Research Paper

JRSM Cardiovascular Disease
Volume 8: 1–4

DOI: 10.1177/2048004019856496
journals.sagepub.com/home/cvd
SAGE

Increased blood pressure variability after acute ischemic stroke increases the risk of death: A secondary analysis of the Virtual International Stroke Trial Archive

Adam de Havenon[1], Greg Stoddard[2], Monica Saini[3], Ka-Ho Wong[1], David Tirschwell[4] and Phillip Bath[5]; on behalf of the VISTA-Acute Collaborators*

Abstract

Background: Despite promising epidemiological data, it remains unclear if increased blood pressure variability is associated with death after acute ischemic stroke. Our objective was to examine this association in a large cohort of acute ischemic stroke patients.

Methods: We conducted a retrospective analysis of anonymized, pooled, participant data from the Virtual International Stroke Trial Archive. We included patients with a 90-day modified Rankin Scale and blood pressure readings in the 24 h after study enrollment. The exposure was blood pressure variability during the day after study enrollment, calculated for the systolic and diastolic blood pressure using six statistical methodologies. The primary outcome was death within 90 days of stroke onset.

Results: Our cohort comprised 1891 patients of whom 277 (14.7%) died within 90 days. All indices of blood pressure variability were higher in patients who died, but the difference was more pronounced for systolic than diastolic blood pressure variability (systolic standard deviation for alive versus dead patients = 13.4 versus 15.9 mmHg, $p < 0.001$). Similar results were found in logistic regression models fit to the outcome of death, but only systolic blood pressure variability remained significant in adjusted models (Odds Ratio for death when comparing highest to lowest tercile of systolic blood pressure variability = 1.41–1.89, $p < 0.03$ for all).

Conclusions and relevance: These results reinforce prior studies that found increased blood pressure variability is associated with worse neurologic outcome after stroke. These data should help guide research on blood pressure variability after stroke and advocate for the inclusion of death as a clinical outcome in future studies that therapeutically reduce blood pressure variability.

Keywords

Stroke, death, blood pressure, blood pressure variability

Received 26 March 2019; Revised received 8 May 2019; accepted 10 May 2019

Introduction

Epidemiological data suggest worse stroke outcomes with extremes of sustained hypo- or hypertension,[1] which has led to numerous clinical trials to determine if pharmacological lowering of blood pressure after stroke is beneficial. The results have been varied from positive through neutral to negative.[2–5] Increased systolic blood pressure variability (BPV) in the days after ischemic and hemorrhagic stroke is associated with

[1]Department of Neurology, University of Utah, Salt Lake City, USA
[2]Department of Preventative Medicine, University of Utah, Salt Lake City, USA
[3]Department of Neurology, Changi General Hospital, Singapore, Singapore
[4]Department of Neurology, University of Washington, Washington, USA
[5]Stroke Trials Unit, Clinical Neuroscience, University of Nottingham, Nottingham, UK

*The list of VISTA-Acute Collaborators is given in Acknowledgments.

Corresponding author:
Adam de Havenon, Department of Neurology, University of Utah, Salt Lake City, USA.
Email: adam.dehavenon@hsc.utah.edu

worse outcome.[6–8] A prior study by Sare et al. of blood pressure levels in the days after ischemic stroke used data from the Virtual International Stroke Trial Archive (VISTA)[9] and reported that increased BPV was associated with poor long-term functional outcome after ischemic stroke. However, Sare et al. did not examine the association with death. Although prior studies have reported a positive association between increased BPV and death, they have been limited by small or restricted cohorts.[10,11] Because the effect of BPV on stroke outcome remains controversial and may, in fact, be an epidemiologic epiphenomenon, we sought to examine the impact of increased BPV on death within 90 days of stroke onset with multiple statistical approaches in a large cohort of acute stroke patients in the VISTA database.

Methods

We conducted retrospective analyses of anonymized individual participant level data from the acute stroke section of the VISTA.[12] Because the data were de-identified, IRB approval was not required. VISTA collects anonymized data from completed clinical trials. As per VISTA regulations, the trial sources from which data are extracted cannot be revealed. However, data were extracted based on the availability of key analysis variables: age, sex, time since stroke onset, medical history, death, a 90-day modified Rankin Scale (mRS) and four or five blood pressure readings in the 24 h after study enrollment. The latter variable was considered during the exposure period. Our primary outcome was death within 90 days of study enrollment. We excluded patients who were lost to follow-up and patients who died during the exposure period. We calculated BPV during the exposure period for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) using six statistical methodologies: standard deviation (SD), coefficient of variation (CV), average real variability (ARV), successive variation (SV), variation independent of mean (VIM), and residual SD (rSD). BPV formulas are: $\mathrm{SD} = \sqrt{\left(\frac{1}{n-1}\right)\sum_{(i=1)}^{(n)}(BP_i - BP_{mean})^2}$; $\mathrm{rSD} = \sqrt{\frac{\sum (BP-BPest)^2}{n-2}}$; $\mathrm{CV} = \left(\frac{\mathrm{SD}}{BP_{mean}}\right)*100$; $\mathrm{ARV} = \left(\frac{1}{n-1}\right)\sum_{(i=1)}^{(n-1)}|BP_{i+1} - BP_i|$; $\mathrm{SV} = \sqrt{(1/(n-1))\sum_{(i=1)}^{(n-1)}(BP_{i+1} - BP_i)^2}$; and $\mathrm{VIM} = (BP_{mean} * \mathrm{SD}/\bar{x}^p)$. We selected these methodologies based on prior literature that advocated multiple approaches to evaluating BPV, many of which take into account the distribution and linear trends of blood pressure in an effort to reduce the dependency of BPV on mean blood pressure level.[6,13] We report the mean values of BPV for patients who died versus those who survived to day 90 and tested for inter-group differences with Student's t-test.

To standardize our regression analyses, all measures of BPV were divided into terciles and we compared the highest tercile of BPV to the lowest. We fit the following logistic models to the primary outcome with the predictor variable of BPV: (1) unadjusted, (2) adjusted a priori for patient age, baseline NIH stroke scale (NIHSS), mean blood pressure and administration of tissue plasminogen activator (tPA), and (3) adjusted for all baseline demographic covariates with a $p < 0.1$ in a stepwise backwards selection. We also fit a Cox proportional hazards model to the highest versus lowest tercile of SBP SD because of its relative ease for

Table 1. Baseline demographics of the entire cohort compared between patients who died or survived in the 90 days after ischemic stroke onset.[a]

Variable	Entire cohort (n=1891)	Alive at day 90 (n=1614)	Dead at day 90 (N=277)	p-Value
Age (mean ± SD)	69.5 ± 12.2	68.4 ± 12.3	75.7 ± 10.0	<0.001
Male sex (n, %)	1013, 53.6	865, 53.6	148, 53.4	0.960
Baseline NIHSS (median, IQR)	13, 9–18	12, 8–17	18, 14-21	<0.001
Hours from stroke onset to study enrollment (mean ± SD)	4.8 ± 2.4	4.7 ± 2.3	5.4 ± 2.7	<0.001
History of hypertension (n, %)	1392, 73.6	1177, 72.9	215, 77.6	0.102
History of diabetes (n, %)	425, 22.5	351, 21.8	74, 26.7	0.067
History of prior stroke (n, %)	364, 19.3	303, 18.8	61, 22.0	0.205
History of myocardial infraction (n, %)	239, 12.6	190, 11.8	49, 17.7	0.006
History of atrial fibrillation (n, %)	502, 26.6	394, 24.4	108, 39.0	<0.001
Current smoker (n, %)	466, 24.6	450, 27.9	16, 5.8	<0.001
Left hemisphere stroke (n, %) (n=1888)	917, 48.6	774, 48.0	143, 51.6	0.271
tPA administered (n, %)	506, 26.8	461, 28.6	45, 16.3	<0.001

[a]Difference between continuous variables tested with Student's t-test, binary variables with the chi-squared test, and for ordinal variables with the Wilcoxon Rank Sum test.

translational clinical use. We conducted a sensitivity analysis in which we excluded patients who received tPA. STATA 15.1 was used for all data analyses, with statistical significance defined as $p < 0.05$.

Table 2. Mean±SD values of BPV indices compared between patients who died or survived in the 90 days after ischemic stroke onset.

BPV variable	Alive at day 90 (n=1614)	Dead at day 90 (N=277)	p-Value
SBP SD	13.4 ± 6.6	15.9 ± 8.9	<0.001
SBP CV	9.1 ± 4.3	10.6 ± 6.0	<0.001
SBP ARV	14.5 ± 7.9	17.6 ± 9.9	<0.001
SBP SV	17.1 ± 9.0	20.5 ± 11.3	<0.001
SBP VIM	13.9 ± 7.0	16.0 ± 10.0	<0.001
SBP rSD	12.0 ± 7.0	14.3 ± 8.7	<0.001
SBP mean	148.5 ± 19.5	151.8 ± 20.5	0.011
DBP SD	9.2 ± 5.0	10.0 ± 5.0	0.017
DBP CV	11.9 ± 6.7	12.9 ± 6.7	0.015
DBP ARV	10.0 ± 5.9	11.0 ± 6.1	0.008
DBP SV	11.8 ± 6.7	13.0 ± 6.8	0.010
DBP VIM	9.5 ± 5.6	10.4 ± 5.6	0.017
DBP rSD	8.3 ± 5.1	8.9 ± 5.1	0.053
DBP mean	79.0 ± 12.2	78.6 ± 13.2	0.623

Note: DBP n = 1889 (1613 vs. 276). SD: standard deviation; CV: coefficient of variation; ARV: average real variability; SV: successive variation; VIM: variation independent of mean; rSD: residual SD; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Results

We included 1891 patients (see Table 1 for additional baseline demographics). The primary outcome of death within 90 days of stroke onset was met by 277 patients (14.7%). The mean (SD) number of days to death was 24.8 (22.9). The mean (SD) hours from stroke onset to study enrollment was 4.8 (2.4) and 534 (27.5%) patients received intravenous tPA. The median (interquartile range [IQR]) values of baseline NIHSS and 90-day mRS were 13 (9–18) and 3 (1–4). All indices of BPV were higher in patients who died (Table 2), but the difference was more pronounced for systolic than diastolic BPV. Similar results were found in the logistic regression models fit to the outcome of death within 90 days of stroke onset, where only systolic BPV remained significant after adjustment for possible confounders (Table 3). Mean blood pressure was not consistently predictive of death in any of our models. In the Cox model, which compared the risk of the highest tercile of SBP SD to the lowest, the hazard ratio for death was 1.59 (95% CI, 1.19–2.13), and remained significant after adjustment for the covariates in Models 2 and 3. The sensitivity analysis, where patients who received tPA were excluded, yielded near identical results.

Discussion

These results reinforce prior studies that found increased BPV is associated with worse neurologic

Table 3. Logistic regression models fit to the outcome of death within 90 days, showing the comparison between the highest to lowest tercile for both SBP and DBP.

	Model 1		Model 2		Model 3	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
SBP						
SD	1.68 (1.22, 2.30)	0.001	1.49 (1.05, 2.10)	0.024	1.55 (1.09, 2.19)	0.014
CV	1.56 (1.14, 2.13)	0.005	1.72 (1.11, 2.20)	0.010	1.61 (1.15, 2.27)	0.006
ARV	1.89 (1.38, 2.59)	<0.001	1.58 (1.23, 2.22)	0.009	1.64 (1.16, 2.31)	0.005
SV	1.84 (1.35, 2.51)	<0.001	1.65 (1.17, 2.31)	0.004	1.74 (1.24, 2.44)	0.002
VIM	1.41 (1.04, 1.91)	0.029	1.70 (1.19, 2.42)	0.004	1.61 (1.15, 2.26)	0.006
rSD	1.63 (1.20, 2.21)	0.002	1.49 (1.07, 2.07)	0.020	1.61 (1.15, 2.26)	0.006
Mean	1.55 (1.14, 2.11)	0.006	1.08 (0.77, 1.52)	0.662	1.14 (0.81, 1.61)	0.469
DBP						
SD	1.41 (1.03, 1.93)	0.033	1.19 (0.85, 1.68)	0.310	1.32 (0.93, 1.88)	0.114
CV	1.47 (1.07, 2.01)	0.017	1.26 (0.89, 1.79)	0.202	1.26 (0.89, 1.79)	0.194
ARV	1.51 (1.11, 2.05)	0.008	1.30 (0.93, 1.81)	0.126	1.34 (0.96, 1.89)	0.088
SV	1.54 (1.13, 2.10)	0.006	1.32 (0.94, 1.85)	0.108	1.41 (1.00, 2.00)	0.049
VIM	1.52 (1.10, 2.09)	0.010	1.29 (0.90, 1.84)	0.168	1.25 (0.89, 1.80)	0.195
rSD	1.43 (1.05, 1.94)	0.024	1.32 (0.94, 1.84)	0.105	1.43 (1.01, 2.00)	0.041
Mean	0.92 (0.68, 1.25)	0.581	1.33 (0.95, 1.86)	0.097	1.34 (0.95, 1.88)	0.097

Note: Model 1: Unadjusted. Model 2: Adjusted for patient age, baseline NIH stroke scale score, administration of tPA, and mean blood pressure (apart from model that includes mean as the predictor). Model 3: Adjusted for patient age, sex, baseline NIH stroke scale score, current cigarette smoking, and stroke hemisphere (right vs. left). n = 1888 for SBP Model 3, n = 1889 for DBP Models 1 and 2, n = 1886 for DBP Model 3. SD: standard deviation; CV: coefficient of variation; ARV: average real variability; SV: successive variation; VIM: variation independent of mean; rSD: residual SD; SBP: systolic blood pressure; DBP: diastolic blood pressure.

outcome after stroke.[6] Specifically, we find that increased systolic BPV in the first day after ischemic stroke onset is associated with a higher risk of death within 90 days of stroke onset. This analysis expands on prior publications that found a similar association, but validates it in a larger cohort with rigorously adjudicated outcomes and the use of multiple statistical measures of BPV, which further strengthens the observed association.[10,11] The mechanism underlying the negative effects of BPV remains unknown, but considering the human body's preference for homeostasis in all central physiological processes, an increase in BPV remains a plausible mediator of worse outcome. Furthermore, without research demonstrating clinical benefit to reducing BPV, we cannot know if it is causal of adverse outcome or merely an epiphenomenon.

Our study has additional limitations, the most important being that this is a not a pre-specified analysis of these prospectively collected data. The relatively few numbers of BP readings and lack of control over the blood pressure measurement methodology limit the accuracy of the BPV calculations. Despite these limitations, these data should help guide research on BPV after stroke and advocate for the inclusion of death as a clinical outcome in future studies that therapeutically reduce BPV.

Acknowledgements

VISTA-Acute Steering Committee: KR Lees (Chair), AV Alexandrov, PM Bath, E Berge, E Bluhmki, N Bornstein, C Chen, L Claesson, SM Davis, G Donnan, HC Diener, M Fisher, M Ginsberg, B Gregson, J Grotta, W Hacke, MG Hennerici, M Hommel, M Kaste, P Lyden, J Marler, K Muir, N Venketasubramanian, R Sacco, A Shuaib, P Teal, NG Wahlgren, S Warach, and C Weimar.

Contributorship

AH conceived of the study, performed the statistical analysis and wrote and edited the manuscript. GS assisted with the statistical analysis. MS, KW, and DT assisted with manuscript drafting and editing. PB assisted with study conception and manuscript editing.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

N/A.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work is supported by the American Heart Association (17SDG33670114; to de Havenon).

Guarantor

AH.

ORCID iD

Adam de Havenon https://orcid.org/0000-0001-8178-8597

References

1. Willmot M, Leonardi-Bee J and Bath P. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension* 2004; 43: 18–24.
2. Bath PM, Appleton JP, Krishnan K, et al. Blood pressure in acute stroke: to treat or not to treat: that is still the question. *Stroke* 2018; 49: 1784–1790.
3. Wang H, Tang Y, Rong X, et al. Effects of early blood pressure lowering on early and long-term outcomes after acute stroke: an updated meta-analysis. *PloS One* 2014; 9: e97917.
4. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016; 375: 1033–1043.
5. 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.
6. Manning LS, Rothwell PM, Potter JF, et al. Prognostic significance of short-term blood pressure variability in acute stroke systematic review. *Stroke* 2015; 46: 2482–2490.
7. 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 Vasc Neurol* 2017; 2: 1–6.
8. de Havenon A, Majersik JJ, Stoddard G, et al. Increased blood pressure variability contributes to worse outcome after intracerebral hemorrhage: an analysis of ATACH-2. *Stroke* 2018; 49(8): 1981–1984.
9. Sare GM, Ali M, Shuaib A, et al. Relationship between hyperacute blood pressure and outcome after ischemic stroke: data from the VISTA collaboration. *Stroke* 2009; 40: 2098–2103.
10. Endo K, Kario K, Koga M, et al. Impact of early blood pressure variability on stroke outcomes after thrombolysis: the SAMURAI rt-PA registry. *Stroke* 2013; 44: 816–818.
11. Stead LG, Gilmore RM, Vedula KC, et al. Impact of acute blood pressure variability on ischemic stroke outcome. *Neurology* 2006; 66: 1878–1881.
12. Ali M, Bath PMW, Curram J, et al. The Virtual International Stroke Trials Archive. *Stroke* 2007; 38: 1905–1910.
13. Yano Y. Visit-to-visit blood pressure variability – What is the current challenge? *Am J Hypertens* 2017; 30: 112–114.