

Blood pressure variability in subacute ischemic stroke

A neglected potential therapeutic target

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Poststroke hypertension is a common complication of acute cerebral ischemia (ACI) occurring in up to 80% of acute ischemic stroke (AIS) patients.¹ Despite its high prevalence, the optimal management of arterial hypertension during the acute stroke stage has not been established and remains an issue of long-lasting debate and little consensus.¹ Notably, the findings of numerous observational studies that have evaluated the association of acute blood pressure (BP) values with early stroke outcomes are contradictory and the available but underpowered randomized controlled trials (RCTs) have yielded inconsistent results.^{2,3}

BP variability has increasingly been recognized as a novel risk factor that can predict first-ever or recurrent stroke risk and provide complementary information to mean BP levels.^{4–6} More specifically, Rothwell et al.⁴ have recently shown that systolic BP (SBP) variability was a strong predictor of stroke independent of mean BP levels. Moreover, drugs that induced the greatest reduction in SBP variability (calcium-channel blockers and diuretics) were associated with the best stroke prevention, independently of SBP values.⁵ In contrast, β -blockers, which increase BP variability in a dose-dependent fashion, were the least effective in stroke prevention.⁵ Finally, in 2 large RCTs the opposite effects of calcium-channel blockers and β -blockers on BP variability accounted for the disparity in observed effects on stroke risk and expected effects based on mean BP.⁶

The association of BP variability in the AIS stage with early stroke outcomes has been assessed in a limited number of studies.^{7–9} Interestingly, increased acute BP variations in AIS have been associated with increased likelihood of poor functional outcome or death and early neurologic deterioration.⁷ Additionally, in AIS patients treated with systemic thrombolysis, increased BP variability was related to greater diffusion-weighted imaging lesion growth resulting in worse clinical course,⁸ as well as increased risk of parenchymal hemorrhage complicating IV tissue plasminogen activator (tPA) infusion.⁹ Notably, in

certain studies the only BP measure that was associated with outcome was BP variability and not mean BP levels.⁸

In this issue of *Neurology*®, Kang et al.¹⁰ present the findings of a retrospective analysis of prospectively collected data over a 6-year period in a tertiary care stroke center. The investigators sought to evaluate the relationship of different BP measures documented in the subacute stage of ischemic stroke (defined as the time period after 72 hours from symptom onset and until hospital discharge or transfer to rehabilitation center occurring within the 21st day of ictus) with 3-month functional outcome assessed by the modified Rankin Scale score (mRS score). They documented that measures of SBP variability (but not mean SBP levels) were linearly and independently associated with a higher odds of death/functional dependence at 3 months. The former relationship persisted even after adjustment for demographic characteristics, vascular risk factors, baseline stroke severity quantified using the NIH Stroke Scale score (NIHSS score), AIS subtypes, and treatment with IV tPA.

The main strengths of this timely study include the adequate sample size ($n = 2,271$), the outcome assessment using a severity-adjusted analysis (responder analysis) that used different cutoffs for dichotomization of mRS score for different baseline NIHSS scores, and the comprehensive statistical analyses adjusting for potential confounders that may have influenced the reported associations. Finally, there are scarce data regarding the optimal management of elevated BP values in the subacute stage of ischemic stroke. This lack of available information underscores the clinical relevance of this investigation that specifically addressed the temporal association of subacute BP variables with early functional outcome.

On the other hand, certain methodologic shortcomings of the present report need to be acknowledged. First, serial BP measurements were performed manually and thus are subject to measurement variability and

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observer bias. Ideally, 24-hour BP recordings should have been performed using automated oscillometric equipment.¹ Second, the retrospective design cannot exclude potential selection bias. Third, the authors did not investigate the association of SBP variability with early functional outcome in the subgroup of patients treated with IV thrombolysis. Different BP thresholds apply for treating poststroke hypertension in this specific subgroup of patients and strict BP pressure control is advocated before, during, and within the first 24 hours following tPA bolus. In view of the former considerations, this supplementary analysis might be of particular clinical relevance. Fourth, BP variability in the AIS setting may differ based on stroke location (brainstem vs hemispheric infarction) or size and these potential confounders were not included in the multivariable analyses. Finally, the authors do not provide any follow-up data on early stroke recurrence and infarct expansion (that could have been quantified by serial neuroimaging studies), which may have outlined a potential underlying mechanism explaining the documented association between increased BP oscillations and worse functional outcome.

This report adds to the accruing data that wide BP fluctuations during the first days of stroke onset have a detrimental effect on functional outcome and underline that SBP variability may be considered as a novel therapeutic target not only in the chronic but also in the subacute stage of ischemic stroke. Despite the fact that current stroke and hypertension guidelines ignore BP variability and episodic hypertension as independent risk factors for first-ever or recurrent stroke, clinicians should be aware that excessive BP variation also contributes to the progression of organ damage, triggering vascular events, and adversely affecting outcome in AIS patients.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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