# Blood Pressure Variability: A New Predicting Factor for Clinical Outcomes of Intracerebral Hemorrhage

Sasan Andalib, PhD,*′†′‡ Simona Lattanzi, MD, PhD,§ Mario Di Napoli, MD, PhD,¶ Alexander Petersen, PhD,# José Biller, MD,$ Tobias Kulik, MD,* Elizabeth Macri, MD,* Taurn Girotra, MD,* Michel T. Torbey, MD, MPH,* and Afshin A. Divani, PhD*

Spontaneous primary intracerebral hemorrhage (ICH) is a stroke subtype associated with the highest mortality rate. High blood pressure (BP) is the most common cause of non-lobar ICH. Recent clinical trials have been inconclusive regarding the efficacy of aggressive BP lowering to improve ICH outcome. The association between high BP and ICH prognosis is rather complex and parameters other than absolute BP levels may be involved. In this regard, there is accruing evidence that BP variability (BPV) plays a major role in ICH outcome. Different BPV indices have been used to predict hematoma growth, neurological deterioration, and functional recovery. This review highlights the available evidence about the relationship between BPV and clinical outcomes among patients. We identified standard deviation (SD), residual SD, coefficient of variation, mean absolute change, average real variability, successive variation, spectral analysis using Fourier analysis, and functional successive variation (FSV) as indices to assess BPV. Most studies have demonstrated the association of BPV with ICH outcome, suggesting a need to monitor and control BP fluctuations in the routine clinical care of ICH patients. When large inter-subject variability exists, FSV is a viable alternative quantification of BPV as its computation is less sensitive to differences in the patient-specific observation schedules for BP than that of traditional indices.

**Key Words:** Intracerebral hemorrhage—Blood pressure variability—Hematoma growth—Neurological deterioration—Functional outcome—Modified ranking score



*Abbreviations:* ARV, average real variability; ATACH-II, Antihypertensive Treatment of Acute Cerebral Hemorrhage-II; BBB, blood-brain barrier; BP, blood pressure; BPV, blood pressure variability; CBF, cerebral blood flow; CI, confidence interval; CPP, cerebral perfusion pressure; CT, computed tomography; CTA, computed tomography angiography; CV, coefficient of variation; DBP, diastolic blood pressure; FSV, functional successive variation; HG, hematoma growth; ICH, intracerebral hemorrhage; INTERACT2, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2; MAC, mean absolute change; MAP, mean arterial pressure; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; RSD, residual standard deviation; SBP, systolic blood pressure; SD, standard deviation; SV, successive variation

From the *Department of Neurology, School of Medicine, University of New Mexico, MSC10-5620, 1, Albuquerque, NM 87131, USA; †Research Unit of Clinical Physiology and Nuclear Medicine, Department of Nuclear Medicine, Odense University Hospital, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark; ‡Neuroscience Research Center, Department of Neurosurgery, Poursina Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran; §Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy; ¶Department of Neurology and Stroke Unit, San Camillo de' Lellis District General Hospital, Rieti, Italy; #Department of Statistics and Applied Probability, University of California, Santa Barbara, USA; and $Department of Neurology, Loyola University, Stritch School of Medicine, Maywood, IL, USA.

Received August 4, 2020; revision received September 10, 2020; accepted September 18, 2020.

Corresponding author. E-mail: adivani@gmail.com.

1052-3057/$ - see front matter



https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105340

## Introduction

Spontaneous primary intracerebral hemorrhage (ICH) accounts for 10−15% of all strokes and carries a mortality of approximately 40% within one month, with the bulk occurring within the first few days.[1] To date, few treatment options are available. Prognosis mostly depends on ICH volume and location.

The pathogenesis of spontaneous non-lobar ICH remains enigmatic. Several risk factors such as high BP, advanced age, diabetes mellitus, cigarette smoking, alcohol consumption, substance abuse, anticoagulants and/or antiplatelets use, and APOE ε2/ε4 genotypes have been identified.[2] Lipohyalinoid necrosis of small vessels in subcortical areas of the basal ganglia, thalamus, pons, and cerebellum, with subsequent rupture due to uncontrolled arterial hypertension, is one of the possible etiologies for non-lobar ICH.[3,4] Since arterial hypertension is the main cause of non-lobar ICH,[5] lowering BP in the acute setting is considered a preventive measure of paramount importance. Elevated BP not only triggers ICH, but is also commonly observed after ICH. Furthermore it is associated with hematoma growth, neurological deterioration, and poor outcomes.[6−8] Although intensive reduction of BP has been proposed to prevent neurological deterioration following ICH, recent randomized trials have casted doubt on the efficacy of aggressive BP-lowering treatment.[7−9] In the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2), intensive BP reduction to a target systolic BP (SBP) of <140 mm Hg within six hours of symptom onset improved functional outcome, compared with SBP of <180 mm Hg. Nevertheless, the treatment failed to reduce the rate of death or severe disability defined by a modified Rankin Scale (mRS) score of 3−6.[7] In the Antihypertensive Treatment of Acute Cerebral Hemorrhage-II (ATACH-II) trial, the reduction of SBP to 110-139 mm Hg within 4.5 hours of ICH onset, in comparison to 140−179 mm Hg, also failed to reduce the rate of death or disability.[9] These findings undermine the efficacy of aggressive BP reduction in the hyperacute stage of ICH and underline the complex nature of the association between BP and ICH.[10] However, an important limitation with both studies was the lack of inclusion of individuals with low Glasgow Coma Score and large intra-parenchymal hematomas, thus providing little data on the safety of intensive lowering of systolic BP among individuals with the highest intracranial pressures where cerebral autoregulation is likely to be further impaired. Therefore, the effect of BP-lowering on the course of ICH cannot be exclusively explained by mean SBP reduction, and other parameters may be involved. The influence of BP variability (BPV) on the outcome of cardiovascular and neurovascular disorders has recently attracted attention. BPV has been associated with the development, progression, and severity of cardiac, vascular, and renal damage, as well as increased risk of cardiovascular events and mortality.[11,12] High BPV may also increase the risk of death following acute ischemic stroke, and has been associated with worse neurologic outcomes.[13,14] In this regard, there has been increasing attention to explore whether BPV can also influence ICH outcome. The present review revisits the literature regarding the indices used to assess BPV and the relationship between BPV and ICH outcomes.

## Suggested indices to measure BPV

BPV refers to data summaries that quantify the variance of BP readings over time. The term BPV encompasses a wide range of BP variations, occurring very short−term BPV (over seconds or minutes), short−term BPV (over 24 hours), mid−term BPV (over days), and long−term BPV.[11,15−17] Generally, the changes in BP can be divided into those without regular features (random or erratic changes) and those characterized by well−defined patterns over time and related to biological or pathophysiological responses, as in the acute phase of ICH. The former can be described using simple measures of dispersion, such as standard deviation (SD) of average values over a given time-window,[18] which can also be adjusted for trends in underlying mean BP as in the coefficient of variation (CV),[18] and residual SD (RSD).[19] Mean absolute change (MAC),[20,21] average real variability (ARV), and variability between successive recordings (successive variation [SV]) are other suggested indices of BPV that take into account the sequence of measurements over time[22] (see Table 1 for the definition of the variables). Among more sophisticated methods in assessing BPV, Fourier spectral analysis techniques are particularly relevant. These techniques can also be used for discontinuous 24 h BP monitoring, where the residual variability is obtained by removing the slower cyclic components of 24 h BPV,[23,24] and functional successive variation (FSV) that accounts for time elapsed between BP measurements.[10]

SD is the simplest and most commonly used measure of BPV. It represents the dispersion of values around the mean but does not consider the order in which BP is measured, and it is confounded by the contribution of BP falls. As variants of SD, both CV and RSD, may suffer from similar problems. MAC, ARV, and SV estimate the variation in successive measurements and thus take the order into account, but do not incorporate the relative spacing between BP measurements, which can differ from patient to patient, especially in retrospective studies.[10] Spectral analysis allows the quantification of BPV at different time scales, for example, long-term (low frequency) or short-term (high frequency) volatility, but often they are assessed using various discrete frequency bands and are generally only suitable for the assessment of short-term variations.

A newly introduced BPV index is FSV, which targets a quantity that is independent of the BP recording intervals.

**Table 1.** *Definition of BPV indices.*

| BP index | Definition | Statistical Comment | Clinical Comment |
|---|---|---|---|
| Standard Deviation (SD)[18] | Classical SD of observed BP values | Reflects only the dispersion of values around the mean | It has been questioned as an appropriate index of short-term BPV, considering the fact that SD only reflects the dispersion of values around the mean, does not account for the order in which BP measurements are obtained, and is sensitive to the low sampling frequency of BP readings. Furthermore, SD is influenced by outliers or extreme BP values. |
| Coefficient of Variation (CV)[18] | SD divided by mean BP | Adjusts for mean BP, but ignores ordering of BP observations | As BPV largely depends upon mean blood pressure values, average SD can be divided by corresponding mean arterial pressure to normalize short-term BPV |
| Residual SD (RSD)[19] | SD of residuals from the linear regression model $BP = a + b \times time$ | Adjusts for linear mean BP trend, ignores ordering of BP observations | Representing the fast BP fluctuations that remain after exclusion of the slower components of the 24-hour BP profile |
| Average Real Variability (ARV)[22] | Average of absolute differences between consecutive recordings over 24 hours | Accounts for consecutive nature of BP recordings, but not the spacing | Focuses on short-term BP changes and is not affected by the circadian (dipping) phenomenon. It is sensitive to the individual BP measurement order and less sensitive to low sampling frequency of BP measurements. |
| Mean Absolute Change (MAC)[21] | Weighted average of absolute differences between consecutive recordings, with weights inversely proportional to the length of time between recordings | Weights account for order of and spacing between recordings | BP changes of same amplitude but differing in duration contribute differently to the overall sum of variability. |
| Successive Variation (SV)[22] | Dispersion between successive recordings, measured as square root of average squared differences between successive values | Similar to ARV, but with squared instead of absolute differences | Although SV accounts for the order, the relative spacing between BP recordings is not incorporated into this index, which can differ from patient to patient, particularly in retrospective datasets. |
| Functional Successive Variation (FSV)[10] | Integral of the absolute value of derivative of SBP curve, the latter being estimated using methods of functional data analysis | Targets a continuous version of SV, obtained as a limit when the number of recordings increases | It is a useful approach where there are irregular longitudinal data in order to estimate outcome trends, as it compensates for both inter-subject variability and intra-subject correlation and ensures that essential trends for recovery patterns are not overlooked due to limitations of the statistical analysis. Unlike other indices, FSV is defined to be independent of the BP measurement intervals and is similar to SV in that it measures variation in successive measurements. It is therefore robust to measurements that are heterogeneous across or between cohorts, due to reasons such as different numbers or spacing of recording intervals or random missing values. |
| Variation Independent of the Mean (VIM)[25] | $SD \times (\text{average mean BP} / \text{mean BP})^x$, where x is estimated from the nonlinear cohort model $SD = a \times (\text{mean BP})^x$ | A correction to CV to decrease correlation with mean SBP | It has no correlation with mean BP level. Furthermore, the estimation of VIM is derived from the distribution of BP within each cohort in study, and thus the value itself cannot be compared across populations. |

FSV is useful for heterogeneous recordings across or between cohorts because of different numbers or spacing of recording times or missing values.[10] The few studies directly comparing the prognostic value of different estimates of BPV have not provided clear indications about the preferred index.[10] At present, a reasonable choice could be to use the indices supported by the strongest outcome evidence, at least until better solutions are found. It is also important to consider that these estimates of BPV may be statistically correlated with mean BP levels, and therefore, it is important to adjust for average BP when assessing outcomes. In research, this can be achieved with statistical methods, while in individual patients, a mathematical correction made by calculating the coefficient of variation ($CV = \frac{SD \times 100}{mean}$) or the variation independent of the mean[25] can be helpful to gauge the entity of BPV relative to the average BP level. Table 1 presents a summary of the discussed BPV indices.

## BPV after ICH and clinical outcomes

Preliminary work on the impact of BP changes and ICH outcome has been done by Rodriguez-Luna and colleagues.[26] In this prospective study, the associations of BPV with hematoma growth (>33% or >6 ml), early neurological deterioration defined as an increase of 4 points or more on the National Institute of Health Stroke Scale (NIHSS) score or death at 24 h, and 3-month mortality in patients with acute supratentorial ICH were studied. Participants were 117 patients who had baseline and 24 h head computed tomography (CT) and CT angiography (CTA) in order to assess the presence of a "spot-sign". BP was recorded every 15 min during the first 24 h. Maximum and minimum BP, maximum BP increase and drop from baseline, and BPV values from SBP, diastolic BP (DBP) and mean arterial pressure (MAP) were calculated. The proportions of recordings >180 and >130 mmHg were considered as SBP and MAP loads, respectively. The results of this study showed that baseline BP parameters (SBP, DBP, and MAP) were not associated with hematoma growth and clinical outcomes. However, SBP >180-load was found to be independently associated with hematoma growth [odds ratio (OR) = 1.05, 95% confidence interval (CI): 1.010 −1.097, p = 0.016]. Moreover, both SBP >180-load (OR = 1.04, 95% CI: 1.001−1.076, p = 0.042) and SD for SBP variability (OR = 1.2, 95% CI: 1.047−1.380, p = 0.009) were independently associated with early neurological deterioration. In the spot-sign-positive group, none of the BP monitoring parameters were associated with hematoma growth. Nevertheless, higher maximum BP increase from baseline, SBP [median (IRQ): 31 (47.8) vs. 12 (24.5) mm Hg, p = 0.008], DBP [median (IRQ): 28 (13.5) vs. 15 (20.5) mm Hg, p = 0.048], and MAP [median (IRQ): 27.5 (22.8) vs. 8 (16.5) mm Hg, p = 0.009] loads were associated with hematoma growth in the spot sign negative group. In the spot sign negative group, higher SBP > 180-load [34.6% (70.5%) vs. 0% (13.4%), p = 0.004] and MAP >130-load [8.6% (39.8%) vs. 0% (8.5%), p = 0.020] were associated with hematoma growth.

A post-hoc analysis of INTERACT2 indicated that SBP variability can be a predictor of poor outcome in patients with acute ICH, and the benefit of lowering SBP to 140 mm Hg may be increased by smooth and sustained control, especially by avoiding SBP peaks.[27] SD of SBP was estimated using five BP measurements in the first 24 hours (hyperacute phase) and 12 measurements during days 2-7 (acute phase) that were categorized into quintiles. In this post-hoc analysis, 2645 (93.2%) patients in the hyperacute phase and 2347 (82.7%) in the acute phase were studied. There was a significant linear association between SD of SBP and the primary outcome in both the hyperacute (highest quintile adjusted OR = 1.41, 95% CI: 1.05-1.90; p = 0.0167) and acute (highest quintile adjusted OR = 1.57, 95% CI: 1.14-2.17; p = 0.0124) phases. The primary outcome was defined as death or major disability at 3 months mRS score ≥ 3) and the secondary outcome as an ordinal shift in mRS score at 3 months. Associations were similar for the secondary outcome (highest quintile adjusted OR = 1.43, 95% CI: 1.14-1.80, p = 0.0014 for the hyperacute phase and OR = 1.46, 95% CI: 1.13-1.88, p = 0.0044 for the acute phase).

In the secondary analysis of the ATACH-II trial,[22] the association of SBP and SBP variability in the acute and subacute stages of ICH (defined as 2-24 hours and 2, 3, and 7 days after ICH onset, respectively) and outcomes were assessed. Primary and secondary outcomes, defined as a mRS score of 3-6 and a utility-weighted mRS at 3 months, respectively, were studied. There were 913 and 877 patients in the acute and subacute phases, respectively. Mean BP and 5 different indices of SBP variability (i.e., SD, CV, ARV, SV, and RSD) were calculated. All indices of SBP variability were associated with the primary neurological outcome in the acute and subacute ICH stages. No association between the mean SBP variability and ICH outcomes was observed.

A pre-planned pooled analysis of individual patient data acquired from the combined INTERACT2 and ATACH-II trials[28] showed that low SD of SBP within 24 hours was associated with HG (>6 mL) from baseline to 24 hours (adjusted OR = 1.21, 95% CI: 1.02−1.43, p = 0.0330), neurological deterioration over 24 hours, defined as 4 points or more increase in baseline NIHSS, 2 points or more decrease in baseline in Glasgow Coma Scale, or treatment-related symptomatic hypotension requiring corrective therapy, (adjusted OR = 1.41, 95% CI: 1.23−1.61, p < 0.0001), death within 3 months (adjusted OR=1.16, 95% CI: 1.01−1.34, p = 0.0373), and any cardiac or renal serious adverse event within 3 months (adjusted OR = 1.22, 95% CI: 1.09−1.36, p = 0.0004).

A retrospective study investigated the influence of SBP and DBP variabilities in 138 patients with ICH. In this study, BP recordings were made during the first

72 hours from symptom onset. Indices of BPV including SD, CV, and the max-min difference of BP were calculated.[29] The study showed a dose-response relationship between poor outcome (defined as 3-month mRS score of 2-6 if the baseline NIHSS score was ≤7, mRS score of 3-6 if the NIHSS score was 8-14, and mRS score of 4-6 if the NIHSS score was ≥15) and each measure of SBP variability (adjusted ORs for the highest thirds of SD = 7.95, 95% CI: 2.88-21.90; CV = 7.74, 95% CI: 2.88-20.80; maximum-minimum = 8.36, 95% CI: 2.72-25.62; all p values < 0.001). The strength of the association with DBP variabilty was weaker and only significant for the higher values of variability (adjusted ORs for the highest thirds of SD = 6.74, 95% CI: 2.52-18.04, p < 0.001; CV = 4.57, 95% CI: 1.77-11.81 p < 0.001; maximum-minimum = 4.34, 95% CI: 1.72-10.93 p < 0.001).

In a multisite cohort, Meek et al.[30] assessed in-hospital SBP variability in ICH patients and evaluated the association between high SBP variability and 3-month severe disability or death and the association of pre-hospital factors with high SBP variability. SBP and inter- and intra-patient SBP variability were quantified with a SD value of 13.0 set as the cut-off point for high SBP variability. A total of 566 ICH patients were examined. Patients with high SBP variability showed a higher risk of 3-month severe disability or death (mRS score of 4−6, relative risk [RR] = 1.20, 95% CI: 1.04-1.39), after adjustment for age, pre-morbid functional status, and other disease severity measures. In addition, a greater likelihood of in-hospital high SBP variability was independently seen in elderly, female patients, those with high admission SBP, and higher baseline glucose.

In a recent retrospective study conducted by Divani et al.,[10] ten years of consecutive data of 762 spontaneous ICH patients at 2 healthcare systems were used to assess the association between SBP variability in the first 24 hours of admission and in-hospital ICH outcome. The authors calculated SD, CV, SV, range, and FSV for SBP, DBP, and MAP variabilities. The primary outcome was the mRS score at discharge categorized into dichotomous (0−3 and 4−6) and trichotomous (0−2, 3−4, and 5−6) variables, in addition to hematoma growth as a secondary endpoint. The ordinal regression analysis showed that SD, CV, SV, range, and FSV for SBP variability were significantly associated with an unfavorable outcome (mRS score of 4−6), while SD, CV, range, and FSV exerted a significant impact upon poor (mRS score of 3-4) and severe/death (mRS score of 5-6) outcomes. The DBP and MAP variabilities were not associated with the primary outcome. ICH patients with normal BP experienced significantly lower mean SBP variability according to all BPV indices in comparison with the untreated-hypertension cohort indices and in 3 out of 5 SBP variability indices (SD, range, and FSV) in comparison with treated-hypertension patients. It is worth noting that lower mean SBP variability of treated-hypertension versus untreated-hypertension patients was only seen in the SV and FSV (p = 0.045). Furthermore, none of the SBP variability indices was associated with HG.

In another study, the association between BPV and ICH outcomes was assessed using SAMURAI-ICH cohort data.[31] A total of 205 patients with hyperacute ICH (<3 hours from onset) and initial SBP >180 mm Hg that was lowered to 120-160 mm Hg using intravenous nicardipine was included. BP was recorded hourly over the first 24 hours, and SD and SV of SBP and DBP were calculated. The associations of SBP variability with neurological deterioration (≥2 decrease in Glasgow Coma Scale or ≥4 increase in NIHSS from baseline in 72 hours), hematoma growth (>33% growth from baseline to 24 hours), and unfavorable outcomes (mRS score of 4−6 at 3 months) were evaluated. Multivariate logistic regression analysis revealed an association between neurological deterioration and SD of SBP (OR = 2.75; 95% CI: 1.45−6.12 per quartile) and SV of SBP (2.37; 1.32−4.83), as well as an association between unfavorable outcomes and SV of SBP (1.42; 1.04−1.97). Additionally, the absolute and relative change of hematoma volume were shown to be significant across quartiles of both the SD and SV of SBP following the adjustment for prognostic factors [absolute difference: SD (p = 0.009) and SV (p = 0.025); relative change: SD (p = 0.033) and SV (p = 0.048]. Both the absolute difference and relative change in hematoma volume were shown to be highest in the upper quartiles of SD and SV.

Using a prospective database, Jeon et al.[20] evaluated 104 patients with spontaneous ICH having intensive antihypertensive treatment aiming at BP of lower than140 mmHg. SBP variability was calculated using the range, SD, CV, and MAC. Hematoma growth and mRS score ≥3 were considered as primary outcomes, and an ordinal shift in mRS at 3 months was considered as a secondary outcome. MAC (adjusted OR = 1.11; 95% CI: 1.02−1.21; p = 0.012) was significantly associated with hematoma growth even after adjustment for mean SBP level. SD (adjusted OR = 1.19; 95% CI: 1.03-1.38) and CV (adjusted OR = 1.27; 95% CI: 1.05-1.55) of SBP were significantly associated with 3-month mRS after adjusting for mean SBP. There was a significant association between MAC of SBP and higher mRS shift at 3 months (adjusted OR = 1.08; 95% CI: 1.02−1.15; p = 0.008).

A post-hoc analysis of data from FAST-MAG investigated the influence of BPV on outcomes of patients with ICH and showed that BPV during the first hours after symptom onset was independently associated with unfavorable (defined as mRS 3-6 at 3 months).[32] BP values were recorded in the hyperacute stage (0 to 6 hours) and the acute stage (0 to 26 hours) subsequent to ICH onset. SD, CV, and SV were considered among the measures of BPV. In the study, an unfavorable outcome (mRS score of 3−6) at 3 months was observed in 270 out of 386 patients (69.9%). In the multivariable analysis, mean and maximum SBP were not associated with unfavorable

outcomes, while all the three measures of BPV were associated in both the hyperacute and acute ICH stages. BPV was associated with unfavorable outcome in the hyperacute phase [for the highest quintile of SD (adjusted OR = 3.73, 95% CI: 1.58-8.80, $p < 0.01$), the highest quintile of CV (adjusted OR = 4.78, 95% CI: 2.00−11.40; $p < 0.001$), and the highest quintile of SV (adjusted OR = 3.39, 95% CI: 1.44-8.00; $p < 0.01$), compared to the lowest quintile. In the acute phase, BPV was associated with unfavorable outcome [for the highest quintile of SD (adjusted OR = 5.06, 95% CI: 1.95-13.1, $p < 0.01$), the highest quintile of CV (adjusted OR = 4.97, 95% CI: 1.93−12.84; $p < 0.001$), and the highest quintile of SV (adjusted OR = 5.60, 95% CI: 2.12-14.7; $p < 0.001$), compared to the lowest quintile. BPV remained strongly associated with the outcome, suggesting that BPV in the hyperacute stage of ICH maybe even of greater prognostic relevance than the absolute BP target. Although one merit of this study was the evaluation of BPV in hyperacute ICH, its drawback was the lack of adjustment for prognostic factors such as hematoma volume, growth, and location. Additionally, this study did not explore the association of BP with early neurological deterioration.

A recent single-center, retrospective chart review of patients admitted with spontaneous ICH compared the effect of nicardipine, labetalol and/or hydralazine. Those individuals treated with nicardipine infusion had significantly less BPV ($p = 0.04$) and were more likely to attain a target SBP <140 mmHg ($p < 0.01$).[33]

These findings build upon the emerging evidence that not only absolute BP levels, but even their fluctuations over time can influence the outcome of ICH,[27,29,32,34] and suggest how sustained BP control and stabilization of BP values during the acute state of ICH might represent a neglected target of intervention.

## Mechanisms underlying the association of BPV and ICH outcomes

The idea that exaggeration of BPV may be detrimental for the brain following ICH is physiologically plausible. Several mechanisms may explain the detrimental effects of BPV during the hyperacute/acute stage of ICH. The brain has a high metabolic demand for oxygen, any process that enhances perfusion variability has the potential to destabilize tissue oxygenation leading to neuronal injury. An excessive perfusion can result in the breakdown of the blood-brain barrier resulting in transudation of fluid into the interstitium with edema development and increasing hematoma volume. Recurrent sudden rises and fluctuations of BP during the active bleeding stage can exacerbate hematoma growth.[26,35] BPV can contribute to hematoma growth and edema formation by impeding cerebral autoregulation.[32] Recurrent sudden falls of BP can increase perihematomal ischemia, as well as ischemia in the areas of remote penetrating arteries.[36] BP rise and fall can disrupt the blood-brain barrier (BBB) and promote vasogenic perihematomal edema.[37] Higher BPV can also cause cell death in the area of impaired cerebral autoregulation through higher fluctuations of cerebral blood flow (CBF) following the active bleeding period.[34] Cerebral perfusion pressure (CPP) in the ICH territory and surrounding perihematomal tissue depends heavily upon systemic BP, and BP fluctuations can amplify the secondary brain injury within the potentially viable perihematomal region by directly influencing CBF and CPP.[32] Therefore, stringent control of CBF is pivotal for normal brain function after ICH. In the acute stage of ICH, the fluctuation of cerebral perfusion pressure is aggravated by short-term BPV due to impaired automatic regulation of CBF.[29] However, while it is generally recognized that BP is an important determinant of CBF, the exact relationship between pressure and flow is more complex as actually known.[38] This concept implies that mechanisms normally involved in systemic blood pressure control are relatively unimportant for CBF in the presence of intact cerebral autoregulation, while they become relevant in the presence of a failure of cerebral autoregulation. Although the precise mechanisms underpinning these features of cerebral autoregulation in ICH are still under investigation,[38] it is clear that CBF exhibits variability, and that BPV is an important determinant of this variability.[39] Finally, different phenotypes are also associated with high BPVy such as female gender, older age, low heart rate, increased heart rate variability, elevated BP,[40] and untreated hypertension.[10]

However, a reverse causality between BPV and outcome cannot be ruled out because more severe strokes may be accompanied by greater autonomic dysfunction and sympathetic imbalance leading to higher BP variability. The independent association between BPV and outcomes after the adjustment for ICH severity parameters, however, can provide evidence for the actual BPV contribution.

BPV has not been consistently found to be associated with hematoma growth[31,41] possibly due to factors such as time of onset to first CT scan or the time of the follow-up CT scan that can lead to underestimating hematoma growth rate. Nonetheless, a link between BPV levels, risk of re-bleeding, and clinical outcome cannot be ignored. Table 2 summarizes the findings of the main studies evaluating the effects of BPV on ICH outcomes.

## The role of BPV indices in the prediction of ICH outcome

In analyzing the outcome of ICH, large intersubject variability in the number and frequency of BP measurements should be taken into account. Some studies have not reported consistent significant effects of the usual BPV indices (e.g., SD, CV, and SV) using standard statistical analysis techniques.[42,43] When large inter-subject

**Table 2.** *Summary of studies exploring the effect of BPV on clinical outcomes after ICH.*

| Authors | Year | Study design | Sample size | BPV indices | Frequency of measurements | Main findings |
|---|---|---|---|---|---|---|
| Rodriguez-Luna et al.,[26] | 2013 | Prospective cohort, acute ICH | 117 | SD of SBP | Every 15 minutes during the first 24 hours | SD was associated with hematoma growth |
| Manning et al.,[27] | 2014 | RCT, hyperacute and acute ICH | 2839 (2645 participants in hyperacute phase and 2347 in acute phase) | SD of SBP | Every 15 minutes during the first hour, every 6 hours between 2-24 hours, and twice a day from days 2−7 | SD was associated with mRS and ordinal shift in mRS |
| Tanaka et al.,[31] | 2014 | Prospective cohort, hyperacute ICH | 205 | SD and SV | Every 15 minutes during the first 2 hours, every hour between 3-24 hours, and once at 48 and 72 hours | SD and SV were associated with unfavorable outcome |
| Lattanzi et al.,[29] | 2015 | Retrospective study, acute ICH | 138 | SD and CV | Every 4 hours during the first 72 hours | A dose-response association between poor mRS and each measure of SBP variability. DBP variability was significant for higher values. |
| Jeon et al., [20] | 2018 | Prospective cohort, acute ICH | 104 | Range, SD, CV, and MAC | Every 15 minutes during the first 2 hours and every hour thereafter | SD and CV were associated with mRS. MAC was associated with higher mRS shift. |
| de Havenon et al.,[22] | 2018 | RCT, acute and subacute ICH | 1000 (913 participants in acute phase and 877 participants in subacute phase) | SD, CV, ARV, SV, and RSD | Every hour between 2 to 24 hours post randomization and on days 2, 3, and 7. | All of the indices were associated with worse neurological outcome. |
| Chung et al.,[32] | 2018 | RCT, hyperacute and acute ICH | 386 | SD, CV, and SV | A total of 11 measurements in the first 24 hours with 4 hour intervals. | All indices of SBP variability were associated with mRS in the hyperacute and acute phases. |
| Moullaali et al.[28] | 2019 | RCT, acute ICH | 3829 | SD | SBP was measured in the first 24 hours. Every 15 minute in the first hour of treatment and then at hours 6,12, 18, and 24 | SD of SBP was associated with good outcome, functional independence, HG, neurological deterioration, death, any serious adverse events. |
| Meek et al.,[30] | 2019 | Prospective cohort, acute ICH | 566 | SD | Serial SBP and DBP recordings | SD of SBP was associated with severe disability or death. |
| Divani et al.,[10] | 2019 | Retrospective study, acute ICH | 762 | SD, CV, SV, range, and FSV | Every hour for the first 6 hours, every 2 hours from 8-24 hours | All indices were associated with unfavorable outcomes. In ordinal models, SD, CV, range, and FSV were found to have a significant effect on the probabilities of poor (mRS 3-4) and severe/death (mRS 5-6) outcomes |

Abbreviations: ARV: average real variability; CV: coefficient of variation; FSV: functional coefficient of variation; ICH: intracerebral hemorrhage; MAC: mean absolute change; mRS: modified Rankin Score; RCT: randomized clinical trial; RSD: residual SD; SBP: systolic blood pressure; DBP: diastolic blood pressure; SD: standard deviation; and SV: successive variation, MAP: mean arterial pressure, CT: computed tomography; ICU: intensive care unit.

variability exists, FSV is a viable alternative quantification of BPV as it is defined in terms of the latent BP curve in continuous time and, hence, is independent of the patient-specific observation schedule for BP monitoring. Practically, however, FSV must be approximated by the BP measurements taken at discrete times. In order to mitigate the bias that may be associated with having fewer BP measurements,[10] FSV is estimated using methods of functional data analysis.[44,45] These methods efficiently utilize BP measurements from all patients in order to more accurately recover each patient's FSV and use it in the evaluation of the association with outcomes. Specifically, estimation of FSV is achieved by first estimating the derivative on a very dense time scale using functional data analysis,[44] followed by numerical integration. An example demonstrating the potential advantage of FSV over other BPV indices in cohorts with large inter-subject variability in BP recordings was shown in the study by Divani et al.,[10] where FSV and SV were the only BPV indices to be significantly different between hypertensive patients who had been treated for their hypertension and those who had not.

## Concluding remarks

The concerns regarding the optimal management of high BP following ICH have not been fully addressed. Randomized controlled trials have failed to demonstrate a positive influence of intensive BP lowering on ICH outcomes.[46,47] Interestingly, some recent studies have suggested a prognostic role for BPV in the prediction of outcomes. Therefore, BPV monitoring should be part of routine clinical practice to identify BPV phenotypes that may warrant attention, especially in the hyperacute and acute-care settings. However, before routinely used in clinical practice, several hypotheses should be tested in well-designed clinical trials to assess the technical accuracy of these new measures of BP variability vis-à-vis their ability to produce useful information under standardized conditions that can determine if these measures have a place in the clinical pathway and management of ICH patients. Finally, the prognostic accuracy of these new measures should be assessed to verify their impact on the ICH outcome. While existing evidence can be used, new evidence will be needed before incorporating the information on BPV into the routine clinical practice. Furthermore, more research is required to better identify the causes and thresholds of BPV that can contribute to worsening ICH outcome. Clinical trials should be aimed not only to achieve BP target levels but also identifying interventions to minimize BPV. In this regard, short half-life antihypertensive medications to achieve steady BP could be usefully considered in future investigations.

## Financial disclosures

None.

## Declaration of Competing Interest

None.

**Sources of funding:** None.

## References

1. van Asch CJ, Luitse MJ, Rinkel GJ, et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 2010;9:167-176. https://doi.org/10.1016/s1474-4422(09)70340-0.
2. Martini SR, Flaherty ML, Brown WM, et al. Risk factors for intracerebral hemorrhage differ according to hemorrhage location. Neurology 2012;79:2275-2282. https://doi.org/10.1212/WNL.0b013e318276896f.
3. Lammie GA. Hypertensive cerebral small vessel disease and stroke. Brain Pathol 2002;12:358-370. https://doi.org/10.1111/j.1750-3639.2002.tb00450.x.
4. Lammie GA, Lindley R, Keir S, et al. Stress-related primary intracerebral hemorrhage: autopsy clues to underlying mechanism. Stroke 2000;31:1426-1428. https://doi.org/10.1161/01.str.31.6.1426.
5. Hevesi M, Bershad EM, Jafari M, et al. Untreated hypertension as predictor of in-hospital mortality in intracerebral hemorrhage: a multi-center study. J Crit Care 2018;43:235-239. https://doi.org/10.1016/j.jcrc.2017.09.010.
6. Ohwaki K, Yano E, Nagashima H, et al. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. Stroke 2004;35:1364-1367. https://doi.org/10.1161/01.STR.0000128795.38283.4b.
7. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013;368:2355-2365. https://doi.org/10.1056/NEJMoa1214609.
8. Leira R, Davalos A, Silva Y, et al. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. Neurology 2004;63:461-467. https://doi.org/10.1212/01.wnl.0000133204.81153.ac.
9. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. NEJM 2016;375:1033-1043. https://doi.org/10.1056/NEJMoa1603460.
10. Divani AA, Liu X, Di Napoli M, et al. Blood pressure variability predicts poor in-hospital outcome in spontaneous intracerebral hemorrhage. Stroke 2019;50:2023-2029. https://doi.org/10.1161/strokeaha.119.025514.
11. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ 2016;354:i4098. https://doi.org/10.1136/bmj.i4098.
12. Parati G, Ochoa JE, Lombardi C, et al. Assessment and management of blood-pressure variability. Nat Rev Cardiol 2013;10:143-155. https://doi.org/10.1038/nrcardio.2013.1.
13. de Havenon A, Stoddard G, Saini M, et al. Increased blood pressure variability after acute ischemic stroke increases the risk of death: a secondary analysis of the virtual international stroke trial archive. JRSM Cardiovasc Dis 2019;8. https://doi.org/10.1177/2048004019856496. 2048004019856496-2048004019856496.
14. Stead LG, Gilmore RM, Vedula KC, et al. Impact of acute blood pressure variability on ischemic stroke outcome.

Neurology 2006;66:1878-1881. https://doi.org/10.1212/01.wnl.0000219628.78513.b5.
15. Mancia G. Short- and long-term blood pressure variability: present and future. Hypertension 2012;60:512-517. https://doi.org/10.1161/hypertensionaha.112.194340.
16. Abellan-Huerta J, Prieto-Valiente L, Montoro-Garcia S, et al. Correlation of blood pressure variability as measured by clinic, self-measurement at home, and ambulatory blood pressure monitoring. Am J Hypertens 2018;31:305-312. https://doi.org/10.1093/ajh/hpx183.
17. Grassi G, Bombelli M, Brambilla G, et al. Total cardiovascular risk, blood pressure variability and adrenergic overdrive in hypertension: evidence, mechanisms and clinical implications. Curr Hypertens Rep 2012;14:333-338. https://doi.org/10.1007/s11906-012-0273-8.
18. Parati G, Stergiou GS, Dolan E, et al. Blood pressure variability: clinical relevance and application. J Clin Hypertens 2018;20:1133-1137. https://doi.org/10.1111/jch.13304.
19. Rothwell PM, Howard SC, Dolan E, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol 2010;9:469-480. https://doi.org/10.1016/s1474-4422(10)70066-1.
20. Jeon JP, Kim C, Kim SE. Blood pressure variability and outcome in patients with acute nonlobar intracerebral hemorrhage following intensive antihypertensive treatment. Chin Med J (Engl) 2018;131:657-664. https://doi.org/10.4103/0366-6999.226886.
21. Hermanides J, Vriesendorp TM, Bosman RJ, et al. Glucose variability is associated with intensive care unit mortality. Crit Care Med 2010;38:838-842. https://doi.org/10.1097/CCM.0b013e3181cc4be9.
22. de Havenon A, Majersik JJ, Stoddard G, et al. Increased blood pressure variability contributes to worse outcome after intracerebral hemorrhage. Stroke 2018;49:1981-1984. https://doi.org/10.1161/strokeaha.118.022133.
23. Parati G, Saul JP, Di Rienzo M, et al. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. Hypertension 1995;25:1276-1286. https://doi.org/10.1161/01.hyp.25.6.1276.
24. Goh CH, Ng SC, Kamaruzzaman SB, et al. Standing beat-to-beat blood pressure variability is reduced among fallers in the Malaysian elders longitudinal study. Med (Baltim) 2017;96:e8193. https://doi.org/10.1097/md.0000000000008193.
25. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:895-905. https://doi.org/10.1016/s0140-6736(10)60308-x.
26. Rodriguez-Luna D, Pineiro S, Rubiera M, et al. Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. Eur J Neurol 2013;20:1277-1283. https://doi.org/10.1111/ene.12180.
27. Manning L, Hirakawa Y, Arima H, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. Lancet Neurol 2014;13:364-373. https://doi.org/10.1016/s1474-4422(14)70018-3.
28. Moullaali TJ, Wang X, Martin RH, et al. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. Lancet Neurol 2019;18:857-864. https://doi.org/10.1016/s1474-4422(19)30196-6.
29. Lattanzi S, Cagnetti C, Provinciali L, et al. Blood pressure variability and clinical outcome in patients with acute intracerebral hemorrhage. J Stroke Cerebrovasc Dis 2015;24:1493-1499. https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.03.014.
30. Meeks JR, Bambhroliya AB, Meyer EG, et al. High in-hospital blood pressure variability and severe disability or death in primary intracerebral hemorrhage patients. Int J Stroke 2019;14:987-995. https://doi.org/10.1177/1747493019827763.
31. Tanaka E, Koga M, Kobayashi J, et al. Blood pressure variability on antihypertensive therapy in acute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. Stroke 2014;45:2275-2279. https://doi.org/10.1161/strokeaha.114.005420.
32. Chung PW, Kim JT, Sanossian N, et al. Association between hyperacute stage blood pressure variability and outcome in patients with spontaneous intracerebral hemorrhage. Stroke 2018;49:348-354. https://doi.org/10.1161/strokeaha.117.017701.
33. Poyant JO, Kuper PJ, Mara KC, et al. Nicardipine reduces blood pressure variability after spontaneous intracerebral hemorrhage. Neurocrit Care 2019;30:118-125. https://doi.org/10.1007/s12028-018-0582-0.
34. Manning LS, Mistri AK, Potter J, et al. Short-term blood pressure variability in acute stroke: post hoc analysis of the controlling hypertension and hypotension immediately post stroke and continue or stop post-stroke antihypertensives collaborative study trials. Stroke 2015;46:1518-1524. https://doi.org/10.1161/strokeaha.115.009078.
35. Qureshi AI. The importance of acute hypertensive response in ICH. Stroke 2013;44:S67-S69. https://doi.org/10.1161/STROKEAHA.111.000758.
36. Menon RS, Burgess RE, Wing JJ, et al. Predictors of highly prevalent brain ischemia in intracerebral hemorrhage. Ann Neurol 2012;71:199-205. https://doi.org/10.1002/ana.22668.
37. Sykora M, Diedler J, Turcani P, et al. Subacute perihematomal edema in intracerebral hemorrhage is associated with impaired blood pressure regulation. J Neurol Sci 2009;284:108-112. https://doi.org/10.1016/j.jns.2009.04.028.
38. Tzeng YC, Ainslie PN. Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. Eur J Appl Physiol 2014;114:545-559. https://doi.org/10.1007/s00421-013-2667-y.
39. Minhas JS, Panerai RB, Ghaly G, et al. Cerebral autoregulation in hemorrhagic stroke: a systematic review and meta-analysis of transcranial Doppler ultrasonography studies. J Clin Ultrasound 2019;47:14-21. https://doi.org/10.1002/jcu.22645.
40. Kato T, Kikuya M, Ohkubo T, et al. Factors associated with day-by-day variability of self-measured blood pressure at home: the Ohasama study. Am J Hypertens 2010;23:980-986. https://doi.org/10.1038/ajh.2010.94.
41. Jauch EC, Lindsell CJ, Adeoye O, et al. Lack of evidence for an association between hemodynamic variables and hematoma growth in spontaneous intracerebral hemorrhage. Stroke 2006;37:2061-2065. https://doi.org/10.1161/01.STR.0000229878.93759.a2.

42. Kahn LE, Zygman ML, Rymer WZ, et al. Effect of robot-assisted and unassisted exercise on functional reaching in chronic hemiparesis. In: In: Proceedings of the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 1342; 2001. p. 1344-1347.
43. Kahn LE, Averbuch M, Rymer WZ, et al. Comparison of robot-assisted reaching to free reaching in promoting recovery from chronic stroke. 2001. p. 39.
44. Liu B, Müller H-G. Estimating derivatives for samples of sparsely observed functions, with application to online auction dynamics. J Am Stat Assoc 2009;104:704-717.
45. Ramsay J, Silvermann B. Functional data analysis. Springer series in statistics. Biom JJ Math Methods Biosci 1998;40:56.
46. Lattanzi S, Cagnetti C, Provinciali L, et al. How should we lower blood pressure after cerebral hemorrhage? A systematic review and meta-analysis. Cerebrovasc Dis 2017;43:207-213. https://doi.org/10.1159/000462986.
47. Lattanzi S, Silvestrini M. Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. Neurology 2015;85:557-558. https://doi.org/10.1212/01.wnl.0000470918.40985.d0.