Increasing Blood Pressure Variability Predicts Poor Functional Outcome Following Acute Stroke

Running Title: Blood Pressure Variability and Stroke Outcome

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Abstract

Introduction

Increasing blood pressure variability has been reported following acute stroke, but there is uncertainty about how best to measure it and about the impact on prognosis following acute ischaemic stroke and transient ischaemic attack.

Methods

Enhanced casual blood pressure and ambulatory blood pressure monitoring were completed at baseline (≤48 hours post symptom onset). Blood pressure variability was defined by standard deviation and coefficient of variation of systolic, diastolic, mean arterial pressure, and pulse pressure. Modified Rankin scale score ≥3 described poor functional outcome assessed at 1- and 12-months post-stroke. Multivariable logistic regression models incorporating blood pressure variability measurement and other factors were performed, and odds ratio and 95% confidence intervals reported.

Results

232 patients were recruited; 45 were dependent at 1-month, and 37 at 12-months. Dependent patients were more likely to be older, with a higher burden of pre-morbid conditions, and with increased blood pressure variability. Enhanced casual standard deviations of diastolic blood pressure [1.19 (1.02 to 1.39)] and mean arterial pressure [1.20 (1.00 to 1.43)] predicted dependency at 1-month. Predictors of 12-month dependency included: enhanced casual standard deviation of mean arterial pressure [1.21 (1.0-1.46)]; 24-hour ambulatory monitor standard deviations of diastolic blood pressure [2.30 (1.08-4.90)] and mean arterial pressure [1.72 (1.09-2.72)], and the coefficient of variation of mean arterial pressure [1.76 (1.05-2.94)]; day-time ambulatory monitor coefficient of variation of systolic blood pressure [1.44 (1.02-2.03)] and mean arterial pressure [1.46 (1.02-2.08)]; and night-time ambulatory standard

deviation of diastolic blood pressure [1.65 (1.03 -2.63)], and the coefficient of variation of mean arterial pressure and [1.38 (1.00- 1.90)] and pulse pressure [1.29 (1.00–1.65)].

Conclusion

Increasing blood pressure variability is independently and modestly associated with poor functional outcome at 1- and 12-months following acute stroke.

Introduction

Stroke is a leading cause of adult long-term functional disability and mortality. Blood pressure (BP) is typically acutely elevated (systolic BP ≥140mmHg) (1), affecting up to 80% of acute ischaemic stroke (AIS) patients (2, 3), though usually declines over the subsequent days following stroke (4, 5). However, there is some evidence that elevation in BP after stroke might actually precede the stroke and be involved in its causation (6). There is also evidence that individuals with increased BP variability (BPV) are at increased risk of stroke and other vascular events (7, 8).

In addition, increased BPV has been observed following acute stroke, which presents additional challenges for acute BP management (9), and may be important in short- and long-term outcomes (1, 3). Nonetheless, for BPV to inform management decisions, its measurement and definition need to be readily accessible and meaningful in everyday clinical practice. Therefore, in this study, we investigated the short- and long-term prognostic significance of BPV following AIS and transient ischaemic attack (TIA). We evaluated BPV data derived from enhanced casual BP measurements, similar to those in previous analyses of trial data, and of 24-hour ambulatory BP monitors (ABPM), and considered different BPV definitions, to better determine the associations of increasing BPV with functional outcome following AIS and TIA.

Methods

Study Design and Settings

This was a prospective observational study conducted between 2013 and 2018 across three NHS [National Health Service] centres in the United Kingdom. London-South East Research Ethics Committee (Reference: 13/LO/0979) approved the present study, and local Research Governance approvals were obtained for each participating centre. The study was registered on a clinical trial registry (ISRCTN86821598). Key inclusion criteria were clinical diagnosis

of AIS or TIA by a stroke physician within 48 hours of symptom onset, and informed participant or consultee consent. Patients were excluded if they were being managed palliatively, or had co-existing life-threatening co-morbidity with life expectancy <3 months, significant pre-stroke dependency (modified Rankin Scale [mRS] >3), atrial fibrillation, pre-existing beta-blocker use and need to continue, and non-stroke final diagnosis.

Study Population

Two-hundred and fifty-eight patients were recruited for this study, of whom 26 were withdrawn or excluded.

Clinical Assessment

Demographic and clinical features of study participants were collected at baseline, within 48 hours of symptom onset, including: age; sex; ethnic origin; past medical history, particularly vascular related events such as previous myocardial infarction (MI), angioplasty, stroke and hypertension; and pre-morbid mRS. In addition, current medication use, family history of vascular events, smoking status, and pre-stroke average weekly alcohol unit consumption were also recorded. Results of neurological examination and key investigation results were recorded, including: neuroimaging, carotid ultrasonography, prolonged electrocardiogram (ECG) and echocardiography where deemed clinically necessary, and other tests to establish aetiology that were completed as part of standard hospital stroke care. Emergency treatments, including thrombolysis or reversal of warfarin or other anticoagulation were also noted.

Blood Pressure Measurement Procedure

All study-related measurements were undertaken in dedicated research laboratories. After five-minute rest and with an appropriately sized cuff, two sets of three consecutive supine brachial systolic (SBP) and diastolic (DBP) BP readings were taken in the non-hemiparetic arm. There was a 10-minute interval between each set using an OMRON device (OMRON 705-IT; Omron

Healthcare, UK Ltd, Milton Keynes, UK); termed "enhanced casual BP". Additional BP phenotypes such as pulse pressure (PP [SBP-DBP], mmHg) and mean arterial pressure (MAP [1/3(SBP + 2xDBP)], mmHg) were subsequently calculated using their most common, and easily obtained formulas in clinical settings; MAP as another expression of BP and PP as pulsatile component of BP. Thereafter, a 24-hour BP (ABPM) recording was undertaken (Spacelabs 90207 BP monitor; Spacelabs Healthcare, Redmond, WA, United States); programmed to record at 20-minute intervals during the day (0700 to 2159), and 60-minute intervals at night (2200 to 0659). Acceptability was defined by the number of successful readings acquired over the set time intervals; ≥20 for the 24-hour BP readings, ≥14 for day-time BP readings, and ≥7 for night-time (10-12).

Blood Pressure Variability Definitions

BPV was determined for SBP, DBP, MAP and PP, as follows: standard deviation (SD, mmHg), $\sqrt{\frac{\sum_{i=1}^{n}(x_i-\bar{x})^2}{(n-1)}}$; coefficient of variation (CoV, %), SD/mean *100; min-max (mmHg), maximum value – minimum value; RSD (mmHg), $\sqrt{\frac{\sum_{i=1}^{n}(x_i-\hat{x}_i)^2}{(n-2)}}$; ARV (mmHg), $\frac{1}{n-1}\sum_{i=1}^{n-1}\left|x_{i+1}-x_i\right|$. These variability indices were calculated for the overall values derived from the two devices (Supplementary material, Table I), though only SD and CoV were used in the subsequent statistical analyses. These are more commonly used and understood metrics; SD is most commonly used in measuring dispersion and CoV is easily comparable as it is unitless.

Outcome Assessments

Functional outcome was assessed at the 1- (short-term) and 12-month (long-term) follow-up visits using the modified Rankin scale (mRS); mRS undertaken by an appropriately trained

individual was recorded. Functional independence was defined as mRS 0-2, and poor functional outcome (dependence/death) as mRS ≥3.

Statistical Analysis

Data analysis was performed in STATA 15. Baseline data, including age, sex, ethnic origin, and routine clinical assessments were described as mean (SD) if continuous and parametric; medians and interquartile ranges (IQR) were reported if discrete and non-parametric. Categorical data were summarized as frequencies and percentages of distributions. Mann-Whitney tests were completed to compare non-parametric data, Chi^2 tests for categorical data, and independent t-test for the parametric data.

We recognise the baseline differences of the study groups and have adjusted accordingly in our analyses. Initially, we fitted single variable logistic regression models to assess the association of different variables with the risk of poor functional outcome of AIS/TIA. Subsequently, we conducted multivariable logistic regression analysis to evaluate the risk of poor functional outcome of AIS/TIA. Age, previous stroke or TIA, anti-platelet medication use, ≥2 anti-hypertensive medication, cholesterol-lowering medication, family history of stroke and baseline mRS ≥3 were included in our final regression model in predicting 1-month functional outcome. The variables adjusted in predicting 12-month functional outcome included age, previous TIA or stroke, cholesterol-lowering medication, family history of stroke, admission mRS ≥3 and a total anterior circulation stroke (TACS) diagnosis. These variables were previously assessed for their interactions, and also collinearity.

The reported odds ratio (OR) is the predictive value for 1 SD increase in the parameter for mRS≥3; p-values are reported, and values <0.05 are indicated as significant.

Results

Baseline Subject Population

A total of 232 met study inclusion, and 219 patients (144 AIS, 75 TIA) were included in the final analysis; 174 functionally independent (mRS 0-2) at one month. Patients were more likely to be dependent at one month if older, with a higher burden of pre-morbid conditions and associated pre-morbid or baseline dependency, taking more cardiovascular drugs (anti-platelet, >1 BP-lowering), increased stroke severity (defined by median NIHSS [National Institute of Health Stroke Scale] score, NIHSS score ≥8 or TACS [total anterior circulation stroke]), and with a computed tomography-confirmed infarct, and receiving intra-venous thrombolysis (Table 1). These baseline characteristics were consistent for dependent (mRS ≥3) participants (n=37) at 12 months (Table 2).

Blood Pressure and Blood Pressure Variability Parameters

At baseline, admission BP were obtained for all participants meeting study inclusion; median (IQR) systolic and diastolic BP were 153 (138-176) and 84 (75-98) mmHg, respectively. With respect to enhanced casual BP measurements, only baseline PP was higher in patients dependent at 1 month (74 vs. 66 mmHg, p=0.02). In addition, increased BPV, defined by both SD and CoV, for DBP, MAP and PP parameters, was found in patients with poor outcome at one month (Supplementary material, Table II). Measures of all night-time BP parameters from 24-hour ABPM were increased in patients with poor outcome at 1 month, though no significant differences were seen with respect to BPV defined from ABPM recordings (Supplementary material, Table II).

At 12 months, enhanced casual DBP at baseline was higher in the independent group (82 vs. 77 mmHg, p=0.01). Only DBP_{CoV} and PP_{SD} as measures of BPV were significantly higher in the dependent group (Supplementary material, Table III). However, with respect to the 24-hour ABPM data, night-time MAP was higher in the dependent group (97 vs. 90 mmHg $p<0.05$), as was day-time DBP_{SD} and PP_{SD} (Supplementary material, Table III).

Functional Dependence at Follow-up

In single variable (unadjusted) models, mean BP values from both enhanced and 24-hour monitoring did not predict functional outcome at one month (Supplementary material, Table IV). However, baseline BPV values from enhanced casual BP measurements were predictive of poor 1-month functional outcome, defined by DBP_{SD}, MAP_{SD}, PP_{SD}, DBP_{CoV} and MAP_{CoV}. Following multivariable (adjusted) regression analysis, only DBP_{SD} and MAP_{SD} remained independent predictors of poor functional outcome at 1-month (Figure 1; Supplementary material, Table IV). In this present study, SD_{DBP} had a 19% increase in the odds of poor short-term functional outcome per unit increase as determined by enhanced casual recordings, and SD_{MAP} a 20% increased risk of poor outcome per unit increase. Baseline $SD_{DBP\ and}$ SD_{MAP} values were also statistically significant ($p<0.01$) when comparisons were made between the two functional outcome groups (Supplementary material, Table II). However, variabilty metrics derived from 24-hour ABPM recordings were not predictive of 1-month functional outcome on single variable (unadjusted) or multivariable (adjusted) analyses.

With respect to assessing functional outcome at 12-months post-stroke, only increased BPV from enhanced casual BP measurements was associated with poor prognosis in the single variable (unadjusted) model, as assessed using DBP_{SD}. However, a mixed pattern of association was observed in multivariable analysis, with increasing BPV, defined by SD_{MAP} being an independent predictor of functional dependence at 12 months. In addition, for 24-hour ABPM measurements, increasing BPV was also an independent predictor of poor functional outcome, including SD_{DBP}, SD_{MAP}, and CoV_{MAP}. For day-time ABPM parameters, CoV_{SBP} and CoV_{MAP}, and for night-time, SD_{DBP}, CoV_{MAP} and CoV_{PP} were independently predictive of poor functional outcome at 12 months post-stroke. The strength and direction of the association of increasing variability with 12-month functional outcome by device and by BPV indices is presented in Figure 2, and in the supplementary material, Table V).

Discussion

Our results corroborate the findings of earlier reports that increasing BPV, assessed by beat-to-beat at 1-month (13) and visit-to-visit readings over 12 months (14), following acute stroke is associated with poor functional outcome. Similar to our finding, increasing variability in DBP and MAP have previously demonstrated significance in association with outcome, in which greater variability resulted in poorer outcome (13). Though investigators demonstrated this in beat-to-beat BPV, and not enhanced casual BP assessments. Importantly, we have demonstrated that increasing BPV derived from enhanced causal BP readings, readily available at the bed-side and defined with commonly understood terms (SD and CoV), are predictive of poor short-term functional outcome. In addition, we have shown that waiting longer, for 24 hours, by undertaking 24-hour ABPM does not provide additional prognostic information for short-term functional outcome. Interestingly, although of borderline significance, more variability metrics derived from the ABPM device reported increasing BPV to be associated with long-term functional outcome. Therefore, demonstrating the baseline assessments of BPV using the ABPM device may in fact provide additional information to predict long-term prognosis.

Enhanced casual BP is immediate and readily applicable at the bedside, and therefore, the finding that increased enhanced causal BPV is predictive of short-term functional dependency (mRS $\geq$3) following acute stroke is of clinical importance. The relationship between increasing BPV and poor functional outcome has been previously demonstrated over different follow-up periods, and with different devices (14-16). However, the present study is the first to confirm this using a simple measuring technique that can be conducted at bedside. In addition, the BPV definitions used were also readily understandable and calculated, and eliminate the need for more complex definitions that account for frequency, sequence and instability of BPV (17).

Moreover, casual BP devices have been previously recommended for professional and home-use (18). Self-management based on home BP recordings in stroke has been demonstrated across study groups (19-21), all of which have suggested the technique was acceptable, reliable and successful, that it can be tolerated in elderly stroke patients and patients with disability. These studies provide meaningful evidence supporting patient self-management, which could be used to ensure improved control of BP and stroke outcome, though needs to be assessed by trial. Therefore, enhanced monitoring in clinical environments and ease of use outside of that setting are important considerations (22).

Nonetheless, ABPM recordings completed over a 24-hour period are often considered the 'gold standard' due to the advantages provided outside of standard clinical monitoring (23); providing clinically meaningful outcome information as demonstrated by various study cohorts and disease states (24). The practicalities of use in clinical practice has been contextually presented in a consensus paper, whereby commonly raised questions were addressed, namely: which patients should have ABPM; the application and interpretation of ABPM in daily practice; and the introduction of ABPM service in routine clinical practice (25). 24-hour ABPM is recognised for its importance in improving the diagnosis and management of hypertension, and there is evidence that 24-hour BP profiles demonstrate superiority to isolated clinic BP recordings in predicting future vascular related events (26, 27), and indeed provide additive long-term prognostic information in the present study. Furthermore, 24-hour ABPM also provides additional information, including profiles for daytime and night-time BP, day-night BP differences, morning BP surge, and BPV (26). In addition, 24-hour ABPM is currently used in the diagnosis and management of hypertension, though patient acceptability and compliance with BP devices varies across cohorts (28, 29). Whilst it has been reported that patients accept that ABPM will provide useful information and further assist their clinical management, patients have reported experiences of discomfort with its use (29). Lindroos and colleagues

247 previously concluded that the acceptability of different BP measurement methods ranged from
248 office BP monitoring being the most preferred, to 24-hour ABPM being the least preferred
249 monitor (30). The reported differences in monitor acceptability were principally attributable to
250 the greater disturbance and discomfort caused by ABPM (30, 31), and therefore worth
251 considering in a stroke cohort as these experiences may impact of completion of recordings.

252 The main strength of this study is that it has addressed important issues concerning BPV
253 measurement and short- and long-term prognostic significance. It confirms the use of readily
254 available bedside information and easily understandable BPV definitions to provide important
255 prognostic information following AIS and TIA. Furthermore, we were also able to demonstrate
256 the reproducibility of enhanced casual BP recordings with an intraclass correlation coefficient
257 for the two sets of three consecutive BP recordings of 0.92 (SBP) and 0.89 (DBP)
258 (Supplementary material, Table VI).

259 Importantly, our findings were from a multi-centre prospective observational study, using
260 consistent methodology, devices and definitions to enhance the generalisability of our findings.
261 In addition, by evaluating BPV and confirming its prognostic significance, we have provided
262 justification for large prospective clinical trials intending to address and manage BPV per se
263 following stroke (32). Nonetheless, our study findings are hypothesis generating, and require
264 prospective evaluation in further observational studies and randomized intervention trials.

265 However, there are a number of limitations, which should be considered. First, this was a study
266 of mild-to-moderate AIS (median NIHSS 4 [IQR 2-7]) and TIA patients, and the findings need
267 to be replicated in more severe ischaemic stroke sub-types and in intracerebral haemorrhage.
268 Secondly, during baseline data collection, not all sought variables were successfully collected
269 for study participants, and importantly we did not have access to pre-morbid BP or BPV values
270 which may be of importance for post-stroke prognosis. Furthermore, changes in BP

management and other co-morbidities and their management were not consistently recorded during the follow-up period; these may have had an important impact on longer-term prognosis, independent of admission/ baseline BP and BPV values. Lastly, our findings are observational, and further intervention studies to alter BPV and to investigate targets for improving outcome are required. Although anti-hypertensive agents were adjusted where necessary in the regression models, this additional information is of clinical relevance given existing evidence of antihypertensive drug-class effects on BPV (33, 34).

Furthermore, a criticism of this present study is the lack of reporting on the effects of thrombolysis in the presence of increasing BPV in acute stroke. Thrombolysis did not remain statistically significant following univariate analysis, this may have been due to the small number of patients in receipt of thrombolytic therapy within the study population. Previously reported findings have demonstrated the importance of recanalization in stroke outcome in the presence of variability, and it is therefore recognised as an important consideration for prospective studies. This will be of particular significance as diffusion-weighted lesion growth and worse clinical outcomes have demonstrated association with BPV, and this is increasingly reported in stroke patients treated with intravenous thrombolysis (16). Further signifying the importance of this, BPV has been linked with haemorrhagic transformation of infarct and symptomatic intracerebral haemorrhage, demonstrating strong and independent association with poor outcome (35, 36).

Moreover, another interesting observation of this present study warranting further investigation is the contribution of various BPV definitions within the same BP parameters in understanding the prognostic significance of BPV. Irrespective of device, defining variability by SD and CoV within the same BP parameter did not result in consistent study findings. Despite their

respective statistical contributions, further investigation in prospective studies is need in further degerming the most appropriate BPV definition and their prognostic significance.

In conclusion, increasing BPV derived from enhanced causal BP assessments is associated with poor functional outcome at 1-month post-stroke. Enhanced casual, rather than ABPM, proved to be an appropriate measure in understanding the prognostic significance of BPV following stroke, as it better predicted adverse outcome at 1-month. Whilst the ABPM device contributed to our understanding of the long-term implications of BPV following stroke, its routine use needs further investigation.

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Conflict(s) of Interest/Disclosure(s)

None declared

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Figure Legends

Figure 1: 1-month functional outcome predicted from BPV by different BP monitoring devices

Figure 2: 12-month functional outcome predicted from BPV by different BP monitoring devices

Table Legends

Table 1: Baseline description of study participants for 1-month post-stroke

Table 2: Baseline description of study participants for 12-months post-stroke

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