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The Time Course and Determinants of Blood Pressure within the First 48 h after Ischemic Stroke

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Key Words
Stroke · Blood pressure · Natural history · Mixed effects models

Abstract
Background and Purpose: Previous research suggests that blood pressure falls acutely after ischemic stroke. We aimed to further characterize this fall with a statistical technique that allows the application of regression techniques to serial blood pressure outcome data. ***Methods:*** In a prospectively recruited ischemic stroke cohort, systolic (SBP) and diastolic (DBP) blood pressure was recorded every 4 h until 48 h after stroke. Potential determinants of blood pressure, including stroke severity and acute infection, were also recorded. Mixed effects models were used to model serial blood pressure measurements over time, adjusted for significant determinants. ***Results:*** In 156 patients, SBP and DBP fell by 14.9 mm Hg (95% CI 6.2–22.6 mm Hg) and 6.2 mm Hg (95% CI 1.4–10.6 mm Hg), respectively, over the first 48 h after stroke. SBP was higher in patients with premorbid hypertension, a previous history of stroke or TIA, current alcohol use, increasing age, stroke of mild to moderate severity (NIHSS 3–13) and in patients treated with antihypertensives. SBP was lower in smokers. There was a progressive rise in SBP in patients with acute infection. No factors other than time were associated with DBP. ***Conclusions:*** The use of mixed effects models has identified a linear SBP and DBP fall over the first 48 h after stroke. The timing and magnitude of this fall should be accounted for in the design of future prognostic and intervention studies.
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Introduction

The natural history of blood pressure after stroke remains unclear. Although there are no studies comparing blood pressure before and after acute stroke in a single cohort, blood pressures after stroke are high compared with community standards [1, 2], suggesting an acute rise around the time of stroke. Previous research suggests that this blood pressure rise is short lived. Blood pressure falls over the first few days after stroke [2, 3] and then reaches a plateau [1, 4].

The completeness of this characterization, however, is limited by reliance on traditional statistical techniques. These techniques rely on single measurements, such as the admission value [5, 6], or using some summary measure, such as a group mean value [3]. Christensen et al. [7], for

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example, studied mean arterial pressure during the first 4 h after admission after stroke. Using traditional regression techniques, which restricted further characterization of the serial data to subgroup analyses, they demonstrated a 9 mm Hg fall in patients with mild to moderate stroke or TIA but not in those with severe stroke. The statistical treatment of blood pressure characterized in this fashion ignores individual variability associated with each measurement, the inherent within-patient correlation between measurements, and any time-dependent relationship that may exist. Ignoring these quantities invariably results in an underestimation of the true variability associated with blood pressure measurements and an increased likelihood of identifying spurious statistical relationships. Instead, repeated measure data and appropriate longitudinal statistical techniques are required to establish the relationship between blood pressure over time.

Mixed effects models, which are an extension of generalized linear models, are one family of longitudinal statistical techniques that can be employed to appropriately analyze serially collected blood pressure data while accommodating the within and between patient variability, the correlation between serial measurements, and any time dependency [8]. These techniques, therefore, make use of all of the available blood pressure data without the loss of detail that accompanies summarization into a single measurement. The analysis provides coefficients for the explanatory variables that can be interpreted in a similar fashion to those derived from traditional regression techniques.

We have used mixed effects models to investigate the relationships between serial blood pressure measurements and several potential influencing factors. Because we expected blood pressure to change after stroke, we included time elapsed poststroke as one of these factors. We also included several variables that might be expected to influence poststroke blood pressure. We performed multivariable regression analyses with mixed effects models to determine which factors had independent associations with blood pressure, and to quantify their effects.

Subjects and Methods

Patients presenting to the Emergency Department within 48 h of stroke or existing inpatients with an intercurrent stroke between June 1, 2002 and March 31, 2003 were enrolled prospectively. Patients with subarachnoid hemorrhage, hemorrhagic stroke or TIA were excluded.

The time of stroke onset was defined as the time of development of the acute neurological deficit. Where this was unclear (e.g. neurological deficit noted upon waking), the time that the neurological deficit was first noted was used. All blood pressure recordings and other events were referred to this time, rather than to the time of admission. The study was approved by the relevant hospital (Protocol 2002/041, 22 April 2002) medical research ethics committees. Informed consent was obtained from the participant or his/her next of kin when the participant was unable to provide consent due to premorbid or stroke-related impairments.

Demographic information including age, sex, premorbid hypertension, a previous history of stroke or TIA and smoking was recorded. Diabetic status, defined as a history of type 1 or type 2 diabetes, was also recorded. Patients in whom diabetes was first diagnosed during the index admission were classified as not having diabetes for the purposes of this analysis. Alcohol use was defined as the consumption of at least one standard drink (10 g ethanol) per day on average. Hypertension was defined as being present if this had been diagnosed prior to the stroke. Baseline stroke information, including stroke severity measured using the National Institutes of Health Stroke Scale (NIHSS), was recorded. The use of antihypertensive agents during the first 48 h after stroke was also recorded, but prestroke use of antihypertensive agents was not. Poststroke administration was analyzed because these two variables are colinear and the documentation of poststroke administration was considered more reliable than a history of prestroke medication adherence. These factors were used as the explanatory variables in the analysis.

Antihypertensive therapy was defined as alpha blockers, beta blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, and long-acting nitrate preparations. These agents were initiated or continued at the discretion of the treating physicians. There was no specific blood pressure management protocol either as part of routine stroke care or as part of this study.

The presence of infection within the first 48 h after stroke was also documented. There were no specific protocols for the investigation of fever or for microbiological detection of asymptomatic infections, either as part of routine stroke care or as part of this study. Laboratory markers that could be interpreted as indicating the severity of infection were not recorded.

The systolic (SBP) and diastolic (DBP) blood pressure was measured manually using standard aneroid sphygmomanometers (Tycos® 767 series wall and mobile aneroid sphygmomanometers, Welch Allyn®, Rydalmere, Australia) at least 4-hourly until 48 h after the stroke by nursing staff. The blood pressure measurements from patients who died during these first 48 h were included in the analysis.

Statistical Analysis

Both SBP and DBP were entered into the same models. The DBP was used as the reference value and an indicator variable was assigned to identify the systolic measurements.

Initially, a line graph of individual patients' blood pressure measurements over time was drawn (known as a 'spaghetti plot') together with a superimposed lowess curve (a nonparametric estimator of the mean function over time). Such plots are usual for visually determining patterns and skewness in the data that might be indicating potentially important violations of the normality assumption. The correlation between successive observations was examined and an appropriate correlation structure specified

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from candidates: unstructured, exchangeable and autoregressive order 1. Random or fixed time and intercept components were studied to determine which more parsimoniously fitted the data. Non-nested model selection used the Bayesian Information Criterion (BIC) [9]. The BIC is an information criterion which considers both the complexity of the model and its goodness of fit to some data. The BIC value rewards increasing goodness of fit but imposes a penalty for including too many terms in a model. The preferred model balances these competing demands and is the one with the lowest value of the criterion. Once this baseline model was established, residual checks were undertaken to test whether there were important violations of the normality assumption.

The explanatory variables were dichotomized, except age and time, which were treated as continuous variables. The BIC was employed to determine whether NIHSS should be treated as a continuous variable, dichotomized or divided into quartiles. Each explanatory variable was entered into a crude mixed effects model of blood pressure versus time. Variables that were statistically significant in these analyses were then entered into a fully saturated model that included main effects and interaction terms. A stepwise backwards elimination process, based on the type III F test, was then undertaken. A final check of regression diagnostics and influence statistics was made to detect any important departures from the model's assumptions, including the PRESS statistic and Cook's distance measure.

Statistical analyses were performed using SAS version 9 and a significance level of $\alpha = 0.1$ was used to determine statistical significance for all tests.

Table 1. Frequencies and percentages of demographics and potential determinants of blood pressure for use in the mixed effects model analyses (subject 176 included)

Variable		n	%
Sex	Male	82	52.2
	Female	75	47.8
Smoking status	Nonsmoker	90	57.3
	Smoker	67	42.7
Hypertension	No	57	36.3
	Yes	100	63.7
Antihypertensive treatment[a]	No	73	46.5
	Yes	84	53.5
Previous stroke or TIA	No	108	68.8
	Yes	49	31.2
Alcohol use[b]	No	117	77.0
	Yes	35	23.0
Infection	No	149	94.9
	Yes	8	5.1
Hyperlipidemia	No	103	65.6
	Yes	54	34.4

[a] Defined as the use of alpha blockers, beta blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers and long-acting diuretics within the first 48 h after stroke.

[b] Defined as current consumption of at least one standard drink (10 g ethanol) per day. Missing data in 5 cases.

Results

Of 220 patients screened, 157 (71%) were considered suitable for enrolment. Of the 63 patients considered unsuitable for enrolment, 28 (13%) had hemorrhagic strokes, 17 (8%) declined consent, 10 (5%) were admitted after 48 h poststroke, 3 (1%) had no blood pressure recordings within 48 h of stroke, 3 (1%) were subsequently given nonstroke diagnoses and 2 (1%) patients had an unknown time of stroke. Two patients died during the first 48 h after their stroke. The median age of the cohort was 76 years (range 16–92; IQR 67–83). Of the 157 patients, 44 (28%) noted their stroke symptoms upon awakening from sleep. Further demographic details and other explanatory variables are displayed in table 1.

Spaghetti plots of patients' SBP and DBP over time were generated from the 4,172 available recordings, together with the lowess curve (fig. 1). The lowess curve revealed a downwards trend in both SBP and DBP over time, and there were no obvious patterns of asymmetries in the line graphs, suggesting that transformation was unnecessary.

The best combination of model parameters was an 'unstructured' correlation structure with time modeled as a random factor. Both SBP and DBP were associated with time, but there was no relationship with the quadratic function of time. A model including the systolic and diastolic relationships with time was used as the basis for the crude models during subsequent analyses of potential factors.

Influence diagnostics revealed a particular subject (subject 176) with disproportionately extreme PRESS and Cook's distance measure statistics. Apart from these statistics, subject 176 did not appear to be unusual in any way. He was a 64-year-old man with no significant previous medical history (including no history of hypertension) who presented with an NIHSS score of 15, within 2 h of a large left middle cerebral artery territory stroke. His blood pressure recording did not stand out on visual inspection of the spaghetti plots. Nevertheless, the exclusion of subject 176 led to substantially improved residual and influence statistics, and this subject was removed from all subsequent analyses.

The NIHSS in its quartile form had the lowest BIC when compared with the dichotomous and continuous forms. The quartile form was therefore used in the analysis. The thresholds for the quartiles were as follows:

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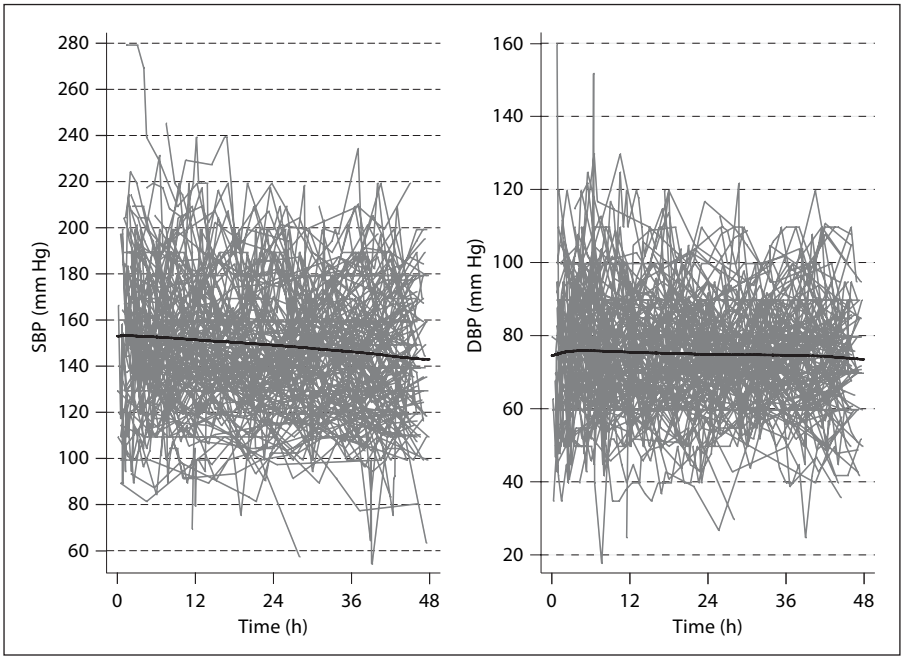

Fig. 1. Spaghetti plots of SBP and DBP over time in 157 patients with ischemic stroke, together with the lowess curves.

Table 2. Results from the crude mixed effects model analysis of each potential determinant of blood pressure, adjusted for time and the time/SBP interaction (n = 151)

Variable	SBP, mm Hg		DBP, mm Hg	
	estimate	95% CI	estimate	95% CI
Age, years	0.33	0.26–0.41*	–0.15	–0.23 to 0.13
Sex (vs. male)	6.38	4.36–8.40*	–3.08	–7.94 to 1.79
Infection	6.83	2.32–11.35*	0.53	–11.46 to 10.41
Hypertension	8.84	6.71–10.97*	0.88	–4.13 to 5.88
Antihypertensive treatment	7.23	5.19–9.27*	–0.23	–5.08 to 4.62
Smoking	–3.70	–5.74 to –1.65*	–1.21	–6.26 to 3.84
Alcohol use	3.32	0.87–5.77*	1.48	–4.42 to 7.39
Previous stroke/TIA	3.95	1.77–6.14*	–2.98	–8.21 to 2.25
NIHSS				
0–2	0	reference	0	reference
3–5	–0.54	–3.58 to 2.49	–1.07	–7.98 to 5.85
6–13	3.69	0.86–6.52*	–3.43	–10.06 to 3.19
≥14	0.90	–1.91 to 3.71	–3.06	–9.98 to 3.87

* $p < 0.1$.

quartile 1 – NIHSS 0–2, quartile 2 – NIHSS 3–5, quartile 3 – NIHSS 6–13, quartile 4 – NIHSS 14 and over.

The serial crude analyses identified no factors associated with DBP. The following were associated with SBP: sex, age, hypertension, blood pressure lowering medication, current alcohol use, infection, smoking, a past history of stroke or TIA and the NIHSS (table 2). When these variables were entered into the multivariable model, only sex was eliminated. Terms representing the interactions between the remaining factors and time were entered

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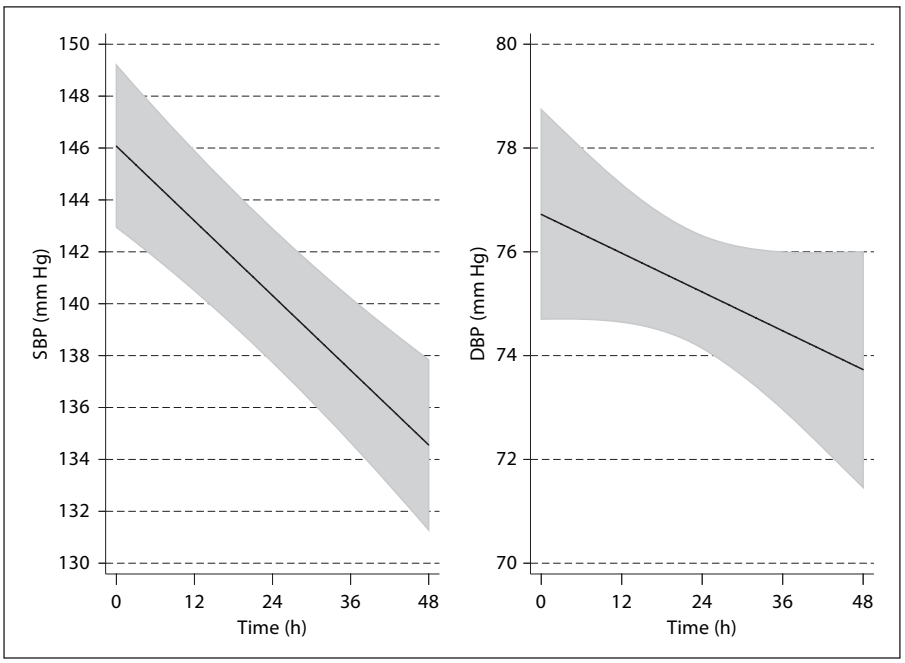

Fig. 2. Mean predicted and 95% CI (shaded area) of SBP[1] and DBP over 48 h after ischemic stroke.

into the model, and all but the interaction between infection, time and SBP were eliminated in the final model (table 3). Residual and influence checks at this stage were satisfactory.

The final model includes intercepts for predicted DBP (77.9 mm Hg) and SBP (126.1 mm Hg). The mean SBP and DBP fell over time, the former by 0.30 mm Hg per hour, and the latter by 0.13 mm Hg per hour. Over the 48 h, the mean SBP fell by 14.9 mm Hg (95% CI 6.2–22.6 mm Hg) and mean DBP fell by 6.1 mm Hg (95% CI 1.6–10.5 mm Hg). Patients with infection have SBPs that rise by 0.04 mm Hg per hour over the first 48 h after stroke. The other factors have a fixed influence on the SBP, which does not change over time. Stroke of moderate severity (NIHSS 3–13), for example, has a higher SBP than mild stroke (NIHSS 0–2), but SBP is not higher in severe stroke (NIHSS ≥14) and DBP is unaffected by stroke severity. Time was the only factor that influenced DBP.

The relationships between poststroke SBP, DBP and time are depicted in figure 2.

[1] Prediction is based on an individual presenting with age 76 years (group median), having no infection, hypertension, antihypertensive treatment, previous stroke/TIA, being a nonsmoker, not taking alcohol and having an NIHSS between 0–2.

Discussion

Both mean SBP and DBP fall linearly during the first 48 h after acute ischemic stroke, by about 14.9 and 6.1 mm Hg, respectively. Several factors were associated with SBP, but the impact of most of these did not change over time. Patients with infection, however, had an approximately 4 mm Hg rise in blood pressure over the first 48 h after stroke.

The cause of the blood pressure change is unclear. Poststroke high blood pressure has been related to both urinary catecholamines [10] and salivary cortisol [11], suggesting that a neuroendocrine stress response explains the poststroke blood pressure changes. The processes leading to activation of this response are not clear, and may include psychological stress including a white-coat effect as suggested by Christensen et al. [7]. Alternatively, a direct effect of neurological damage may be responsible as suggested by the finding of a positive association between stroke severity and cortisol in another study by Christensen et al. [12]. Our findings could be consistent with either hypothesis.

We found higher SBP after stroke of moderate severity (NIHSS 3–13) but not severe stroke (NIHSS ≥14) when compared with stroke with minimal deficits (NIHSS 0–2). This parallels the findings of Christensen et al. [7] in that their patients with mild to moderate stroke, defined

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Table 3. Results from the multivariable mixed effects model analysis of potential determinants of blood pressure (n = 151)

Variable	SBP, mm Hg		DBP, mm Hg	
	estimate	95% CI	estimate	95% CI
Intercept	126.1	116.2–136.1	77.9	74.5–81.4
Time, h	–0.30	–0.14 to –0.47	–0.13	–0.22 to –0.03
Age, years	0.28	0.20–0.36	NS	
Infection	1.63	–5.95 to 9.22	NS	
Infection × time	0.35	0.05–0.66	NA	
Hypertension	6.22	3.73–8.71	NS	
Antihypertensive treatment	2.52	0.12–4.93	NS	
Smoking	–4.60	–6.85 to –2.35	NS	
Alcohol use	6.37	3.66–9.08	NS	
Previous stroke/TIA	2.47	0.26–4.67	NS	
NIHSS			NS	
0–2	0	reference		
3–5	3.69	0.68–6.70		
6–13	4.74	1.99–7.49		
≥14	0.30	–2.57 to 3.18		

NS = Not significant; NA = not applicable.

as a Scandinavian Stroke Score >25, had higher blood pressures than after severe stroke, and of Leonardi-Bee et al. [5] who found lower admission SBPs after large strokes in the IST blood pressure substudy. We do not have an explanation for this observation. Coexisting physiological factors, such as sepsis, heart failure etc., might explain a lower blood pressure in some individuals with severe stroke, but our analysis does not suggest that this would be sufficient to lower the mean blood pressure for this group of patients.

Several other factors affected SBP in the final model. The prestroke diagnosis of hypertension has been associated with high poststroke blood pressure previously [2, 13]. The presence of hypertension and blood pressure-lowering therapy in the model probably reflects prestroke detection and treatment of raised SBP, respectively. Although systolic hypertension is a potent risk factor for first stroke [14], it is also a risk factor for recurrent stroke [15], so it was unsurprising that the model showed SBP to be higher in patients with previous stroke or TIA. Despite the association between DBP and recurrent stroke [15], however, we did not detect any relationship between these two factors in this study.

Other factors associated with higher SBP include age [16] and alcohol [17, 18] which are established risk factors for systolic hypertension in the community. Smoking is also known to be associated with lower SBP [18, 19], and its impact is reflected in the model by a negative regression coefficient. These factors had established relationships with SBP and were included to control for their potentially confounding effects.

There was no interaction between most of these factors and time, suggesting that SBP remains affected to the same extent throughout the 48-hour poststroke. Patients with infection, however, exhibited a mean rise in SBP of around 4 mm Hg, compared with the 14.9-mm Hg fall seen in patients without infection. There are several possibilities for this. Infection may have caused discomfort and distress leading to higher blood pressures. This blood pressure rise may have been dynamic, with a rise in blood pressure that increased in magnitude over the 48 h after stroke. Alternatively, the effect may have been static, and the relationship with time may reflect an accumulation of patients as new infections occur during the 48 h after stroke. We did not attempt to measure markers of physical discomfort or psychological distress, so we cannot clarify the mechanisms behind this statistical relationship.

There are several limitations in this study. The normalization of blood pressure has been shown to mostly occur over a period of 4–5 days [1, 4] and we have only studied the first 48 h after stroke. It is likely, however, that therapeutic manipulation of blood pressure would begin during these first 48 h, so we chose to focus on this pe-

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riod, though we note that Nazir et al. [20] studied blood pressure lowering with perindopril in a subgroup recruited up to 8 days after stroke. Our study did not include a protocol for the use of antihypertensive therapy because we felt there was insufficient evidence to guide the development of a protocol. We did not attempt to measure weight or height, because a large proportion of the patients were expected to be too unwell to be positioned for accurate measurement. We were therefore unable to adjust for body mass index, which is a known determinant of hypertension [21]. Although our study was restricted to a small number of patients at a single center, we suggest that because we focused on the patients rather than an intervention, the results are likely to be generalizable. We also note that the condition of generalizability does not imply the necessity of a representative sample, as noted by Rothman and Greenland [22].

The strengths of the study are that we have analyzed frequent blood pressure measurements related to the time of stroke (rather than the time of admission) and that we have used a relatively new statistical technique to allow the generation of multivariable models using all of the available blood pressure data. This has allowed a statistically thorough characterization of the time course and determinants of poststroke blood pressure. In addition, our use of an unselected ischemic stroke population and standard blood pressure recording equipment allows our results to be generalizable to other stroke centers.

Our major finding was that SBP and DBP fell by 14.9 and 6.1 mm Hg, respectively, during the first 48 h after stroke. This fall occurs during the time window for recruitment into intervention studies [23, 24]. The impact of these early blood pressure changes on prognosis in individual patients remains unclear, as does the potential impact of blood pressure therapies in the acute phase. Our description of the time course and magnitude of poststroke blood pressure change provides additional background information which may help address these questions.

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