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ORIGINAL RESEARCH

Mediation of Time-Related Blood Pressure Variability on Intensive Blood Pressure Lowering and Functional Outcomes Post Endovascular Therapy: A Post Hoc Analysis of the OPTIMAL-BP Trial

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BACKGROUND: We investigated whether the association between blood pressure (BP) management in patients with successful reperfusion following endovascular therapy (EVT) and functional outcomes is mediated by BP variability parameters.

METHODS AND RESULTS: This is a post hoc analysis of the OPTIMAL-BP (Outcome in Patients Treated With Intra-Arterial Thrombectomy-Optimal Blood Pressure Control) trial, conducted at 19 centers in South Korea. The primary outcome was the 90-day functional outcome, assessed using the modified Rankin Scale. Multivariable logistic regression analysis was conducted for the association between BP variability and outcomes including 90-day modified Rankin Scale score, symptomatic intracranial hemorrhage, and final infarction volume. Mediation analysis was performed to evaluate the causal inference whether the relationship between intensive BP management and the 90-day modified Rankin Scale scoreis mediated by 24-hour BP variability parameters (time rate [TR], SD, coefficient of variation, and variability independent of the mean). Among various BP variability parameters, higher TR was associated with an unfavorable ordinal shift of the 90-day modified Rankin Scale score (adjusted odds ratio [aOR], 1.17 [95% CI, 1.04–1.32], P=0.007) and an increase in final infarction volume (β coefficient, 21.24 [95% CI, 3.99–38.48], P=0.016), but did not increase the risk of symptomatic intracranial hemorrhage. TR fully mediated the association between intensive BP management and functional outcomes. The proportion of the association explained by TR was 40.93%.

CONCLUSIONS: TR mediated the relationship between intensive BP management and poor functional outcome in successfully reperfused patients with ischemic stroke by contributing to an increase in infarct volume. Efforts to modulate TR after EVT may be helpful in improving clinical outcomes.

Key Words: blood pressure ■ cerebral infarction ■ endovascular therapy ■ time rate ■ variability

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CLINICAL PERSPECTIVE

What Is New?

- Time rate acted as a mediator between blood pressure management strategy and functional outcomes in successfully reperfused patients with ischemic stroke by influencing infarct volume growth.

What Are the Clinical Implications?

- This study is the first to investigate the causal relationship between blood pressure variability and clinical outcomes, highlighting the need to consider time-related blood pressure variability modulation strategies in future blood pressure management research.

Nonstandard Abbreviations and Acronyms

BPV	blood pressure variability
EVT	endovascular therapy
TR	time rate
VIM	variation independent of the mean

Recent studies have revealed that intensive blood pressure (BP) lowering during the first 24 hours is associated with an increased risk of functional dependence in patients who have achieved successful reperfusion with endovascular therapy (EVT) for acute ischemic stroke with large vessel occlusion. Lowering systolic blood pressure (SBP) to <120 to 140 mm Hg resulted in worse clinical outcomes and did not reduce the risk of intraparenchymal hemorrhage compared with conventional BP management targeting levels <180 to 185 mm Hg.[1–4] A meta-analysis, including the 5 recent randomized controlled trials comparing different post-EVT BP targets, also concluded that aggressive BP reduction after successful EVT resulted in a decreased probability of achieving function independence.[5] A potential explanation for the lack of success of those randomized controlled clinical trials could be the failure to consider BP variability (BPV) during BP management.

The association between short-term BPV during the first 24 hours and functional outcomes in patients with stroke treated with EVT is well established.[6–8] As the reperfused oligemic brain tissue may be more vulnerable to even minor fluctuations in BP, the influence of BPV may be more prominent in successfully recanalized patients after EVT. Previous studies indicated that attempting to reduce mean BP using antihypertensive agents resulted in increased BPV, emphasizing the need for delicate protocols to achieve the goal of reducing both mean BP and BPV.[7,9]

However, it remains uncertain whether the relationship between high BPV and poor outcomes represents a causal relationship or if high BPV is merely a bystander or a consequence of humoral factors (renin-angiotensin-aldosterone system, nitric oxide, catecholamines, atrial natriuretic peptide), rheological factors (blood viscosity, arterial stiffness, endothelial dysfunction), and emotional factors (stress, anxiety, emotional reactivity, psychological distress) associated with poor outcomes.[10–12] Additionally, whether reducing BPV can directly improve clinical outcomes has not been adequately evaluated due to various reasons.[11] We hypothesized that 24-hour BPV mediates the relationship between intensive BP reduction following successful reperfusion post EVT and functional outcomes at 3 months. Using post hoc analysis of the OPTIMAL-BP (Outcome in Patients Treated With Intra-Arterial Thrombectomy-Optimal Blood Pressure Control) trial data, we aimed to determine whether BPV explains this causal relationship.

METHODS

This is a post hoc analysis of OPTIMAL-BP, a prospective multicenter, randomized, open label, blinded end point clinical trial. The data that support the findings of this study are available from the corresponding author upon reasonable request. The OPTIMAL-BP trial was conducted at 19 centers in South Korea from June 18, 2020, to November 29, 2022, comparing intensive (SBP <140 mm Hg) and conventional (SBP 140–180 mm Hg) BP management for functional outcomes in patients with successful reperfusion post EVT. Detailed methods and protocol of the study are described in the previous publication.[1,13] The OPTIMAL-BP trial included patients with acute large vessel occlusive stroke who underwent EVT and achieved successful reperfusion of the occluded artery, as determined by a modified Thrombolysis in Cerebral Infarction score of 2b or greater, and had elevated BP (SBP ≥140 mm Hg) confirmed by at least 2 measurements within a 2-minute interval within 2 hours of successful reperfusion. BP data were recorded for the first 24 hours from randomization. BP was initially measured at 15-minute intervals during the first hour and then hourly for the subsequent 23 hours. In cases where intravenous antihypertensive medication was used, BP was measured every 15 minutes for the first hour, every 30 minutes for the following 2 hours, and then hourly for the remaining hours. At each participating center, BP was measured using either the automated BP device (Omron HEM 7130) or an equivalent noninvasive automatic BP monitor certified

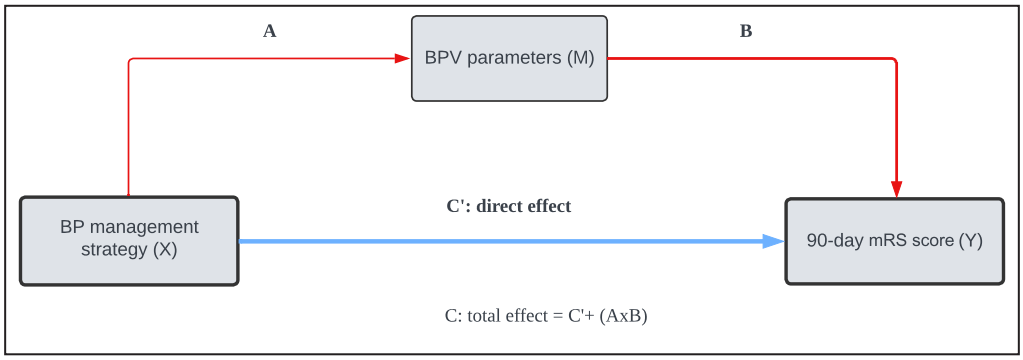

Figure 1. Hypothetical causal pathway model of intensive BP lowering impact on 90-day functional outcome post endovascular therapy mediated by BP variability parameters.
A, Step 2. Association between intensive BP reduction and BPV parameters. **B,** Step 3. Association between BPV parameters and 90-day functional outcome. **C,** Step 1. Association between intensive BP reduction and 90-day functional outcome. **C'**, direct effect and **(AxB)** indirect effect. X is the independent variable (BP management strategy), M the mediator variable (SBP TR), and Y the dependent variable (90-day mRS score: the ordinal shift across the range of mRS scores toward a worse outcome). BP indicates blood pressure; BPV, blood pressure variability; mRS, modified Rankin Scale; SBP, systolic blood pressure; and TR, time rate.

by the American Medical Device Association and the European Society of Hypertension, supported by grade A clinical study evidence. Local treatment protocols allowed the use of intravenous BP lowering medications to achieve and maintain the target SBP. Although nicardipine was the preferred choice, other drugs such as labetalol and hydralazine could be used at the discretion of the treating physician. The final infarct volume was measured using MRIcro software by an independent neuroradiologist, using diffusion-weighted images from brain magnetic resonance imaginbg (n=295) or computed tomography scans (n=5) conducted at 24 (±12) hours post EVT.

All participating hospitals in the OPTIMAL-BP trial received ethical approval from their respective institutional review boards, and the trial adhered to the principles of the Declaration of Helsinki. Informed consent was obtained from each participant or their legal representative before any study-related procedures. To ensure consistency across centers, a standardized informed consent protocol was implemented, outlining clear steps for explaining the study's purpose, risks, and benefits. The protocol was monitored for compliance, and any site-specific adaptations were approved by the coordinating IRB. For the post hoc analysis, we adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines, ensuring rigorous standards in the reporting of observational research.

BPV Parameters

Currently evaluated BPV parameters for SBP included time rate (TR), SD, coefficient of variation (calculated as SD divided by mean SBP), and variability independent of the mean (VIM) during the first 24 hours after randomization.

TR is defined as the first derivative of the SBP with respect to time within the selected time interval, which represents the rate of change of SBP over time. TR reflects the speed and direction of successive BP fluctuation over time. It considers the sequence and the slope of BP changes.[14–16] VIM is a nonlinear transformation of SD through designed to eliminate correlation with mean levels.[17] Data S1 and Figure S1 provide detailed explanations and calculation formulas for the BPV parameters.

Due to the skewed distribution, BPV parameters (TR, SD, coefficient of variation, VIM) were log-transformed to reduce skewness and kurtosis when used in the linear regression model.

Mediation Analysis

Mediation analysis was performed to evaluate the causal inference between BP management strategy and functional outcome at 3 months with each BPV parameter as a mediator of the relationship. Figure 1 illustrates the hypothetical causal pathway model of the impact of intensive BP lowering on the 90-day functional outcome post EVT, mediated by BPV parameters. The main outcome variable for the mediation analysis was the ordinal shift of 90-day modified Rankin Scale (mRS) score. Following the Baron and Kenny method, 4 pathways were evaluated to conduct the mediation analysis.[18,19] Step 1 assessed the association between intensive BP reduction following EVT and 90-day functional outcome (path C). Step 2 examined the association between intensive BP reduction and BPV parameters (path A). Step 3 assessed the association between BPV parameters and 90-day functional outcome (path B). The final step established the indirect effect (AB) by estimating the direct effect (path C').

The association of BP management strategy with BPV parameter was tested with linear regression model, and other associations were tested with ordinal logistic regression model with and without multivariable adjustment. The proportion for the causal relationship between intensive BP management and functional outcomes, mediated by BPV parameters, was derived by dividing the indirect effect by the total effect. The CI for the proportion of the effect mediated were tested using bootstrapping with 1000 replications.

Sensitivity Analysis

As part of the sensitivity analysis, mediation analysis was performed using logistic regression with generalized estimating equations to address variability across centers. To evaluate whether BPV parameters serve as mediators in the relationship between intensive BP reduction post EVT and functional outcomes, particularly among a subset of participants characterized by low BPV, we performed further sensitivity analysis. Given the observation that BPV decreased with a higher degree of reperfusion, we performed a sensitivity analysis on patients who achieved complete reperfusion, as indicated by a modified Thrombolysis in Cerebral Infarction score of 3. Moreover, considering that beta-blocking agents are associated with an increase in BPV compared with calcium channel blockers, we further performed an analysis that excluded patients who were administered intravenous beta blockers for acute BP management.

Statistical Analysis

For the comparison of baseline characteristics, the chi-square test or Fisher's exact test was used for categorical variables, and the independent *t* test or Mann–Whitney *U* test was used for continuous variables. Multivariable regression analysis was performed using clinically relevant adjustment variables, including age, sex, risk factors (hypertension, diabetes, and dyslipidemia), the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification, initial National Institutes of Health Stroke Scale score, infarction volume, degree of recanalization (modified Thrombolysis in Cerebral Infarction score), symptomatic intracranial hemorrhage, and mean SBP. These adjustments were made to estimate the odds ratio (OR) and 95% CI for the association between time-related BPV and various outcomes: the 90-day mRS score as an ordinal variable (analyzed using ordinal logistic regression), the 90-day mRS score 0 to 2, the occurrence of symptomatic intracranial hemorrhage (both analyzed using binary logistic regression), and final infarction volume (analyzed using linear regression). Missing data were excluded from the analysis. All statistical analyses were performed using Stata 13.0 software (Stata Corp, College Station, TX) and SAS version 9.4 (SAS institute Inc., Cary, NC). All tests were 2 sided and $P<0.05$ was considered significant.

RESULTS

Of the 306 patients enrolled in the OPTIMAL-BP trial, 300 patients were included in the analysis. We excluded 4 patients without functional outcome information, and 2 patients with incomplete baseline demographics (missing infarct volume data, Figure 2). The median age was 75.0 (66.0–82.0) and 179 (59.7%) were male. Intravenous antihypertensive medication was used in 141 (47%) patients, with the majority of them receiving nicardipine (133 patients, 94.3%). Demographics and baseline characteristics were statistically similar across both groups. Compared with the conventional management group, the intensive management group exhibited poorer functional outcomes at 90 days, with lower median mRS scores (3.0 [1.0–5.0] versus 2.0 [1.0–4.0], $P=0.01$) and a higher percentage of patients achieving mRS scores of 0 to 2 (39.4% versus 55.2%, $P=0.01$). Although initial SBP was similar, 24-hour mean SBP was significantly higher in patients receiving conventional BP management (137.9±13.6 versus 129.2±7.7, $P<0.01$). The number of BP measurements was significantly higher in patients receiving intensive BP management (36.0 [30.0–54.0] versus 25.0 [25.0–29.0], Table 1). Among various BPV parameters, only the 24-hour TR of SBP was significantly higher in the intensive BP management group (0.36 [0.24–0.51] versus 0.24 [0.19–0.32], $P<0.01$). There were no significant differences in SD, coefficient of variation, and VIM between the 2 groups.

In the multivariable analysis using the current data set, TR was significantly associated with an ordinal shift of 90-day mRS score, with higher TR associated with an unfavorable shift (adjusted OR [aOR], 1.17 [95% CI, 1.04–1.32], $P=0.007$). However, it was not significantly associated with achieving a 90-day mRS score of 0 to 2. High TR significantly increased the final infarction volume (β coefficient, 21.24 [95% CI, 3.99–38.48], $P=0.016$) but did not increase the risk of symptomatic intracranial hemorrhage (Table 2).

The result of the mediation analysis is presented in Table 3. The significant association between the intensive BP management and the ordinal shift of the mRS score was confirmed (step 1, path C). Intensive BP management was significantly associated with TR, with a beta coefficient of 0.38 (95% CI, 0.26–0.50, $P<0.001$, step2, path A). High TR significantly increased the likelihood of an unfavorable shift in the 90-day mRS score (adjusted common OR [acOR], 1.17 [95% CI, 1.05–1.31], $P=0.005$, step 3, path B). After adjusting for TR as a mediator, intensive BP management no longer had a substantial association with functional outcome

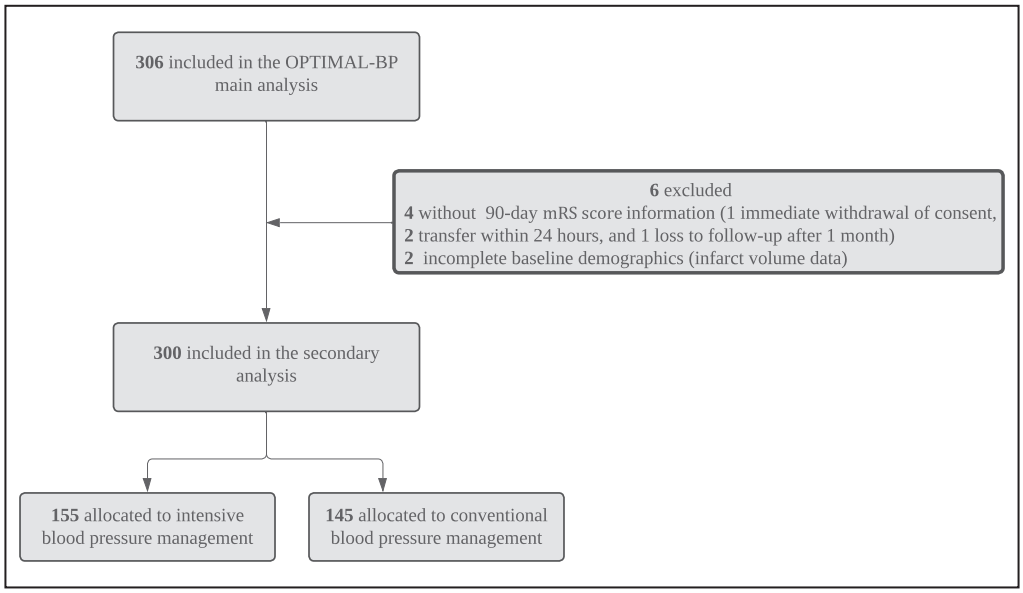

Figure 2. Flow diagram of the study participants.
mRS indicates modified Rankin Scale; and OPTIMAL-BP, Outcome in Patients Treated With Intra-Arterial Thrombectomy-Optimal Blood Pressure Control.

(acOR, 1.33 [95% CI, 0.82–2.15], *P*=0.253, path C′, direct effect). The indirect effect through the mediator TR was significant (*P*=0.030, 95% CI, 0.003–0.068), and the proportions of the association explained by TR was 40.93% (95% CI, 3.93–90.85) in the adjusted analysis (Table 3). Because the indirect effect was statistically significant and the direct effect was no more significant, SBP TR fully mediated the association between the BP management strategy and clinical outcomes.

In the sensitivity analysis considering intercenter clustering effects, the results were consistent with the original analysis. The indirect effect remained significant (*P*=0.030), with TR explaining 40.93% (95% CI, 3.81–91.85) of the association in the adjusted analysis (Table S1). Another sensitivity analysis, which only included patients who achieved complete recanalization (Thrombolysis in Cerebral Infarction 3), or excluded labetalol users (n=10), also demonstrated results consistent with the primary analysis, confirming the role of TR as a significant mediator (Tables S2 and S3).

DISCUSSION

TR was identified as the mediator explaining the association between intensive BP management and poor functional outcomes in successfully reperfused patients with ischemic stroke. High TR was associated with larger final infarct volumes, indicating that time-related BP fluctuations could have a deleterious effect on functional recovery through hypoperfusion-related infarct growth, even after successfully recanalization.

In the ENCHANTED/MT (Enhanced Control of Hypertension and Thrombectomy Stroke Study) trial, intensive BP lowering after endovascular thrombectomy for acute ischemic stroke was associated with more frequent early neurological deterioration and worse neurological outcomes, although it did not significantly increase the risk of symptomatic hemorrhage.[3] The higher OR of poor functional recovery observed in the intensive BP control arm in previous randomized controlled trials could be attributed not only to high BP acting as a compensatory mechanism against poor perfusion but also to high BPV resulting from the intensive lowering of SBP with various antihypertensive agents. Most clinical studies have reported an independent association between high BPV and poor functional outcomes, primarily driven by sustained hypoperfusion despite successful reperfusion rather than symptomatic hemorrhage.[6,16] The findings of the current study align with the previous research, demonstrating that high TR is significantly associated with hypoperfusion-related infarct growth. Avoiding rapid BP reduction and hypoperfusion during the acute phase could be the most crucial aspect of post-EVT care and needs to be considered in further clinical trials on BP management.

Whereas other BPV parameters, including SD, coefficient of variation, and VIM, reflect the degree of dispersion, the TR considers the sequence and velocity of changes in BP over time, which is more useful in reflecting multiple changes in BP between measurements as an antihypertensive treatment response.[14,20] Moreover, in clinical studies, when BP measurement

Table 1. Demographics, Baseline Characteristics, and Clinical Outcomes of the Included Subjects

Variables	Total (N=300)	Conventional (n=145)	Intensive (n=155)	*P* value
Age, y, median (IQR)	75.0 (66.0–82.0)	73.0 (66.0–81.0)	77.0 (66.0–82.0)	0.44
Sex, male, n (%)	179 (59.7)	87 (60.0)	92 (59.4)	1
Initial National Institutes of Health Stroke Scale score, median (IQR)	12.0 (8.0–17.0)	11.0 (7.0–17.0)	13.0 (8.0–18.0)	0.19
Acute Stroke Prognosis Early Computed Tomography Score, median (IQR)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (7.0–10.0)	0.34
Trial of ORG 10172 in Acute Stroke Treatment classification, n (%)				0.3
Cardioembolism	151 (50.3)	75 (51.7)	76 (49.0)	
Large artery atherosclerosis	84 (28.0)	43 (29.7)	41 (26.5)	
Undetermined, negative	42 (14.0)	21 (14.5)	21 (13.5)	
Undetermined, ≥2	18 (6.0)	5 (3.4)	13 (8.4)	
Other determined	5 (1.7)	1 (0.7)	4 (2.6)	
Risk factors, n (%)				
Hypertension	231 (77.0)	110 (75.9)	121 (78.1)	0.75
Diabetes	125 (41.7)	60 (41.4)	65 (41.9)	1
Dyslipidemia	115 (38.3)	54 (37.2)	61 (39.4)	0.8
Atrial fibrillation	145 (48.3)	68 (46.9)	77 (49.7)	0.71
Prior stroke	66 (22.0)	30 (20.7)	36 (23.2)	0.7
Infarction volume, median (IQR)	17.1 (6.0–52.5)	16.8 (5.4–40.7)	18.6 (6.7–62.6)	0.11
Modified Thrombolysis in Cerebral Infarction 3, n (%)	194 (64.7)	91 (62.8)	103 (66.5)	0.58
Outcome variables				
90-d mRS score, median (IQR)	3.0 (1.0–5.0)	2.0 (1.0–4.0)	3.0 (1.0–5.0)	0.01
90-d mRS score 0–2, n (%)	141 (47.0)	80 (55.2)	61 (39.4)	0.01
Symptomatic hemorrhage	24 (8)	10 (6.9)	14 (9.0)	0.64
Initial SBP, median (IQR)	150.0 (145.0–162.0)	151.0 (145.0–160.0)	150.0 (144.0–164.5)	0.97
24-h mean SBP, mean±SD	133.4 (11.8)	137.9 (13.6)	129.2 (7.7)	<0.01
BP measurement number, median (IQR)	30.0 (25.0–40.0)	25.0 (25.0–29.0)	36.0 (30.0–54.0)	<0.01
BP variability parameters, median (IQR)				
24-h SBP time rate	0.28 (0.20–0.44)	0.24 (0.19–0.32)	0.36 (0.24–0.51)	<0.01
24-h SBP SD	13.58 (10.82–16.81)	13.68 (11.11–16.98)	13.36 (10.71–16.69)	0.38
24-h SBP coefficient of variation	0.10 (0.08–0.12)	0.10 (0.08–0.12)	0.10 (0.08–0.13)	0.34
24-h SBP variability independent of the mean	17.35 (13.85–21.46)	17.58 (14.13–21.50)	17.06 (13.67–21.24)	0.32
Use of intravenous antihypertensive medication, n (%)	141 (47.0)	26 (17.9)	115 (74.2)	<0.01

BP indicates blood pressure; IQR, interquartile range; mRS, modified Rankin Scale; and SBP, systolic blood pressure.

intervals vary across different situations, such as before the administration of antihypertensive medication or when BP deviates from the target range, traditional BPV parameters may fail to adequately reflect the extent of BPV over time. In such cases, time rate, which considers changes in measurement intervals, may serve as a more accurate indicator of BPV.

Studying the impact of BPV modulation on clinical outcomes has been challenging due to the retrospective nature of BPV analysis and its complex interaction with BP management strategies. Mean BP can be assessed at a single time point and adjusted in real-time based on that measurement. In contrast, BPV requires sequential BP measurements over a period of time for calculation, making it difficult to establish real-time targets or modulate effectively during acute interventions. Moreover, intensive BP lowering, while aiming to reduce mean BP, often increases BPV, complicating efforts to isolate the effects of BPV from those of BP reduction itself. These limitations make it challenging to design clinical trials that can definitively determine whether reducing BPV directly improves clinical outcomes.[14,17]

The current study is significant in that it identified a causal relationship between time-related BPV and post-EVT functional outcomes. Once TR is identified as a contributing factor to poor functional recovery in the intensive BP management group, efforts to reduce

Table 2. Time-Related BP Variability and Outcomes

	Model 1	*P* value	Model 2	*P* value	Model 3	*P* value
90-d mRS score	1.24 (1.11–1.38)	<0.001	1.19 (1.07–1.34)	0.002	1.17 (1.04–1.32)	0.007
90-d mRS score 0–2	0.84 (0.73–0.96)	0.009	0.86 (0.74–1.01)	0.069	0.88 (0.74–1.04)	0.133
Symptomatic hemorrhage	1.18 (1.00–1.41)	0.064	1.15 (0.95–1.38)	0.142	1.15 (0.95–1.40)*	0.163
Final infarction volume (β, 95% CI)†	26.51 (8.37–44.65)	0.004	23.15 (5.85–40.45)‡	0.009	21.24 (3.99–38.48)§	0.016

Model 1: age, sex. Model 2: age, sex, NIHSS score, final infarction volume. Model 3: age, sex, TOAST, smoking, diabetes, hypertension, hyperlipidemia, initial NIHSS score, final infarction volume, symptomatic hemorrhage, degree of recanalization (mTICI), mean SBP. Odds ratio per 0.1 units increment for TR. BP indicates blood pressure; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; and TR, time rate.

*Adjusted by age, sex, TOAST, smoking, diabetes, hypertension, hyperlipidemia, initial NIHSS score, final infarction volume, degree of recanalization (mTICI), mean SBP.

†SBP TR was log-transformed to best satisfy the linear regression model.

‡Adjusted by age, sex, NIHSS.

§Adjusted by age, sex, TOAST, smoking, diabetes, hypertension, hyperlipidemia, initial NIHSS score, symptomatic hemorrhage, degree of recanalization (mTICI), mean SBP.

TR values could mitigate the adverse effects of intensive BP management and improve clinical outcomes. Several steps can be taken to achieve this. First, to address the limitation of real-time analysis, the integration of continuous, noninvasive BP monitoring using devices using finger arterial pressure monitoring or other ambulatory BP monitoring devices, combined with simultaneous spectral analysis for rapid BPV assessment, may be necessary.[21] These technologies could facilitate the rapid calculation and real-time monitoring of TR during modulation, providing a more precise approach to BP management following EVT. Second, implementing a detailed infusion protocol for intravenous antihypertensive medication and selecting the optimal class of antihypertensive agent. Third, appropriate fluid management to maintain euvolemic status. Fourth, effective management of distressing conditions such as headache, pain, or urinary retention. Additionally, meticulous infection control and fever management, serves as adjunctive strategies in ameliorating BPV and fostering improved patient outcomes.

There are several limitations in the current study. First, the number and timing of BP measurements are different among individuals. Although a unified BP measurement protocol was employed, the time intervals for BP measurement could not be standardized and may have varied depending on spontaneous changes in BP or in response to the use of intravenous antihypertensive medication, whether or not within the target ranges of SBP. More frequent BP measurements are required until BP outside the target range is restored within the target level. Second, this study exclusively included patients who achieved successful reperfusion following EVT. As a result, it remains unclear whether TR serves as a mediator of poor outcomes in patients who do not achieve successful reperfusion. Additional research is needed to explore TR's role in these patients and to establish tailored BP

Table 3. Proportion of the Association Between BP Management and the Ordinal 90-Day mRS Score Mediated by Time Rate

	Unadjusted analysis			Adjusted analysis		
Pathway	Measure	Value (95% CI)	*P* value	Measure	Value (95% CI)	*P* value
A (X→M)*	β	0.36 (0.25–0.47)	<0.001	β	0.38 (0.26–0.50)	<0.001
B (M→Y)†	cOR	1.27 (1.14–1.41)	<0.001	acOR	1.17 (1.05–1.31)	0.005
C (X→Y)	cOR	1.78 (1.19–2.66)	0.005	acOR	1.58 (1.00–2.49)	0.050
C′ (X+M→Y)	cOR	1.41 (0.92–2.15)	0.114	acOR	1.33 (0.82–2.15)	0.253
Proportion of total effect mediated (%) (95% CI‡)		45.27 (15.88–93.46)			40.93 (3.93–90.85)	
Indirect effect (95% CI‡)		0.063 (0.024–0.102)			0.030 (0.003–0.068)	

Adjusted for age, sex, TOAST, smoking, diabetes, hypertension, hyperlipidemia, initial National Institutes of Health Stroke Scale score, final infarction volume, symptomatic hemorrhage, degree of recanalization (modified Thrombolysis in Cerebral Infarction), mean SBP. X is the independent variable (BP management strategy), M the mediator variable (SBP TR), and Y the dependent variable (90-day mRS score: the ordinal shift across the range of mRS scores toward a worse outcome). acOR indicates adjusted common odds ratio; BP, blood pressure; cOR, common odds ratio; mRS, modified Rankin Scale; SBP, systolic blood pressure; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; and TR, time rate.

*SBP TR was log-transformed to best satisfy the linear regression model.

†Per 0.1 units increase.

‡Nonparametric bootstrap CIs with the percentile method (with 1000 replications).

management strategies for this subgroup. Third, this study was a post hoc analysis, which inherently carries limitations such as potential biases in data interpretation and the lack of prospective validation. The findings should therefore be interpreted with caution and require confirmation in prospective studies.

CONCLUSIONS

In conclusion, the time-related BPV parameter, TR mediated the association of intensive BP management and poor functional outcome in successfully reperfused patients with ischemic stroke. Efforts to modulate and reduce TR after EVT, such as implementing detailed protocols for continuous infusion with intravenous antihypertensive medication or using continuous BP monitoring with simultaneous data analysis, could improve clinical outcomes. Future clinical trials need to be designed to evaluate whether reducing TR improves functional recovery in successfully reperfused patients with ischemic stroke post EVT, potentially guiding more effective BP management strategies.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1. Supplemental Methods
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REFERENCES

1. Nam HS, Kim YD, Heo J, Lee H, Jung JW, Choi JK, Lee IH, Lim IH, Hong SH, Baik M, et al. Intensive vs conventional blood pressure lowering after endovascular thrombectomy in acute ischemic stroke: the OPTIMAL-BP randomized clinical trial. *JAMA*. 2023;330:832–842. doi: 10.1001/jama.2023.14590
2. Mistry EA, Hart KW, Davis LT, Gao Y, Prestigiacomo CJ, Mittal S, Mehta T, LaFever H, Harker P, Wilson-Perez HE, et al. Blood pressure management after endovascular therapy for acute ischemic stroke: the BEST-II randomized clinical trial. *JAMA*. 2023;330:821–831. doi: 10.1001/jama.2023.14330
3. Yang P, Song L, Zhang Y, Zhang X, Chen X, Li Y, Sun L, Wan Y, Billot L, Li Q, et al. Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): a multicentre, open-label, blinded-endpoint, randomised controlled trial. *Lancet*. 2022;400:1585–1596. doi: 10.1016/S0140-6736(22)01882-7
4. Mazighi M, Richard S, Lapergue B, Sibon I, Gory B, Berge J, Consoli A, Labreuche J, Olivot JM, Broderick J, et al. Safety and efficacy of intensive blood pressure lowering after successful endovascular therapy in acute ischaemic stroke (BP-TARGET): a multicentre, open-label, randomised controlled trial. *Lancet Neurol*. 2021;20:265–274. doi: 10.1016/S1474-4422(20)30483-X
5. Katsanos AH, Catanese L, Sahlas DJ, Srivastava A, Veroniki AA, Perera K, Ng KKH, Joundi R, van Adel B, Larrazabal R, et al. Blood pressure management following endovascular stroke treatment: a feasibility trial and meta-analysis of outcomes. *Stroke: Vasc Interv Neurol*. 2024;4:e001287. doi: 10.1161/SVIN.123.001287
6. Palaiodimou L, Joundi RA, Katsanos AH, Ahmed N, Kim JT, Goyal N, Maier IL, de Havenon A, Anadani M, Matusevicius M, et al. Association between blood pressure variability and outcomes after endovascular thrombectomy for acute ischemic stroke: an individual patient data meta-analysis. *Eur Stroke J*. 2024;9:88–96. doi: 10.1177/23969873231211157
7. Mistry EA, Mehta T, Mistry A, Arora N, Starosciak AK, de Los Rios La Rosa F, Siegler JE, Chitale R, Anadani M, Yaghi S, et al. Blood pressure variability and neurologic outcome after endovascular thrombectomy: a secondary analysis of the BEST study. *Stroke*. 2020;51:511–518. doi: 10.1161/STROKEAHA.119.027549
8. Chang JY, Jeon SB, Lee JH, Kwon OK, Han MK. The relationship between blood pressure variability, recanalization degree, and clinical outcome in large vessel occlusive stroke after an intra-arterial thrombectomy. *Cerebrovasc Dis*. 2018;46:279–286. doi: 10.1159/000495300
9. Maier B, Gory B, Lapergue B, Sibon I, Escalard S, Kyheng M, Labreuche J, de Havenon A, Petersen N, Anadani M, et al. Effect of blood pressure variability in the randomized controlled BP TARGET trial. *Eur J Neurol*. 2022;29:771–781. doi: 10.1111/ene.15194
10. Parati G, Ochoa JE, Lombardi C, Bilo G. Blood pressure variability: assessment, predictive value, and potential as a therapeutic target. *Curr Hypertens Rep*. 2015;17:537. doi: 10.1007/s11906-015-0537-1
11. Messerli FH, Rimoldi SF, Bangalore S. Blood pressure variability and arterial stiffness-chicken or egg? *JAMA Cardiol*. 2019;4:1050. doi: 10.1001/jamacardio.2019.2730
12. Kajikawa M, Higashi Y. Blood pressure variability and arterial stiffness: the chicken or the egg? *Hypertens Res*. 2024;47:1223–1224. doi: 10.1038/s41440-024-01589-8
13. Nam HS, Kim YD, Choi JK, Baik M, Kim BM, Kim DJ, Heo J, Shin DH, Lee KY, Jung YH, et al. Outcome in patients treated with intra-arterial thrombectomy: the optiMAL blood pressure control (OPTIMAL-BP) trial. *Int J Stroke*. 2021;17:17474930211041213. doi: 10.1177/17474930211041213
14. Schutte AE, Kollias A, Stergiou GS. Blood pressure and its variability: classic and novel measurement techniques. *Nat Rev Cardiol*. 2022;19:643–654. doi: 10.1038/s41569-022-00690-0
15. Zakopoulos NA, Tsivgoulis G, Barlas G, Papamichael C, Spengos K, Manios E, Ikonomidis I, Kotsis V, Spiliopoulou I, Vemmos K, et al. Time rate of blood pressure variation is associated with increased common

carotid artery intima-media thickness. *Hypertension*. 2005;45:505–512. doi: 10.1161/01.HYP.0000158306.87582.43
16. Zompola C, Palaiodimou L, Voumvourakis K, Stefanis L, Katsanos AH, Sandset EC, Boviatsis E, Tsivgoulis G. Blood pressure variability in acute stroke: a narrative review. *J Clin Med*. 2024;13:1981. doi: 10.3390/jcm13071981
17. 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;375:895–905. doi: 10.1016/S0140-6736(10)60308-X
18. Boers AMM, Jansen IGH, Brown S, Lingsma HF, Beenen LFM, Devlin TG, Roman LS, Heo JH, Ribo M, Almekhlafi MA, et al. Mediation of the relationship between endovascular therapy and functional outcome by follow-up infarct volume in patients with acute ischemic stroke. *JAMA Neurol*. 2019;76:194–202. doi: 10.1001/jamaneurol.2018.3661
19. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51:1173–1182. doi: 10.1037//0022-3514.51.6.1173
20. Parati G, Stergiou GS, Dolan E, Bilo G. Blood pressure variability: clinical relevance and application. *J Clin Hypertens (Greenwich)*. 2018;20:1133–1137. doi: 10.1111/jch.13304
21. Imholz BP, Wieling W, van Montfrans GA, Wesseling KH. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovasc Res*. 1998;38:605–616. doi: 10.1016/s0008-6363(98)00067-4
22. Howard SC, Rothwell PM. Reproducibility of measures of visit-to-visit variability in blood pressure after transient ischaemic attack or minor stroke. *Cerebrovasc Dis*. 2009;28:331–340. doi: 10.1159/000229551