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COMMENTARY

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Blood pressure variability and stroke: A risk marker of outcome and target for intervention

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In the current issue of *The Journal of Clinical Hypertension*, the study by Dr Zhao and colleagues aimed to examine the influence of fluctuations in blood pressure (BP) levels on outcome in patients with stroke.[1] By analyzing the data of the Controlling Hypertension After Severe Cerebrovascular Event (CHASE) study—a multicenter, randomized controlled trial comparing the efficacy and safety of individualized versus standard BP lowering in severe stroke—blood pressure variability (BPV) was estimated in 442 patients during the acute phase and 390 patients during the subacute phase of acute cerebrovascular events.[1] Increased BPV resulted strongly associated with poor 90-day functional status after adjustment for potential confounders, including age, sex, randomized group, stroke type, and severity on admission.[1]

The post hoc analysis of the CHASE trial adds to the growing body of literature that links BP variations to stroke course and reinforces prior studies that found increased BPV related with worse functional outcome after ischemic and hemorrhagic stroke.

1 | BLOOD PRESSURE VARIABILITY AND STROKE

One of the oldest and most challenging questions in acute stroke care is how to manage BP. Numerous clinical studies have been performed in acute ischemic and hemorrhagic strokes, which compared active or intensive BP reduction with no or guideline-based lowering.[2] So far, every trial failed to provide a definitive answer and ongoing uncertainties exist with respect to the entity and timing of BP reduction.[3,4]

The relationship between BP and outcome is not simply linear, and the effects depend on how and when BP is lowered. Mechanisms other than absolute BP reduction can play a role, and the benefit of early treatment can be enhanced by smooth and consistent BP control.[5,6] Variability of BP values over time represents more than a confounding phenomenon,[7-9] and it has been shown to act as a determinant of stroke outcome, independently of BP level.[10-13] Several mechanisms may explain the detrimental effects of BPV following brain infarct and cerebral hemorrhage, and they are only partially understood. As cerebral autoregulation is commonly impaired in the stroke area, minor fluctuations in BP may lead to under- or over-perfusion.[14] In the hours after the onset of brain ischemia, sudden drops in BP reduce the chance of reperfusion of potentially viable penumbra around the ischemic core and increase the risk of tissue ischemia and lesion size expansion.[15] Further, elevations in systemic BP levels can increase the risk of hemorrhagic transformation of damaged tissue. In hemorrhagic stroke, wide variations in BP during the active bleeding stage can worsen hematoma growth and expansion, and recurrent decreases in BP can favor perihematomal ischemia and amplify cell death and secondary injury.[16,17] Extreme fluctuations in BP can also contribute to the breakdown of the blood–brain barrier, promote vasogenic edema, and increase intracranial pressure.[18]

[Correction added on February 8, 2021, after first online publication: The copyright line was changed.]

Remarkably, the impairment of cerebral autoregulation can be influenced by infarct size. Blood pressure variability may exert a greater influence in patients with severe than mild cerebral infarct,[19] and the extent to which systolic BP reduction may influence the outcome has been shown to depend heavily on the initial hematoma size.[20] Although a reverse causality between BPV and outcome cannot be ruled out, since more severe strokes are associated with greater autonomic dysfunction, sympathetic imbalance, and higher BP fluctuations, the independent association with neurological outcome after the adjustment for stroke severity can substantially provide evidence for the actual contribution of BPV.[21]

2 | BLOOD PRESSURE VARIABILITY AS A THERAPEUTIC TARGET

The consistency of the association between BPV and stroke outcome suggests that interventions are warranted. Clinical stroke trials aimed not only to achieve BP target levels but also to minimize BPV are needed. Nonetheless, important questions are still unanswered, including how to reduce BPV and which patients to enroll.

One major issue is the complex and mutual relationship between absolute BP levels and BPV as any attempt to reduce mean BP can increase BPV. In the secondary analysis of the Blood Pressure after Endovascular Therapy for Ischemic Stroke (BEST) trial—a prospective, multicenter cohort study to identify post-endovascular stroke therapy peak systolic BP threshold discriminating good from bad functional outcome—BPV resulted lowest in patients who did not receive any intravenous antihypertensive medications and highest in patients who received intravenous drugs.[22] Further, there were no meaningful differences in BPV based on continuous intravenous versus as-needed antihypertensive medications.[22] Trials to determine optimal BP management approach and protocol-based strategies must also consider the individual effects of BP-lowering agents. In this regard, calcium channel blockers and thiazide diuretics have been shown to reduce interindividual variance, whereas beta-blockers and angiotensin-converting enzyme inhibitors increase BPV.[23-26]

Interventional trials could target patients with a higher likelihood of elevated BPV, and efforts are needed to identify the predicting variables. Clinical factors including left hemisphere stroke, age, diastolic BP at admission, and diabetes mellitus have been found to predict the highest tertile of systolic BPV in patients with anterior circulation ischemic stroke undergoing endovascular therapy.[22] The area under the receiver operating curve for the model including these variables, however, strongly suggested that further refinement of predictive scores would be worth pursuing.[22] It is likely that a variety of patient-specific factors, like stroke subtype, volume and site, status of collateral circulation, comorbidities as pre-existing hypertension, and heart failure, may influence the range of optimal BP values and vulnerability to the detrimental effects of BP fluctuations.

3 | VARIABILITY OF BLOOD PRESSURE IN CLINICAL STROKE CARE

Stabilization of BPV after stroke represents a promising strategy to improve the prognosis of patients. Significant challenges remain before the observed association between BPV and the neurological outcome can be translated into clinical practice. The combined goal of reducing both BP mean and variability appears the optimal hemodynamic intervention and protocol-based medication titration need to be developed.[22] Taking into account the heterogeneity and reciprocal interaction of the causes and effects of BP variations, a personalized approach will allow to weight therapeutic options and reach the best benefit from the intervention.

CONFLICT OF INTEREST

None.

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