26 (1.04–1.53)
CV Rate-pressure product	1.07 (0.88–1.28)
VIM Rate-pressure product	1.07 (0.88–1.28)
ASV Rate-pressure product	1.48 (1.21–1.80)

Abbreviations: ASV, average successive variability; CI, confidence interval; CV, coefficient of variation; DBP, diastolic blood pressure; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation; VIM, variation independent of mean.

oxidative stress, including tumor necrosis factor-alpha (TNF-α) [24]. Evidence suggests that higher levels of TNF-α are associated with increased myocardial oxygen demand, possibly due to elevated systemic vascular resistance [25]. These findings suggest that higher variability in cardiac oxygen consumption may lower adherence to antihypertensive medication. Since RPP is an indicator of cardiac oxygen consumption, and beta-blockers reduce cardiac workload by lowering the RPP [26], these findings emphasize the importance of considering not only variability in HR and BP but also in cardiac oxygen consumption when using beta-blockers to manage hypertension. In clinical practice, beta-blockers are also used in patients with myocardial ischemia, such as those with stable angina, as they reduce HR and myocardial contractility, thereby decreasing myocardial oxygen consumption [27]. This further underscores the need to monitor and address variability in cardiac oxygen demand to optimize adherence and therapeutic outcomes in patients receiving beta-blocker therapy.

The current study primarily focused on metoprolol succinate. However, beta-blockers do not exhibit a class effect, meaning that similar benefits cannot be generalized across all beta-blockers [28]. It is therefore crucial to investigate how our findings extend to other selective beta-1 blockers, such as metoprolol tartrate, bisoprolol, and nebivolol. While metoprolol succinate and tartrate share the same active ingredient, their pharmacologic profiles differ significantly. Succinate provides a more sustained release, whereas tartrate requires multiple daily doses. Similarly, bisoprolol and nebivolol are also highly selective beta-1 blockers, with nebivolol offering additional vasodilatory effects through nitric oxide modulation [29]. These variations in pharmacokinetics and pharmacodynamic properties may lead to differing effects on BP variability, HR variability, and patient adherence. Further research directly comparing these agents is necessary to clarify their relative efficacy within the subclass of beta-blockers.

Previous studies have indicated that calcium-channel blockers reduce the risk of stroke more than would be expected based

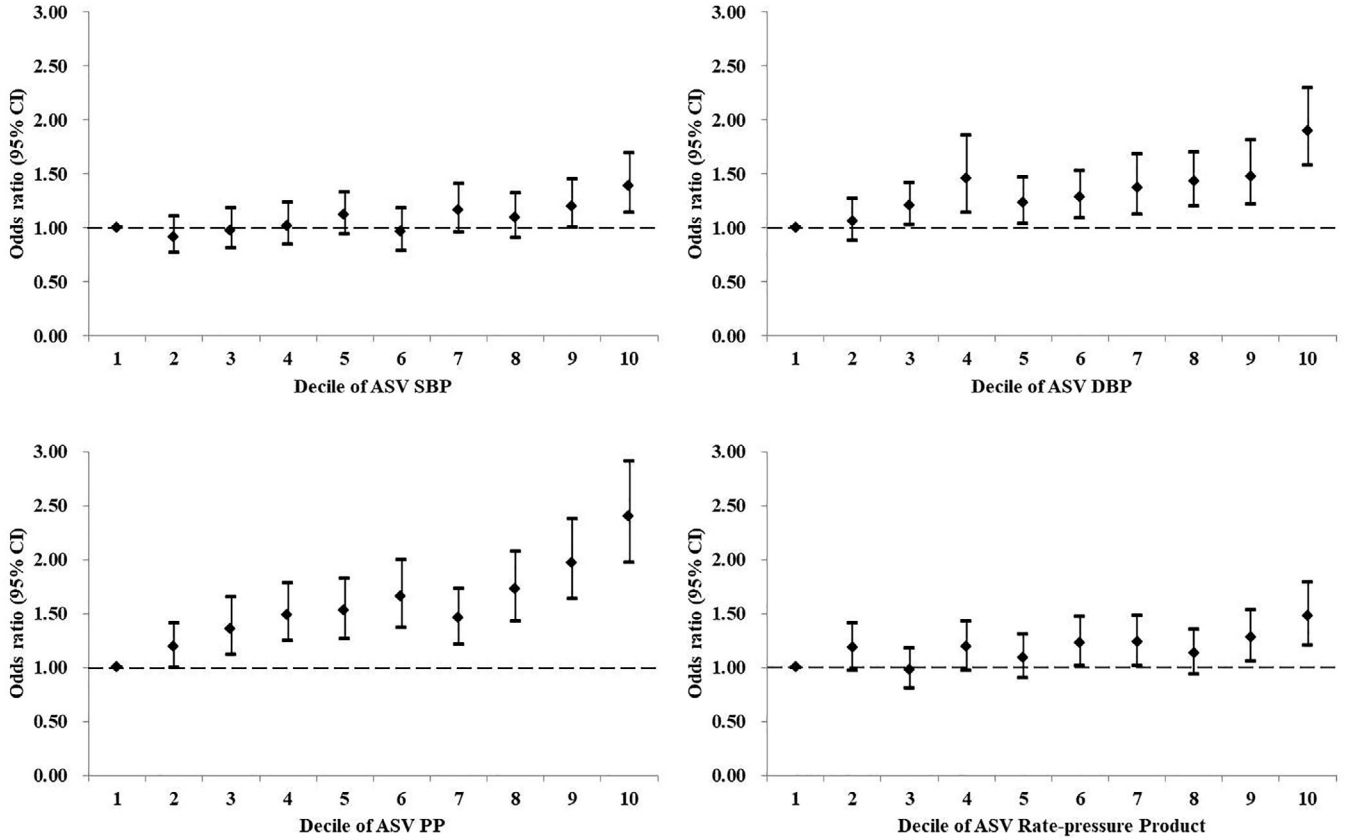

FIGURE 2 | Odds ratios for the risk of nonadherence to beta-blocker therapy by deciles of ASV for SBP, DBP, PP, and RPP. ASV, average successive variability; DBP, diastolic blood pressure; PP, pulse pressure; RPP, rate-pressure product; SBP, systolic blood pressure.

on mean BP alone, while beta-blockers are less effective than anticipated. This discrepancy may be due to the differential effects of these two classes of drugs on BP variability. Specifically, beta-blockers are associated with increased visit-to-visit variability in SBP compared to placebo, which may explain the observed disparity between stroke risk reduction and the outcomes predicted by mean BP levels alone [11]. Our study further suggests that the elevated visit-to-visit variability associated with beta-blocker therapy may negatively affect patient adherence and contribute to adverse cardiovascular outcomes. Given the reduced role of beta-blockers in hypertension management, we recommend that blood-pressure-lowering medications should focus on reducing mean BP without increasing visit-to-visit variability, in order to enhance patient adherence and reduce cardiovascular risk. Ideally, these medications should minimize both mean BP and variability, with particular attention to the effects of beta-blockers.

One main limitation of the present study is the use of self-reported medication adherence at the 1-month and 2-month follow-ups. However, we believe that self-reported data are appropriate for this investigation for several reasons. First, despite decades of research on medication adherence, no gold standard exists for its assessment [30]. Second, self-reported instruments are the most widely used method for evaluating medication adherence [31]. Compared to objective or direct measures, self-reported methods are more feasible for large populations, nonclinical settings, and community-based studies, requiring fewer resources [30]. A second limitation is the lack of data on socio-economic factors that could influence medication adherence, particularly in low- and middle-income countries [31]. These factors warrant further investigation in future research. Additionally, the potential side effects of beta-blockers, such as fatigue, dizziness, bradycardia, depression, and sexual dysfunction [32–34], which may contribute to nonadherence, were not addressed in this study. Since these side effects can lead patients to reduce or discontinue their medication, investigating how these factors affect treatment efficacy and overall health remains an important question to be addressed in future research. Lastly, considering that medication adherence is a dynamic process that evolves over time, particularly with prolonged treatment, a third limitation is that we assessed adherence at 2 months. Therefore, the results regarding long-term adherence still require further assessment.

5 | Conclusions

This study assesses short-term adherence to beta-blockers and suggests that physicians should take into account visit-to-visit variability in DBP, PP, and RPP (calculated by multiplying SBP by HR), as factors influencing adherence to beta-blocker therapy in hypertensive outpatients.

Author Contributors

Shi-Wei Yang and Yan Li developed the hypothesis. Jia-Yin Sun, Qian-Yun Guo, Hong-Ya Han, De-An Jia, Zhi-Ming Zhou, Zhi-Jian Wang, Ying-Xin Zhao, Yu-Jie Zhou, and Shi-Wei Yang

participated in the multicenter study and collected the data. Shi-Wei Yang provided guidance on data analysis, supervised all analyses, and reviewed and commented on the drafts. Yan Li conducted the analyses and drafted the manuscript.

Ethics Statement

This study was approved by the ethics committee of Beijing Anzhen Hospital of Capital Medical University.

Consent

All participants provided informed consent to participate in the study before enrollment.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting this article were provided by Beijing Anzhen Hospital, Capital Medical University. Access to these data can be granted upon request to the corresponding author, subject to approval from Beijing Anzhen Hospital.

Permission to Reproduce Material From Other Sources

None.

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