RESEARCH ARTICLE

Autoregulation-Guided Blood Pressure Targets After Stroke Thrombectomy

Impact on Secondary Brain Injury and Neurologic Outcomes

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Abstract

Background and Objectives

The optimal blood pressure (BP) target after endovascular thrombectomy (EVT) remains elusive. The aim of our study was to assess the relationship between individualized autoregulation-based BP thresholds, secondary brain injury, and functional outcomes.

Methods

We conducted a prospective observational study of patients with acute ischemic stroke who underwent EVT. Simultaneous recordings of arterial BP and near-infrared spectroscopy were used to continuously monitor each patient's limits of autoregulation for up to 24 hours. Time outside limits of autoregulation was correlated with short-term clinical end points, radiographic biomarkers of secondary brain injury, and functional outcomes.

Results

Personalized BP targets were successfully computed in 199 patients. Percent time outside limits of autoregulation was independently associated with early neurologic deterioration (OR 1.2, 95% CI 1.1–1.4, $p < 0.001$) and worse modified Rankin Scale scores at 90 days (OR 1.22, 95% CI 1.09–1.36, $p < 0.001$). Patients with hemorrhagic transformation and symptomatic intracranial hemorrhage spent significantly more time above the upper limit of autoregulation compared with those without (18.7% vs 11%, $p = 0.02$, and 24.9% vs 12.3%, $p = 0.024$, respectively). Furthermore, time above the upper limit of autoregulation was correlated with net water uptake, a radiographic biomarker of cerebral edema ($\beta = 1.6$, 95% CI 0.4–2.8, $p = 0.009$). In nonrecanalized patients, every 60 minutes below the lower limit of autoregulation was associated with an infarct progression of 16.2 mL ($p < 0.001$).

Discussion

Deviations from personalized BP targets were associated with an increased risk of secondary brain injury and worse functional outcomes. The study proposes autoregulation-oriented BP management as a promising strategy for improving recovery after ischemic stroke.

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Introduction

Large vessel occlusions (LVOs) are responsible for approximately one-quarter of acute ischemic stroke, yet they result in more than half of all stroke-related severe disability and mortality.[1,2] There is a growing recognition of LVO-associated strokes as unique entities with distinctive cerebrovascular pathophysiology and treatment approaches. Cerebral autoregulation, essential for maintaining cerebral homeostasis,[3] can be severely compromised after acute neurologic injury.[4] Moreover, the impairment of autoregulation after LVO stroke can persist even after successful revascularization, rendering the brain vulnerable to post-thrombectomy blood pressure

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Glossary

ASPECTS = Alberta Stroke Program Early CT Score; **BP** = blood pressure; **EVT** = endovascular thrombectomy; **HI** = hemorrhagic infarction; **HT** = hemorrhagic transformation; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **LVO** = large vessel occlusion; **MAP** = mean arterial pressure; **MAPopt** = optimal MAP; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **NIRS** = near-infrared spectroscopy; **PH** = parenchymal hematoma; **PRx** = pressure reactivity index; **rSO_2** = regional cerebral oxygen saturation; **TICI** = Thrombolysis in Cerebral Infarction; **ULA** = upper limit of autoregulation.

(BP) fluctuations.[5] In such cases, low BP can worsen cerebral blood flow, leading to infarct progression, whereas elevated BP may result in excessive blood flow, cerebral edema, and hemorrhagic transformation (HT).

Personalized autoregulation-guided BP management has emerged as a promising strategy for hemodynamic management after stroke. Previous work showed that near-infrared spectroscopy (NIRS) monitoring could determine the optimal BP range for individual patients at which cerebral autoregulation functions best.[6] Furthermore, several small observational studies have shown that deviation from the autoregulation-preserved range, measured in percent time or burden, is associated with poor functional outcomes.[6-8] These studies have also suggested that HT and infarct progression may be potential pathways leading to worse outcomes in these patients.

However, before testing autoregulation-based BP targets in a clinical trial, it is essential to confirm these preliminary findings and to better define the relationship between autoregulation-based BP targets and post-thrombectomy cerebrovascular complications. To this end, we conducted a large prospective observational study with comprehensive data collection to evaluate the impact of deviations from individualized, autoregulation-based BP targets on radiographic biomarkers of secondary brain injury and short-term clinical end points. Our objective was to establish a plausible mechanistic link between BP, autoregulation, stroke injury mechanisms, and outcomes.

Methods

Study Design and Participants

This prospective observational study was conducted at Yale New Haven Hospital between 2017 and 2022. All patients with acute anterior circulation ischemic stroke and CT angiography–confirmed LVO of the intracranial internal carotid artery or middle cerebral artery were screened for inclusion. Eligible participants were 18 years of age or older and underwent treatment with endovascular thrombectomy (EVT). The original study protocol specified initiation of monitoring within 4 hours of EVT completion; this window was subsequently extended to 12 hours after intensive care unit (ICU) arrival to include patients treated overnight before research staff availability, thereby enhancing enrollment. Exclusion criteria encompassed procedural intracranial hemorrhagic complications, previous stroke within the past 3 months, or a baseline modified Rankin Scale (mRS) score ≥3. During the study period, BP management generally followed American Heart Association (AHA)/American Stroke Association (ASA) guidelines (<180/105 mm Hg in the first 24 hours), although treating teams often used lower systolic targets after complete reperfusion (Thrombolysis in Cerebral Infarction [TICI] score 2b–3). Target selection was based on physician judgment and not systematically recorded. A list of vasoactive medications used during the study is provided in eTable 1 of the Data Supplement.

Patient Characteristics and Physiologic Data

At the time of enrollment, we systematically collected relevant data on patient demographics, comorbidities, imaging characteristics, stroke severity, and treatment.

NIRS optodes were positioned on the patient's forehead to measure regional cerebral oxygen saturation (rSO_2) as a surrogate for cerebral blood flow (ForeSight, Edwards Lifesciences). To monitor arterial BP, either an intra-arterial catheter or finger photoplethysmography (ClearSight, Edwards Lifesciences) was used. The NIRS and BP data were collected for up to 24 hours after EVT. All signals were recorded at 200 Hz using Intensive Care Monitor + research software (Cambridge Enterprises, United Kingdom).

Calculation of Optimal BP and Limits of Autoregulation

In each patient, we calculated the percentage of time that mean arterial pressure (MAP) was outside the limits of autoregulation. Autoregulatory function was assessed by analyzing changes in NIRS-derived rSO_2 over the affected hemisphere in relation to spontaneous fluctuations in arterial BP. The cerebral oximetry index (COx) was computed as a moving correlation coefficient between 10-second averaged values of the arterial BP waveform and corresponding rSO_2 signals over a window of 5 minutes. Positive COx values indicate worse autoregulation (cerebral blood flow passively follows changes in pressure) while low or negative values indicate better autoregulation (cerebral vasculature is independent of or actively resisting changes in pressure). We used a previously published curve-fitting algorithm to determine the optimal MAP (MAPopt) and the limits of autoregulation for each patient.[9,10] A detailed description is provided in the Data Supplement (eMethod 1). NIRS-derived rSO_2 values were not accessible to the treating clinicians, and autoregulation indices with corresponding personalized BP targets were computed on a separate research computer, ensuring that clinicians were blinded and hemodynamic management remained independent of these measures.

Clinical and Neuroimaging Outcomes

The primary efficacy variable was functional outcome as defined by the mRS score at 90 days. We assessed for shifts across the entire mRS range and dichotomized into good (mRS scores 0–2) and poor (mRS scores 3–6) outcomes. End points were determined through a telephone interview at 3 months by a member of the research team who was blinded to the monitoring results.

Secondary clinical outcomes included early neurologic deterioration, defined as a NIH Stroke Scale (NIHSS) increase≥4 from the post-EVT baseline,[11] and symptomatic intracerebral hemorrhage (ICH). Radiographic end points were used to evaluate the mechanism underlying the relationship between BP deviations from autoregulation thresholds and poor neurologic outcomes, including HT, cerebral edema, and infarct progression.

HT was assessed on the post-EVT CT imaging at 24 ± 6 hours using the European Cooperative Acute Stroke Study scale.[12] In cases where an MRI was obtained closer to the 24-hour time point, it was used to evaluate for HT.[13] Patients were divided into 3 groups based on the type of HT: none, hemorrhagic infarction (HI), and parenchymal hematoma (PH). A PH-type HT leading to clinical deterioration with an increase of ≥4 points on the NIHSS was deemed symptomatic ICH.

Cerebral edema was measured using a combination of established and novel quantitative imaging biomarkers, including midline shift, net water uptake, and CSF ratio measurements.[14] After excluding patients with PH-type HT, a fully automated stroke edema image processing pipeline was used to calculate these biomarkers.[15] The pipeline incorporated a deep learning–based image segmentation algorithm to measure brain, CSF, and infarct volumes from CT scans obtained at both baseline and 24-hour time points. The ratio of the CSF volume of the affected hemisphere to that of the contralateral hemisphere was computed as the CSF ratio. In addition, net water uptake was calculated as the density ratio within the infarcted tissue relative to the mirrored contralateral region. Midline shift was measured as midline deviation at the septum pellucidum.

The final infarct volume was measured on MRI scans obtained at 36 ± 12 hours using Rapid Processing of Perfusion and Diffusion (RAPID) software (iSchemaView) and defined as the area with apparent diffusion coefficient values below $680*10^{-6}$ mm^2/second. In cases with significant HT, manual tracings were used to calculate the final infarct volume (AnalyzeDirect). Infarct growth was calculated as the difference between the core infarct volume, defined as cerebral blood flow less than 30% of the contralateral hemisphere on initial CT perfusion, and the final infarct volume.

The degree of reperfusion after EVT was assessed using the modified TICI scale.[16] Successful reperfusion was defined as a score of 2b or higher.

Statistical Analysis

Baseline characteristics of all participants were summarized using means and SDs for normally distributed continuous variables, medians and interquartile ranges (IQRs) for skewed continuous variables, and numbers (%) for categorical variables. The percentage of time above, below, or outside autoregulation limits was treated as a continuous variable, and tertiles were created for these variables, with the lowest tertile serving as the reference category. For the primary analysis, we used an ordered logistic regression model that considered the entire distribution of the mRS. We accounted for well-established clinical confounders and known predictors of outcome after LVO stroke, including age, sex, baseline mRS score, admission NIHSS score, Alberta Stroke Program Early CT Score (ASPECTS), tPA administration, and TICI score. In addition, we used a similar model that implemented restricted cubic splines for poor outcomes (mRS scores 3–6), describing the percentage of time outside personalized limits of autoregulation. Zero percent was used as the reference. Given the low proportion of missing data (<5%), we conducted a complete record analysis without multiple imputations. All statistical analyses were considered significant at a two-sided alpha level of ≤0.05. Statistical analyses were performed using R, version 4.1.3 (R Foundation, Austria), and Statistical Package for the Social Sciences statistics, version 28.0 (IBM). The sample size estimation and power analysis are provided in the Data Supplement (eMethod 2).

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval for this study was granted by the Yale University Institutional Review Board (Protocol No. 1503015485). Written informed consent was obtained from each participant or their legally authorized representative in accordance with institutional and federal regulations. This article adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[17]

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Patient Characteristics, Hemodynamic Variables, and Autoregulation Parameters

The study enrolled a total of 209 patients, of which 199 were eligible for autoregulation analysis. Ten patients were excluded because of insufficient monitoring time or poor signal quality. The baseline demographic data are presented in Table 1. Continuous arterial BP was recorded predominantly using an invasive arterial catheter (174/199, 87%) while the remaining 25 patients (13%) were monitored using noninvasive finger photoplethysmography. The median time from reperfusion to initiation of monitoring was 481 minutes. The median (IQR) monitoring time was 17.2 (9.7, 20.7)

Table 1 Baseline, Hemodynamic, and Outcome Characteristics of the Study Cohort (n = 199)

Demographics	
Age (y), mean ± SD	70 ± 16
Female sex, n (%)	90 (45.2)
Race, n (%)	
White	157 (78.9)
Black, African American	28 (14.1)
Asian	2 (1.0)
Hispanic	10 (5.0)
Other	2 (1.0)
Clinical and procedure characteristics	
Admission NIHSS score, mean ± SD	13.8 ± 6.5
Admission ASPECTS, median (IQR)	9 (7, 10)
CBF<30 (mL), median (IQR)	0 (0, 12.0)
Admission MAP (mm Hg), mean ± SD	103 ± 22.7
Admission glucose (mmol/dL), mean ± SD	138 ± 52.9
Affected side, n (%)	
Left	101 (50.8)
Right	98 (49.2)
Site of occlusion on angiography, n (%)	
ICA	18 (9.0)
M1 MCA	110 (55.3)
M2 MCA	58 (29.1)
Other	13 (6.5)
Medical history, n (%)	
Hypertension	149 (74.9)
Coronary artery disease	36 (18.1)
Myocardial infarction	9 (4.5)
Congestive heart failure	17 (8.5)
Atrial fibrillation	67 (33.7)
Hyperlipidemia	98 (49.2)
Diabetes mellitus	50 (25.1)
Ischemic stroke	32 (16.1)
Current smoker	27 (13.6)
Past smoker	63 (31.7)
Treated with tPA, n (%)	87 (43.7)
Time from last known normal to reperfusion (minutes), median (IQR)	441 (294, 787)
Time from reperfusion to initiation of neuromonitoring, median (IQR)	481 (188, 809)
Successful recanalization, n (%)	160 (80.4)
TICI score, n (%)	
0	23 (11.6)
1	6 (3.0)
2a	10 (5.0)
2b	52 (26.1)
2c	48 (24.1)
3	60 (30.2)
Neuromonitoring and hemodynamics	
MAP (mm Hg), mean ± SD	91.4 ± 12.6
MAPopt (mm Hg), mean ± SD	90.9 ± 12.3
Upper limit of autoregulation (mm Hg), mean ± SD	101.5 ± 12.6
Lower limit of autoregulation (mm Hg), mean ± SD	81.0 ± 11.9
Clinical and radiographic outcomes	
Final infarct volume (mL), median (IQR)	31 (6, 102.1)
Hemorrhagic transformation, n (%)	
None	118 (59.3)
HI I and II	66 (33.2)
PH I and II	15 (7.5)
Symptomatic hemorrhagic transformation, n (%)	18 (9.0)
Neurologic worsening, n (%)	74 (37.2)
In-hospital mortality, n (%)	19 (9.5)
Ninety-day mortality, n (%)	46 (23.1)

Abbreviations: ACA = anterior cerebral artery; ASPECTS = Alberta Stroke Program Early CT Score; CBF = cerebral blood flow; HI = hemorrhagic infarction; ICA = internal carotid artery; IQR = interquartile range; MAP = mean arterial pressure; MAPopt = optimal MAP; MCA = middle cerebral artery; NIHSS = NIH Stroke Scale.
Data are mean (SD), median (IQR), and n (%).

hours, and optimal BP and limits of autoregulation were calculated for an average of 90% of the total monitoring period. Patients spent a median of 71.3% (43.4, 82.3) of their monitored time within personalized limits of autoregulation, 14.6% (6.7, 27.2) above the upper limit of autoregulation (ULA), and 12.3% (5.5, 24.9)% below the lower limit of autoregulation (LLA). The proportion of monitoring time outside personalized autoregulatory limits was highest within the first 6 hours after reperfusion (43%) and declined over subsequent intervals (6–12 hours: 38%; 12–18 hours: 36%; 18–24 hours: 34%). A complete list of hemodynamic variables and autoregulation parameters is provided in eTable 2 of the Data Supplement.

Patients were classified into 3 equal-sized groups based on the percent time they spent outside the personalized limits of autoregulation. The lower tertile group spent less than 21% of their monitored time outside their limits of autoregulation, corresponding to a mean duration of 1.9 ± 1.3 hours. The middle tertile spent between 22% and 45% (mean 4.3 ± 2.1 hours) while the upper tertile spent more than 46% of their monitored time outside their limits of autoregulation (mean 8.8 ± 5.2 hours). Group differences were observed for age and admission NIHSS score, with patients in the lower tertile being younger and having less severe strokes. These patients were also less likely to experience neurologic deterioration and had lower in-hospital and 90-day mortality rates (eTable 3).

Early Neurologic Deterioration and Functional Neurologic Outcomes

The distribution of mRS scores at 90 days from patients in each tertile group is shown in Figure 1A. A higher proportion of patients with poor outcomes was observed in the middle (64%, n = 40) and upper (78%, n = 49) tertiles compared with those in the lower tertile (35%, n = 23, p 0.001). Moreover, patients in the upper tertile group had significantly more global disability, as indicated by an unfavorable shift in the distribution of mRS scores, than did patients in the lowest tertile group (adjusted OR for a shift toward worse outcome 3.4; 95% CI 1.7–6.7; p 0.001). While mean BP during the recording period did not differ across mRS groups, there was a progressive increase in the time spent outside limits of autoregulation, with worsening grades on the mRS at discharge and 90 days (Figure 1B). After adjusting for age, sex, baseline mRS score, admission NIHSS score, ASPECTS, tPA administration, and degree of reperfusion, percent time with MAP outside personalized limits of autoregulation was independently associated with higher (worse) mRS scores at discharge (adjusted OR per 10% 1.15, 95% CI 1.04–1.29, p = 0.009) and at 90 days (adjusted OR per 10% 1.22, 95% CI 1.09–1.36, p 0.001, Figure 1C). No interaction was observed between IV tPA administration or time from reperfusion to monitoring initiation and the association between deviations from individualized autoregulatory limits and functional outcome (p = 0.953 and p = 0.651 for interaction, respectively). A summary of unadjusted and confounder-adjusted estimates for all clinical outcomes is provided in eTable 4 of the Data Supplement.

Seventy-four patients (35.4%) experienced early neurologic deterioration within the first 24 hours. While mean BP did not significantly differ between groups (93.3 vs 90.1 mm Hg, p = 0.08), patients with early neurologic deterioration spent considerably more time outside their personalized limits of autoregulation than those without (median 39.0% vs 26.1%, p < 0.001, Figure 2). After adjusting for potential confounders, percent time outside limits of autoregulation was associated with an increased risk of early neurologic deterioration (adjusted OR per 10% time outside limits of autoregulation 1.2, 95% CI 1.1–1.4, p < 0.001). Compared with the lowest tertile, patients in the middle and upper tertiles had a significantly higher risk of early neurologic deterioration (adjusted OR 3.8, 95% CI 1.7–8.8, p = 0.002, and adjusted OR 3.9, 95% CI 1.7–9.0, p < 0.001).

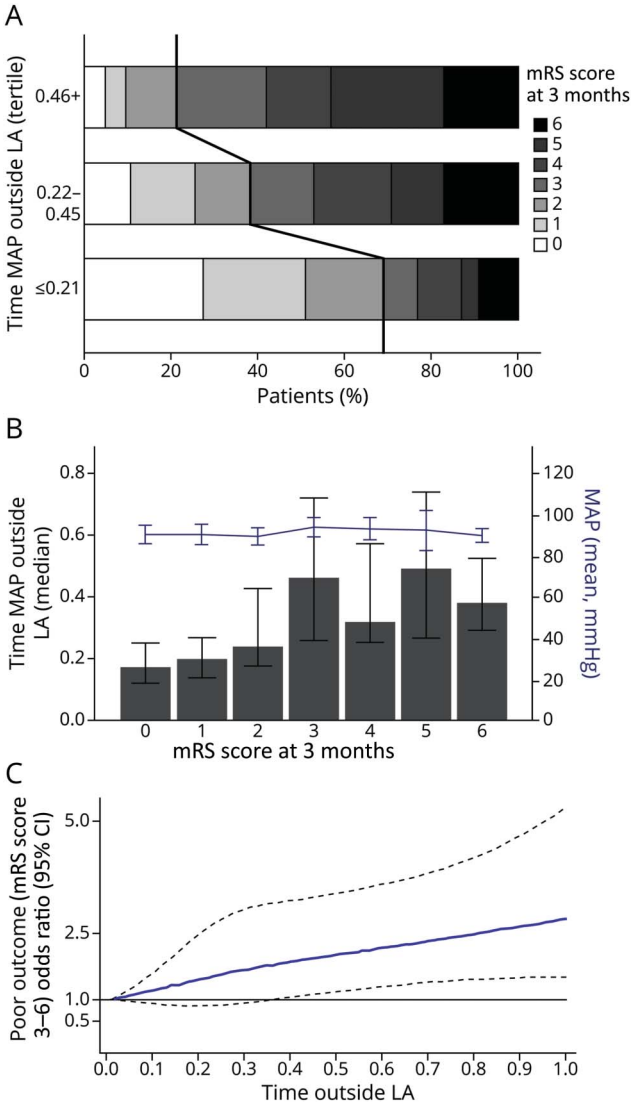
HT, Cerebral Edema, and Infarct Progression

Radiographic HT was seen in 81 of 199 patients (41%). The proportion of time spent above the ULA increased with HT severity. Patients without HT spent a median of 11% of their monitored time above the ULA, compared with 18.7% among those with HI and 19.4% among those with PH-type HT (p = 0.025; eFigure 1). Similarly, patients who developed symptomatic ICH (n = 18) spent a greater proportion of time above the ULA than those who did not (median 12.3% vs 24.9%, p = 0.024). Regression analysis demonstrated that percent time above the ULA was independently associated with both HT (adjusted OR per 10% 1.24, 95% CI 1.03–1.5, p = 0.025) and symptomatic ICH (OR per 10% 1.31, 95% CI 1.03–1.67, p = 0.031). Figure 3A shows the predicted probabilities of HT and symptomatic ICH across increasing percent time above the ULA. The risk of hyperperfusion-related injury seemed to vary according to the degree of reperfusion, with the strongest associations observed among patients achieving complete or near-complete recanalization (TICI score 2b–3; p for interaction = 0.032 for HT and 0.09 for symptomatic ICH). Stratified regression results are provided in eTable 5 of the Data Supplement.

Midline shift was only present in 21 patients (11%) at 24 hours. The average midline shift across the entire cohort was 0.4 mm (range 0–10 mm). The presence of midline shift did not significantly differ across tertiles of percent time above the ULA. No correlation was seen between the time or burden of hyperperfusion and the degree of midline shift. Net water uptake could be measured in a subset of 70 patients with clearly identifiable infarcts on 24-hour CT imaging. On average, these patients had more severe stroke symptoms with a greater admission NIHSS score and were less likely to achieve successful recanalization. Their complete baseline characteristics compared with the remainder of the cohort are presented in eTable 6 of the Data Supplement. After adjusting for age, admission NIHSS score, ASPECTS, and TICI score, we observed a significant correlation between the percentage of time above the ULA and net water uptake (β = 1.6, 95% CI 0.4–2.8, p = 0.009, Figure 3B). This association was not modified by reperfusion status (p = 0.81 for interaction). CSF ratio was computed in 149 patients. No association was seen between the CSF ratio at 24 hours and time spent above the ULA. There was no correlation between the average post-thrombectomy MAP and any of the edema imaging biomarkers (midline shift, net water uptake, or CSF ratio).

In patients with unsuccessful reperfusion (TICI score 0-2a), time below the lower limit correlated with infarct progression (β = 32.2, 95% CI 15–50, p < 0.001, eFigure 2). A summary of unadjusted and confounder-adjusted estimates for all radiographic outcomes is provided in eTables 7 and 8 of the Data Supplement.

Figure 1 Associations of Individualized Limits of Autoregulation With Functional Outcome



Panel A shows the distribution of the modified Rankin Scale (mRS) scores at 90 days by tertile group of percent time outside personalized limits of autoregulation (LA). The lines demarcate good (mRS scores 0–2) vs poor (mRS scores 3–6) outcome classifications. The bar graph shows the median percent time outside personalized LA for each mRS group. The blue line represents the mean MAP (Panel B). Restricted cubic spline curve showing adjusted odds ratios (solid line) with 95% CIs for poor outcome (mRS scores 3–6) associated with percent time outside personalized LA (Panel C).

Discussion

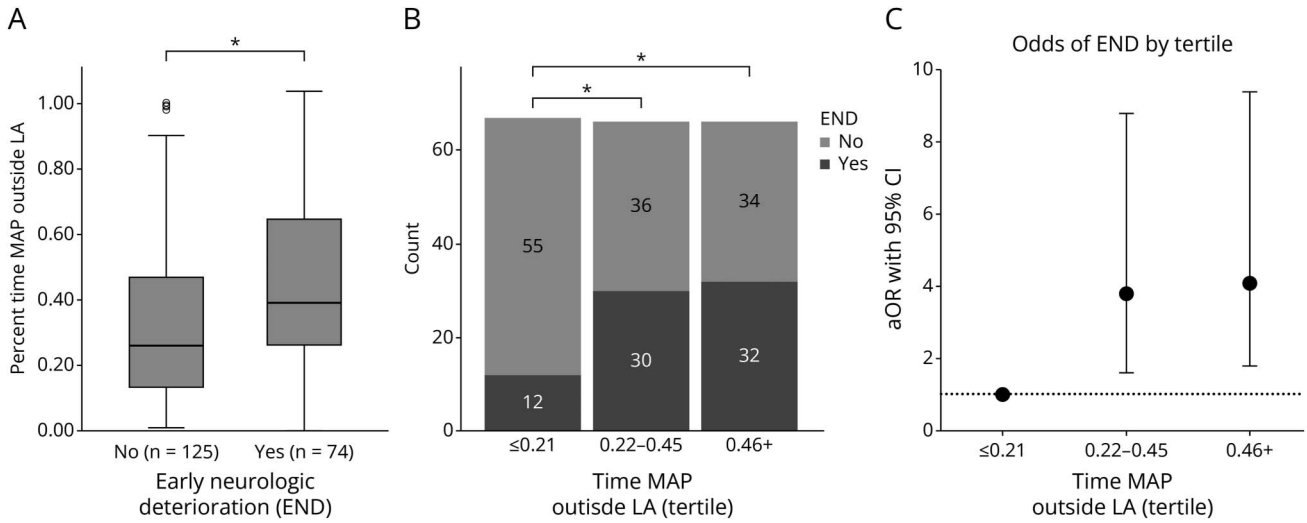
In this prospective study of 199 patients with LVO stroke treated with thrombectomy, we found that deviations from individually derived autoregulatory thresholds were independently associated with early neurologic deterioration and worse functional outcomes, even after adjusting for potential confounders. Patients who spent more than 46% of monitoring time outside their personalized limits of autoregulation (upper tertile) were approximately 4 times more likely to experience early neurologic deterioration and unfavorable functional recovery compared with those who spent less than 22% outside their limits of autoregulation (lower tertile). Cerebral hyperperfusion with BP excursions above the ULA was correlated with a higher risk of HT and cerebral edema, measured as net water uptake. By contrast, cerebral hypoperfusion with BP below the LLA in nonrecanalized patients was associated with infarct progression. Collectively, these findings support a more personalized approach to BP management after thrombectomy, guided by individualized autoregulatory thresholds.

The management of BP in post-EVT care has been the subject of considerable debate. Although multiple observational studies have reported an increased risk of HT and worse functional outcomes with sustained BP elevations after thrombectomy,[18] 4 randomized trials failed to demonstrate a benefit of BP lowering after successful EVT.[19-22] The BP-TARGET trial found no improvement in the incidence of ICH with lowering BP to <130 mm Hg[20] while the ENCHANTED-2/MT and OPTIMAL-BP trials were terminated early after patients who were treated with intensive BP lowering showed greater rates of neurologic deterioration and overall worse functional outcome.[21,22] Blood Pressure after Endovascular Stroke Therapy–II (BEST-II) was a Phase 2 trial conducted to assess whether reducing BP to less than 160 mm Hg or less than 140 mm Hg would decrease infarct volume and improve disability at 90 days enough to justify a larger Phase III trial. Although the trial did not meet futility thresholds, it predicted a low likelihood of success of a large trial of BP lowering after EVT.[19]

One plausible explanation for these results is that high BP after EVT merely reflects more severe injury and a predisposition toward poor outcomes. However, it is equally conceivable that applying a uniform BP target for all patients contributed to the lack of efficacy of intensive BP lowering. The management of BP after stroke presents a complex challenge, and it is unlikely that we will find a single BP target that is universally beneficial for all patients. Stratifying by reperfusion status alone may not be sufficient as it fails to consider individual patient physiology. Patients with significant intracranial atherosclerosis, chronic hypertension, or impaired microvascular reperfusion (i.e., no-reflow phenomenon[23]) may require higher perfusion pressures and probably react adversely to intense BP reductions. Conversely, patients with large infarcts, extensive blood-brain barrier damage, concomitant carotid revascularization, and treatment with tPA may be at higher risk of HT or edema development if their BP remains elevated.

Our findings support more individualized BP management after a stroke that is routed in physiology and tailored to each patient's unique needs rather than relying on the traditional "one-size-fits-all" approach. Furthermore, this study offers insights into the potential pathophysiologic mechanisms associated with suboptimal BP management. Cerebral edema, HT, and infarct progression are all linked to unfavorable outcomes after EVT and

Figure 2 Blood Pressure Outside Personalized Limits of Autoregulation and Early Neurologic Deterioration

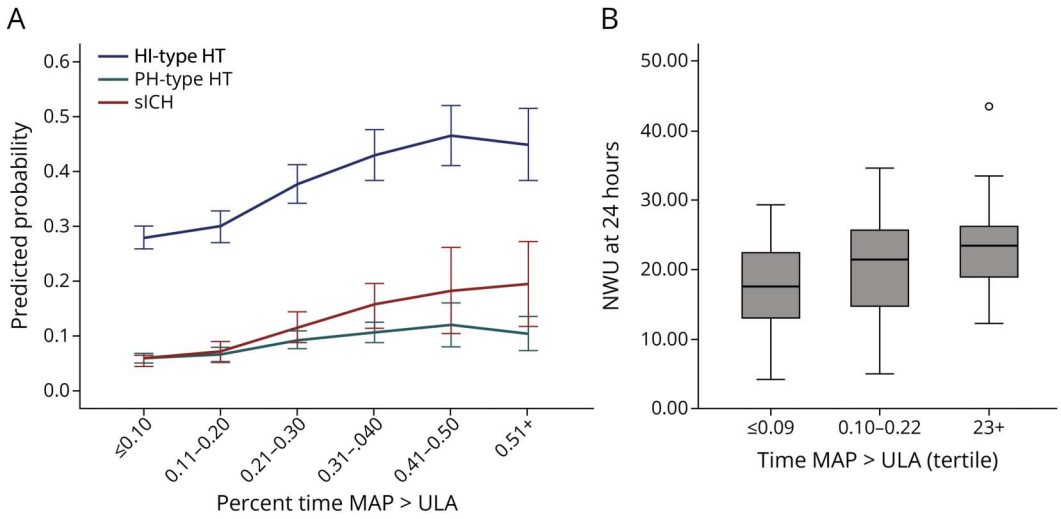


Panel A displays the percentage of time that patients spent with mean arterial pressure (MAP) outside their personalized autoregulation limits (LA) for patients with and without early neurologic deterioration (END). In Panel B, the occurrence of END is presented according to the tertiles of time spent outside LA. Panel C provides the adjusted odds ratios (midpoints) and 95% CIs (error bars) for END. LA = limits of autoregulation.

represent plausible pathways by which BP management outside personalized limits of autoregulation could result in secondary brain injury and worse functional outcomes.[24-26] We found a significant correlation between the percentage of time with MAP above the ULA and net water uptake but not any of the other edema biomarkers. This may, at least in part, be explained by the timing of the edema assessment. Midline shift develops relatively late in the edema course when room to compensate for the increased brain volume has been exhausted.[27] Net water uptake may reflect a distinct early form of hydrostatic edema that arises when pressures exceed the upper limit of autoregulation and the vasculature becomes pressure-passive. In this state, increased capillary filtration leads to extravasation of fluid into brain tissue.[28] It is also important to note that net water uptake has also been associated with an increased risk of symptomatic ICH after stroke, establishing a possible connection between postischemic hyperperfusion, edema, and HT.[29]

Previous investigations by our group and others have demonstrated that impaired autoregulation and suboptimal BP control

Figure 3 Radiographic Biomarkers of Secondary Brain Injury



Panel A shows the predicted probability for hemorrhagic transformation (blue line = hemorrhagic infarction, green line = parenchymal hematoma) and symptomatic intracerebral hemorrhage (red line) for increasing time spent above the upper limit of autoregulation. The boxplots in panel B show the median (IQR) net water uptake (NWU) by tertile group of percent time with MAP above the upper limit of autoregulation (ULA).

above the ULA in the early phase after ischemic stroke are correlated with an increased likelihood of HT.[6-8] Consistent with these findings, post-ischemic hyperperfusion assessed by MRI arterial spin labeling has been associated with a higher risk of hemorrhagic transformation.[30] The significant correlation between hyperperfusion and HT in our study reinforces previous findings, supporting the hypothesis that compromised autoregulation contributes to heightened regional vulnerability to HT in stroke patients. This vulnerability may stem from breakthrough hyperperfusion and microvascular injury. Our analysis of BP trajectories indicates that patients exhibiting elevated BP shortly after EVT are at the greatest risk of symptomatic ICH.[31] While retrospective studies have reported varying associations between sustained post-EVT hypertension and HT,[32,33] the inconsistencies could be attributed to differences in individual autoregulatory capacities. In our study, the percent time that patients spent above the ULA, but not high BP by itself, was associated with an increased risk of HT and symptomatic HT. Notably, this association was most evident among patients with successful reperfusion (TICI score 2b–3), suggesting that restoration of flow to previously ischemic, pressure-passive tissue may predispose patients to hyperperfusion-related injury. Although preclinical studies suggest that tPA may alter cerebrovascular reactivity through NMDA receptor–mediated and LRP-mediated signaling,[34,35] we did not detect any independent effect of thrombolysis on autoregulatory metrics, nor did it modify the relationship between time spent outside individualized autoregulatory limits and clinical outcome. While HT is a multifactorial process, these findings highlight that exceeding the ULA may contribute to reperfusion injury, underscoring the importance of effective hemodynamic management for achieving optimal outcomes.

BP management below the LLA correlated with increased infarct progression and larger final infarct volumes among patients who had incomplete reperfusion (TICI score 0-2a). Every 60 minutes spent below the LLA was associated with an infarct progression of 16.2 mL. These results align with previous studies, showing the detrimental impact of pre-reperfusion decreases in BP and prolonged periods below critical BP thresholds on infarct size and functional outcomes.[36-38] This collective evidence suggests that BP reductions below the LLA could increase the transition from ischemic to irreversibly injured tissue. Furthermore, beyond incomplete reperfusion and impaired autoregulation, microcirculatory dysfunction and distal embolization emerge as plausible mechanisms that may elevate susceptibility to relative hypoperfusion. Avoiding cerebral hypoperfusion seems to be particularly critical for patients with partial reperfusion.

Taken together, autoregulation-guided targets may provide mechanistic insight into the pathways underlying secondary brain injury, although no single imaging biomarker can fully characterize these complex relationships. Some associations—such as the link between time above the upper limit of autoregulation and net water uptake—were derived from a subset of patients and should, therefore, be interpreted with caution.

Although the computation of NIRS-derived autoregulatory thresholds is grounded in established physiologic principles, and previous work—including ours—has shown that deviations from these thresholds are clinically relevant and correlate with worse outcomes after stroke and subarachnoid hemorrhage,[6,7,39] the technique remains investigational. Reported agreement between NIRS-derived indices and established methods—such as the ICP-derived pressure reactivity index (PRx) and the transcranial Doppler–based mean flow velocity index (Mx)—has generally been good, although cutoffs for impaired autoregulation vary.[39-41] Furthermore, studies in piglets using reference measures such as PRx and laser Doppler flowmetry further support the validity of COx for identifying the lower limit of autoregulation.[42,43] The main advantages of NIRS are its noninvasiveness and feasibility for continuous bedside monitoring; however, the signal remains susceptible to poor or shifting sensor placement, extracranial contamination, and device-related variability. Furthermore, the calculation of COx assumes that short-term changes in rSO_2 reflect changes in frontal cortical cerebral blood flow (CBF), an approach limited by spatial resolution and the assumption that other determinants of rSO_2 remain stable within the analysis window.

Despite the strength of our study, with its extensive patient cohort and detailed monitoring, certain limitations must be acknowledged. First, while this is the largest observational study of autoregulation-based BP targets, some outcomes, such as symptomatic ICH, are relatively rare. Thus, we could only perform adjustments for a limited number of potential confounders. Second, net water uptake could be determined in only 35% of patients (70/199), primarily because computation required a clearly visible infarct on 24-hour CT imaging. Consequently, these patients represent a distinct subgroup with more severe strokes, as reflected by higher admission NIHSS scores and lower rates of successful recanalization, which may restrict the applicability of the findings to the broader EVT population. Third, the study cohort was biased toward patients with very small or minimal core infarcts, as reflected by a median CBF <30 volume of 0, which limits generalizability to patients with larger cores. In addition, nearly 30% of patients in our cohort had M2 occlusions; although EVT for these cases reflected standard practice during the study period, the recent MeVO trials suggest that some of these patients might not be treated with EVT today. Fourth, enrollment was limited by logistical constraints because autoregulation monitoring required setup by a study coordinator available only during weekday daytime hours, potentially introducing selection bias. Systematic screening logs for all patients with LVO were initiated only in January 2021, leaving limited information on nonenrolled individuals and further restricting assessment of external validity. In addition, these logistical challenges resulted in longer delays

between reperfusion and monitoring initiation for patients treated overnight compared with those treated during daytime hours (median 648 vs 237 minutes). However, the consistent relationship between autoregulatory deviations and outcome across time intervals suggests that this association was robust despite practical variations in monitoring initiation. Fifth, we recognize that BP variability is an important determinant of post-EVT outcomes and acknowledge that higher BP variability, particularly in the setting of impaired autoregulation, may contribute to the associations observed in our study. A detailed examination of the interaction between BP variability, autoregulation, and outcome is beyond the scope of this article but has been reported separately.[44] Finally, information generated by this study is descriptive and correlational. Conclusions about whether an autoregulation-guided therapy protocol will improve patient physiology or outcome are not possible at this stage and would require a prospective clinical trial. There is also uncertainty regarding the degree of deviation from MAPopt that warrants intervention. While directly targeting MAPopt or a fixed range around it would be a reasonable approach, it ignores the fact that, in some patients, a broader MAP range might provide similar autoregulation benefits. Our research suggests that it is possible to dynamically estimate the upper and lower limits of autoregulation for each patient, providing a personalized target for poststroke BP management.

This study demonstrates the feasibility of continuous, noninvasive autoregulation monitoring to define personalized BP targets after EVT. Deviations beyond individualized autoregulatory limits were associated with secondary brain injury and poorer functional outcomes, underscoring the potential of physiology-guided hemodynamic management to improve poststroke care. Although promising, NIRS-derived autoregulatory BP targets remain investigational, and further studies are needed to validate their reproducibility, safety, and clinical efficacy before integration into routine practice.

Author Contributions

N.H. Petersen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. L. Begunova: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Olexa: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Kumar: analysis or interpretation of data. Y. Chen: analysis or interpretation of data. R. Dhar: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G.J. Falcone: drafting/revision of the manuscript for content, including medical writing for content. E.J. Gilmore: drafting/revision of the manuscript for content, including medical writing for content. J.A. Kim: drafting/revision of the manuscript for content, including medical writing for content. J.R. Magid-Bernstein: drafting/revision of the manuscript for content, including medical writing for content. A. de Havenon: drafting/revision of the manuscript for content, including medical writing for content. R.S. Marshall: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. E.C. Miller: drafting/revision of the manuscript for content, including medical writing for content. C. Matouk: drafting/revision of the manuscript for content, including medical writing for content. R. Hebert: drafting/revision of the manuscript for content, including medical writing for content. K.N. Sheth: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. S. Ortega-Gutierrez: drafting/revision of the manuscript for content, including medical writing for content; study concept or design.

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