

Determinants of the impact of blood pressure variability on neurological outcome after acute ischaemic stroke

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To cite: de Havenon A, Bennett A, Stoddard GJ, *et al*. Determinants of the impact of blood pressure variability on neurological outcome after acute ischaemic stroke. *Stroke and Vascular Neurology* 2017;2:e000057. doi:10.1136/svn-2016-000057

Received 18 November 2016
Accepted 9 December 2016
Published Online First
27 January 2017

ABSTRACT

Introduction: Increased blood pressure variability (BPV) is detrimental after acute ischaemic stroke, but the interaction between BPV and neuroimaging factors that directly influence stroke outcome has not been explored.

Methods: We retrospectively reviewed inpatients from 2007 to 2014 with acute anterior circulation ischaemic stroke, CT perfusion and angiography at hospital admission, and a modified Rankin Scale (mRS) 30–365 days after stroke onset. BPV indices included SD, coefficient of variation and successive variation of the systolic blood pressure between 0 and 120 hours after admission. Ordinal logistic regression models were fitted to mRS with predictor variables of BPV indices. Models were further stratified by CT perfusion volumetric measurements, proximal vessel occlusion and collateral score.

Results: 110 patients met the inclusion criteria. The likelihood of a 1-point rise in the mRS increased with every 10 mm Hg increase in BPV (OR for the 3 BPV indices ranged from 2.27 to 5.54), which was more pronounced in patients with larger ischaemic core volumes (OR 8.37 to 18.0) and larger hypoperfused volumes (OR 6.02 to 15.4). This association also held true for patients with larger mismatch volume, proximal vessel occlusion and good collateral vessels.

Conclusions: These results indicate that increased BPV is associated with worse neurological outcome after stroke, particularly in patients with a large lesion core volume, concurrent viable ischaemic penumbra, proximal vessel occlusion and good collaterals. This subset of patients, who are often not candidates for or fail acute stroke therapies such as intravenous tissue plasminogen activator or endovascular thrombectomy, may benefit from interventions aimed at reducing BPV.

INTRODUCTION

Increased blood pressure (BP) variability (BPV), independent of the BP mean, is harmful after ischaemic and haemorrhagic stroke.^{1–7} Under normal circumstances, dynamic autoregulation of the cerebrovascular bed maintains a relatively constant cerebral blood flow (CBF) across a wide range of

BPs.^{8,9} However, after ischaemic stroke, the ability to autoregulate is often impaired in the area of the lesion core and ischaemic penumbra.^{10,11} As a result, the penumbra can be directly exposed to deleterious fluctuations in systemic BP and increased BPV has been shown to result in lesion core growth on diffusion-weighted MRI 36–48 hours post-stroke.¹² Prior analyses of BPV have not evaluated the impact of admission lesion core volume or other characteristics of the ischaemic penumbra, which are important radiological predictors of clinical outcome and response to acute stroke treatments.^{13,14} Additional neuroimaging determinants of outcome, such as proximal vessel occlusion (PVO) and cerebral collateral vessel status, have likewise not been evaluated in past BPV studies.^{8,9} To address these questions, we examined the impact of CT perfusion (CTP) volumetric measurements, PVO and collateral vessel status on the interaction between BPV and neurological outcome among a cohort of patients with acute ischaemic stroke.

METHODS

Patient selection

Patients were retrospectively identified by searching the electronic medical record of an academic medical centre for ischaemic stroke International Classification of Diseases (ICD)-9 codes between 2007 and 2014. Patients were included who had a CTP and angiographic imaging at hospital admission, an anterior circulation stroke confirmed by a neurologist, BP data available for 120 hours after admission and a follow-up mRS 30–365 days after stroke onset. If mRS was 0 (no symptoms) or 6 (death) at hospital discharge, it was carried forward as a follow-up mRS. Lacunar strokes were excluded because CTP imaging is not sensitive to small perfusion abnormalities. We



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selected the 120-hour interval for calculating BPV because the two largest studies of BPV included BP data for up to 7 days after stroke onset and many other studies focused on the first 72 hours after onset.¹⁵ The 120-hour interval allowed us to include most patients while also acquiring a

sufficient number of BP readings per patient to reliably determine variability. Additional information was obtained from the chart, including admission National Institutes of Health (NIH) Stroke Scale (NIHSS), patient demographics, medical comorbidities, admission laboratory values, data from angiographic imaging, administration of intravenous tissue plasminogen activator (tPA) and performance of endovascular therapy (defined as mechanical or aspiration thrombectomy or intra-arterial tPA).

Imaging parameters and analysis

Symptomatic intracerebral haemorrhage (sICH) was identified on non-contrast head CT or MRI and defined using the European Cooperative Acute Stroke Study 2 criteria.¹⁶ CTP was performed using a 64-section scanner (Definition or Definition AS; Siemens) using a four-dimensional spiral technique as previously described.¹⁷ Standard imaging parameters were 80 kVp, 200 mAs, 4 mm slice thickness, 8.4 cm total coverage. Approximately 40 mL of non-ionic iodinated contrast was administered intravenously at 7 mL/s using a power injector.

CTP source images were used to assess for the presence of cerebral collateral blood vessels (CTP collaterals) in the region of the Sylvian fissure and leptomeningeal convexity based on a validated ordinal scale.¹⁸ Collateral vessels were graded by comparing the symptomatic hemisphere to the contralateral hemisphere as follows: (1) absent; (2) less than the contralateral normal side; (3) equal to the contralateral normal side; (4) greater than the contralateral normal side. For both sICH and CTP collaterals, two experienced raters (AdH, JSM) graded a representative portion (30%) of the cohort and the results were compared with two additional raters (AB, SO), who were allowed to continue grading the remainder of the cohort because their inter-rater reliability (κ) with the experienced readers was >0.9 . For statistical analysis, the cohort was stratified by good collaterals (CTP collateral score 3–4) versus bad collaterals (CTP collateral score 1–2). Further stratification was made by PVO, which was defined as occlusion of the internal carotid artery or M1 segment of the middle cerebral artery on admission MR, CT or digital subtraction angiogram.

For volumetric analysis, we used the Food and Drug Administration (FDA)-approved Olea Sphere software (Olea Medical: La Ciotat, France) to generate CTP maps with a Bayesian-based probabilistic deconvolution method, which recent data suggest is superior to other delay-insensitive methods.^{19–21} On the basis of previously validated CTP threshold definitions, we defined a lesion core as relative CBF $<40\%$ and absolute arterial tissue delay >2 s, and hypoperfused tissue as relative mean transit time $>135\%$.^{19 22 23} The CTP data were used to create dichotomous patient stratifications based on three volumetric categories (figure 1): upper and lower halves of lesion core volume, hypoperfused volume, and mismatch volume

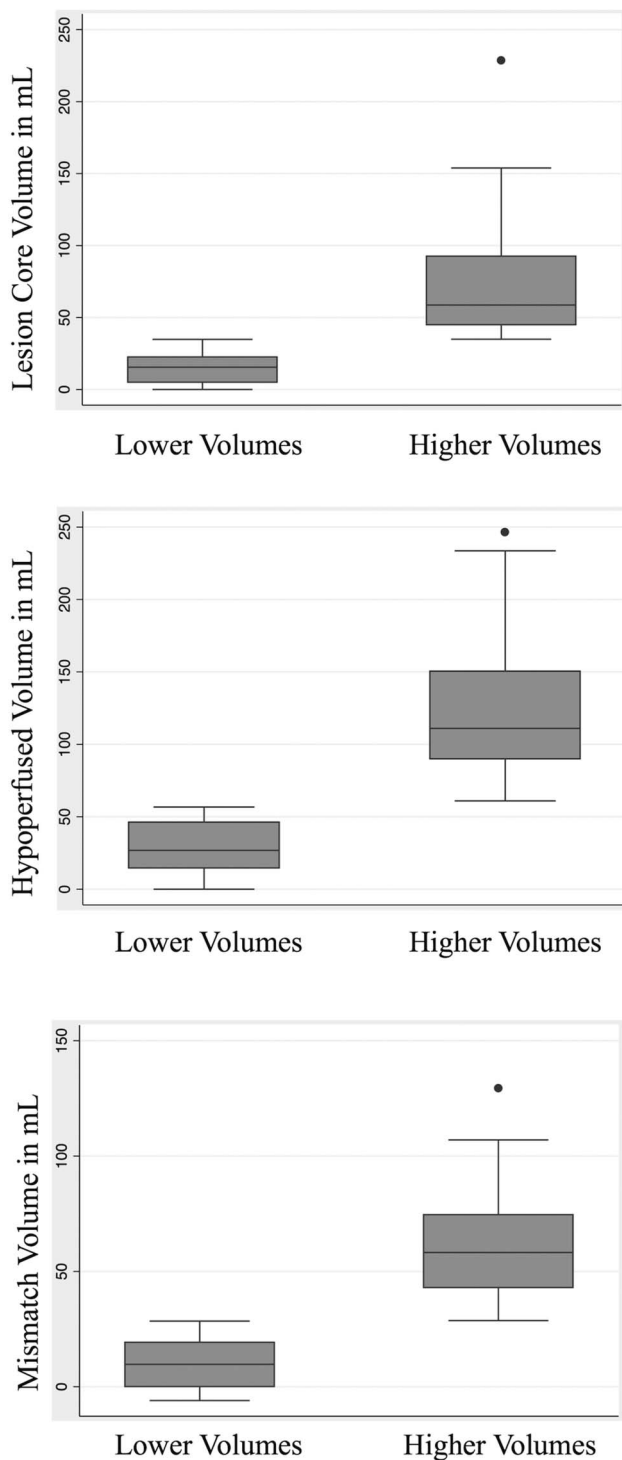


Figure 1 CT perfusion volumetric measurements shown for dichotomous stratifications of lesion core volume, hypoperfused volume, and mismatch volume with box plot representation of median line and IQR, whisker representation of data range, and outliers as single data points.

(hypoperfused–lesion core volume), which correspond to the concept of ischaemic penumbra. A fourth dichotomous stratification was made by the ‘Target Mismatch’ profile (hypoperfused:lesion ratio >1.8, mismatch volume >15 mL and lesion core volume <70 mL), which has been validated for both MR perfusion and CTP.^{24 25}

Statistical analysis

BPV was calculated using systolic BP (SBP) readings between 0 and 120 hours from hospital admission. Over 80% of patients had haemodynamic data starting within 6 hours of stroke onset and the remainder had it within 24 hours. Haemodynamic data that were considered non-physiological (SBP>280 or <50 mm Hg) were changed to missing, which was fewer than 0.05% of available measurements. BPV was calculated in three

ways—SD: $\sqrt{(1/(n-1)) \sum_{(i=1)}^{(n)} (BP_i - BP_{\text{mean}})^2}$, coefficient

of variation (CV (%)): $SD/BP_{\text{mean}} \times 100$, and successive variation (SV) calculated as the square root of the average difference in BP between successive measurements

using the equation: $\sqrt{(1/(n-1)) \sum_{(i=1)}^{(n-1)} (BP_{i+1} - BP_i)^2}$.⁶

We choose SD, CV and SV based on prior literature suggesting that multiple approaches to measuring BPV should be employed.⁴

Stata V.14.1 was used for all data analyses, with statistical significance defined as $p < 0.05$. Intergroup differences were evaluated with Spearman’s rank correlation, independent sample t-test, χ^2 test and the Mann-Whitney U test. The regression analyses were calculated with ordinal logistic regression fitted to the outcome of mRS. This statistical methodology allows measurement of shift in mRS, the odds of moving to the next score, which is particularly beneficial when the effect of the intervention or clinical factor is spread across the entire range of ordinal values.^{26–28} An ordinal logistic regression model was fitted to the outcome of mRS with individual BPV indices. Multivariable ordinal regression models were fitted to control for possible confounders using an interactive backward variable selection (inclusion with $p < 0.05$). The ordinal logistic regression models were stratified by the four dichotomous categories of the upper and lower halves of lesion core volume, hypoperfused volume, mismatch volume and Target Mismatch. In keeping with recommendations from the recent meta-analysis on BPV, ORs and 95% CIs are reported per 10 mm Hg increment in the BPV parameter.¹⁵ If 2/3 of the BPV indices were significant for a given model, it was considered a relevant finding.

RESULTS

One hundred and ten patients met the inclusion criteria. Patient demographics are shown in table 1. There were 6587 BP readings between 0 and 120 hours after stroke

onset and the median number of BP readings per patient was 57 (IQR 50–66). There were a high number of PVOs at hospital admission (58/110, 53%). An additional 32/110 (29%) had an M2 or A1 segment occlusion with the remainder of patients (20/110, 18%) having more distal M3 or A2 occlusions. Half of the patients were administered intravenous tPA and 40% (44/110) had endovascular intervention, and 22% (24/110) had both. The high number of acute stroke interventions is secondary to the referral pattern for CTP at our institution. A relatively high number of patients developed sICH (13/110, 11.8%), reflecting the increased risk for sICH with interventional stroke therapy and the high median NIHSS (12, IQR 7–19) in our cohort. The mean±SD lesion core and hypoperfused volumes were 43.8±40.6 mL and 75.9±56.9, creating a moderate mismatch volume (hypoperfused–lesion volume) of 36.8±31.1 mL. The median CTP collateral score was 3, but the most common value was 2 (44/110, 40%).

In the adjusted and unadjusted ordinal logistic regression models fitted to the outcome of mRS, all three measures of BPV (SBP CV, SD and SV) were predictive of a one-point shift in the mRS (OR 2.27 to 5.54, $p < 0.05$; table 2). SBP mean was not predictive of outcome and

Table 1 Patient demographics, clinical information and initial imaging data

Variable	All patients (n=110)
Age, years, mean±SD	61.5±17.0
Male, n (%)	60 (55.6)
Caucasian, n (%)	95 (86.4)
Admission NIHSS, median (IQR)	12 (7–19)
Follow-up mRS, median (IQR)	3 (1–4)
Time to follow-up mRS from stroke, days, mean±SD	96±51
Hypertension, n (%)	60 (54.6)
Hyperlipidaemia, n (%)	41 (37.3)
Atrial fibrillation, n (%)	33 (30.0)
Diabetes mellitus, n (%)	23 (20.9)
Congestive heart failure, n (%)	14 (12.7)
Current cigarette smoking, n (%)	24 (21.8)
Admission glucose level, mg/dL, mean±SD	127.1±40.2
Collateral score (1–4), median (IQR)	3 (2–4)
Lesion volume, mL, mean±SD	43.8±40.6
Hypoperfused volume, mL, mean±SD	75.9±56.9
Mismatch volume, mL, mean±SD	36.8±31.1
tPA administered, n (%)	55 (50.0)
Endovascular therapy, n (%)	44 (40.0)
Symptomatic intracerebral haemorrhage, n (%)	13 (11.8)
Proximal vessel occlusion, n (%)	58 (52.7)
SBP SD, 0–120 hours, mean±SD	14.4±4.8
SBP CV, 0–120 hours, mean±SD	11.1±3.7
SBP SV, 0–120 hours, mean±SD	14.1±4.5
SBP mean, 0–120 hours, mean±SD	131.0±16.7

CV, coefficient of variation; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SV, successive variation; tPA, tissue plasminogen activator.

Table 2 Unadjusted and adjusted ORs for a one-point shift in mRS at follow-up with predictor blood pressure indices of SBP SD, CV, SV and mean. ORs are shown for a 10 mm Hg shift

Blood pressure indices	OR for a 1-point mRS shift	95% CI	p Value	Adjusted OR for a 1-point mRS shift*	95% CI	p Value
SBP CV	3.30	1.48 to 7.35	0.003	3.02	0.86 to 10.6	0.085
SBP SD	5.54	1.72 to 17.9	0.004	2.78	1.16 to 6.70	0.022
SBP SV	2.27	1.01 to 5.10	0.047	3.03	1.28 to 7.17	0.012
SBP mean	1.00	0.98 to 1.02	0.722	1.02	1.00 to 1.05	0.038

*Adjusted for admission NIHSS, patient sex, history of congestive heart failure, history of diabetes mellitus and symptomatic intracranial haemorrhage.

CV, coefficient of variation; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SV, successive variation.

hence was not included in subsequent models. In unadjusted ordinal models, the CTP dichotomous stratifications demonstrated an association between increased BPV and worse outcome in patients with larger lesion core volume (OR 8.37 to 18.0, $p < 0.05$), larger hypoperfused volume (OR 6.02 to 15.4, $p < 0.05$) and mismatch volume (OR 3.66 to 9.41, $p < 0.05$), but the association was not significant in the lower halves of the stratifications. These relationships maintained significance after adjusting for possible confounders, including admission NIHSS, patient sex, tPA administration, sICH and admission glucose (table 3).

Additional stratifications were made based on the Target Mismatch profile, PVO at hospital admission and collateral score. In the unadjusted model, patients without Target Mismatch had an association between increased BPV and worse neurological outcome (OR 5.26 to 8.43, $p < 0.05$), which continued to be significant in the adjusted model (table 4). Patients with PVO and good collaterals also demonstrated an association between increased BPV and worse outcome (OR 5.20 to 9.60, 3.58 to 31.9, $p < 0.05$). These associations also remained significant in the adjusted models (table 4).

DISCUSSION

Our results confirm earlier reports that increased BPV is harmful after acute ischaemic stroke¹⁻⁷ and the inclusion of stratifications based on neuroimaging determinants such as CTP volumetric data, PVO and cerebral collateral status adds a novel perspective. These analyses revealed that patients with larger ischaemic core or hypoperfused volumes are particularly vulnerable to the detrimental effects of increased BPV. This relationship was also seen in patients with a larger mismatch and without the Target Mismatch profile. Taken together, these findings suggest that the impact of increased BPV is, at its most fundamental level, driven by the larger absolute volumes of infarcted and peri-infarct tissue.

Increased BPV has been linked to the development of sICH after ischaemic stroke,²⁹ which would be one plausible mechanism for why patients with larger core and hypoperfused volumes had a worse outcome with higher BPV, but the incidence of sICH was not different in any of the stratifications and it was included as a covariate in the adjusted models. A more compelling explanation is that after moderate-to-severe ischaemic stroke, the lesion core and its ischaemic penumbra often

Table 3 Adjusted ORs for a one-point shift in mRS at follow-up with predictor variables of SBP SD, CV and SV; stratified by lesion core volume, hypoperfused volume, mismatch volume, Target Mismatch status, proximal vessel occlusion on admission and collateral score

BPV indices	OR*	95% CI	p Value	BPV indices	OR*	95% CI	p Value
Higher lesion core volume (n=55) (mean±SD=72.7±39.2 mL)				Lower lesion core volume (n=55) (mean±SD=15.1±10.3 mL)			
SBP SD	9.27	2.36 to 36.3	0.001	SBP SD	0.74	0.21 to 2.63	0.643
SBP CV	20.2	3.00 to 137	0.002	SBP CV	0.30	0.05 to 2.07	0.224
SBP SV	18.9	3.69 to 97.1	<0.001	SBP SV	1.27	0.44 to 3.66	0.664
Higher hypoperfused volume (n=55) (mean±SD=121.3 ±44.9 mL)				Lower hypoperfused volume (n=55) (mean±SD=30.5 ±17.6 mL)			
SBP SD	5.41	1.24 to 23.6	0.025	SBP SD	0.85	0.23 to 3.10	0.804
SBP CV	12.9	1.70 to 98.8	0.013	SBP CV	0.28	0.04 to 2.01	0.204
SBP SV	4.09	0.99 to 16.9	0.052	SBP SV	1.63	0.52 to 5.08	0.402
Higher mismatch volume (n=55) (mean±SD=62.3±22.9 mL)				Lower mismatch volume (n=55) (mean±SD=11.4±10.4 mL)			
SBP SD	3.35	1.03 to 11.0	0.045	SBP SD	2.58	0.58 to 11.4	0.212
SBP CV	5.97	1.05 to 34.0	0.044	SBP CV	1.24	0.16 to 9.36	0.838
SBP SV	3.76	1.13 to 12.5	0.031	SBP SV	2.44	0.61 to 9.87	0.210

*Adjusted for admission NIHSS, patient sex, tPA administration, symptomatic intracranial haemorrhage and admission glucose value.

BPV, blood pressure variability; CV, coefficient of variation; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SV, successive variation; tPA, tissue plasminogen activator.

Table 4 Adjusted ORs for a one-point shift in mRS at follow-up with predictor variables of SBP SD, CV and SV; stratified by lesion core volume, hypoperfused volume, mismatch volume, Target Mismatch status, proximal vessel occlusion on admission and collateral score

BPV indices	OR*	95% CI	p Value	BPV indices	OR*	95% CI	p Value
Target Mismatch (n=57)				No Target Mismatch (n=53)			
SBP SD	1.94	0.63 to 6.02	0.250	SBP SD	6.61	1.40 to 31.1	0.017
SBP CV	2.39	0.45 to 12.7	0.305	SBP CV	5.32	0.70 to 40.1	0.105
SBP SV	2.56	0.81 to 8.09	0.109	SBP SV	5.96	1.20 to 29.6	0.029
Proximal vessel occlusion (n=58)				No proximal occlusion (n=52)			
SBP SD	5.38	1.44 to 20.2	0.013	SBP SD	1.63	0.53 to 5.03	0.398
SBP CV	8.14	1.19 to 55.5	0.032	SBP CV	1.49	0.35 to 6.25	0.588
SBP SV	3.47	1.05 to 11.4	0.041	SBP SV	3.55	0.91 to 13.8	0.068
Good collaterals (n=60)				Bad collaterals (n=50)			
SBP SD	5.78	1.23 to 27.2	0.027	SBP SD	1.85	0.60 to 5.74	0.289
SBP CV	8.60	1.02 to 72.5	0.048	SBP CV	1.51	0.26 to 8.83	0.650
SBP SV	3.82	1.15 to 12.7	0.029	SBP SV	2.09	0.58 to 7.47	0.258

*Adjusted for admission NIHSS, patient sex, tPA administration, symptomatic intracranial haemorrhage and admission glucose value. BPV, blood pressure variability; CV, coefficient of variation; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SV, successive variation; tPA, tissue plasminogen activator.

exhibit impaired cerebral autoregulation.^{10 11} In patients with blunted autoregulation, increased BPV could produce deleterious fluctuations in cerebral perfusion,³⁰ and would be particularly relevant in patients with large lesion, hypoperfused and mismatch volumes.

The detrimental effect of increased BPV was also seen in patients with PVO, which has been reported in previous studies,^{12 31} and in patients with good collaterals, which is a novel finding. Patients with PVO are more likely to have a large lesion core and hypoperfused volume, which could account for the differential effect. However, the susceptibility of patients with good collaterals was unexpected. Following ischaemic stroke, collateral blood vessels will dilate to provide additional blood flow³² and patients with PVOs recruit more collateral vessels than those with distal occlusions. We propose that patients with PVO and good collaterals transmit the harmful increase in BPV to the area of the stroke, while those with worse collaterals or distal occlusions have a more isolated lesion core and ischaemic penumbra. The good collaterals could also expose the brain to cellular mediators of inflammation, which are elevated in patients with high BPV.^{33 34} Finally, we cannot exclude other possible mechanisms such as cerebral oedema formation or other organ system damage resulting from increased BPV.¹⁵

This retrospective study has several limitations, including the non-uniform time intervals between BP measurements, time from stroke onset to first BP measurement and hospital discharge to clinical follow-up. Cataloguing use of BP-lowering or vasopressor medications was impractical given the many complexities in how patients were treated. The inclusion of only patients with CTP and angiographic imaging introduces the possibility of selection bias, although the baseline characteristics of our cohort were comparable to other studies of moderate-to-severe ischaemic stroke. We only included patients who had BP data for

120 hours after admission, but given the more severe strokes in our cohort and our ability to continue recording BP measurements if patients were transferred to the rehabilitation service, we do not feel this biased results.

CONCLUSION

BPV is a predictor of neurological outcome in patients with a large lesion core volume, concurrent viable ischaemic penumbra, PVO and good collaterals. Prior analyses of BPV have not accounted for perfusion imaging volumetric measurements or collateral status, rendering our findings novel and important for future BPV research in patients with acute ischaemic stroke. Dozens of clinical trials involving over 20 000 patients have been conducted to determine if pharmacologically lowering BP after ischaemic stroke is beneficial. The results have been persistently neutral or negative.^{35–38} In contrast, there have been no clinical trials on the efficacy of reducing BPV after ischaemic stroke. Our study should help begin to clarify the inclusion criteria for such a trial. Furthermore, patients with ischaemic stroke who are not candidates for endovascular therapy (no Target Mismatch, low ASPECTS score from a large lesion core volume) or may not respond to intravenous tPA (PVOs recanalise in less than a quarter of patients administered tPA)³⁹ could specifically benefit from therapies aimed at reducing BPV, such as calcium channel blockers⁴⁰ or low-dose vasopressors.^{41 42}

Contributors AdH conceived of the study, reviewed all data, performed statistical analysis, and drafted and edited the manuscript. GJS assisted with statistical analysis. AB, LC and SO reviewed patient charts and performed assessment of imaging end points. JSM performed imaging assessment and edited the manuscript. JMM helped conceive the study, draft and edit the manuscript. GS and DT helped conceive the study and edit the manuscript.

Funding Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number KL2TR001065.

Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing interests None declared.

Ethics approval The study was approved by the local Institutional Review Board and is retrospective research that did not involve a medical or surgical intervention.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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