Characteristics of Blood Pressure Profiles as Predictors of Long-Term Outcome After Acute Ischemic Stroke

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Background and Purpose—Most patients have elevated blood pressure (BP) in the early phase after an acute ischemic stroke. Mechanism and effects of this BP elevation are not well understood. The benefits of intervention by lowering the initial BP or waiting for spontaneous return to normal values remain debated. We studied the hypothesis that increased BP level and profile variability will adversely affect long-term outcome after stroke with and without thrombolytic treatment.

Methods—We studied the 615 patients with acute ischemic hemispheric stroke in the first European Cooperative Acute Stroke Study (ECASS). BP was measured at 2-hour intervals during the first 20 hours after randomization, and then every 4 hours, up to 72 hours after admission. Studied features of individual 0- to 72-hour BP profiles were: baseline BP, maximum and minimum BP, mean level, and successive variation in the BP profile. The end point was good functional recovery (modified Rankin Scale [mRS] score of 0 to 1) at 90 days. Logistic regression was used to adjust for known prognostic factors, demographic, initial stroke severity, disease and medication histories, and computed tomography signs.

Results—Higher systolic BP or diastolic BP at baseline were associated with favorable outcome assessed on modified mRS at 90 days (adjusted odds ratio [OR], 1.22; 95% CI, 1.01 to 1.49; and OR, 1.22; 95% CI, 1.01 to 1.49 per 10 mm Hg), lower within-patient 0- to 72-hour average systolic BP (SBP), or DBP implied favorable outcome (OR, 0.74; 95% CI, 0.61 to 0.90; and OR, 0.61; 95% CI, 0.41 to 0.90 per 10 mm Hg). Reduced variability of 0- to 72-hour DBP profile was an independent predictor of favorable outcome (OR, 0.58; 95% CI, 0.39 to 0.85 per 5 mm Hg).

Conclusions—Higher baseline SBP or DBP was associated with favorable outcome after stroke. Other characteristics of first 72-hour BP profiles: lower mean level of SBP or DBP and reduced successive variability of DBP profile were independent predictors of favorable outcome at 90 days. (Stroke. 2005;36:000-000.)

Key Words: blood pressure ■ outcome ■ stroke, ischemic ■ tissue plasminogen activator

Elevations in systolic or diastolic blood pressure (BP) are observed in up to 80% of patients after an acute ischemic stroke, even in previous normotensives. The elevated BP often returns to normal spontaneously within several days after stroke. The mechanism and effect of the elevated BP have not been well understood. Elevated BP may be attributable to stress after the stroke, or it is a protective response to improve cerebral perfusion. Furthermore, the guidelines about the treatment of hypertension in acute stroke patients are not supported by evidence. An investigation of the natural course of BP in the early phase of stroke and the prognostic significance of the short-term profile of BP after stroke for survival and long-term outcome may be important for optimal acute stroke management.

Many strokes are caused by thromboembolism or atherothrombosis. Intravenous alteplase (recombinant tissue plasminogen activator [rt-PA]) is the only approved therapy to improve stroke outcome. In June 1996, the US Food and Drug Administration approved rt-PA of 0.9 mg/kg, with the restriction that treatment should begin within 3 hours of stroke onset as a treatment for acute ischemic stroke. However, safety of thrombolytic treatment is a concern. Parenchymal hemorrhage and hemorrhagic transformations have been observed in several trials. The higher likelihood of intracranial bleedings is the main motivation for BP management after thrombolytic treatment. What requires further investigation still is the difference between profile in rt-PA– and placebo-treated patients and the extent to which BP should be controlled in the rt-PA–treated stroke patients.

The present study addressed the following 2 questions: (1) Are the characteristics of BP profiles different between the rt-PA and placebo groups; and (2) Which characteristics of BP profiles are independent predictors of functional outcome at 3 months after an acute stroke?
Materials and Methods

Patient Population

The intention-to-treat cohort of the first European Cooperative Acute Stroke Study (ECASS) was used. ECASS was a multicenter, randomized, double-blind, placebo-controlled trial to test the efficacy and safety of rt-PA in acute hemispheric stroke. A total of 620 eligible patients were randomly assigned to either 1.1 mg/kg rt-PA or placebo; 5 did not receive trial medication. Among the 615 patients, 7 were lost to follow-up. Intravenous administration of trial medication was required to start within 6 hours after onset of symptoms.

Aims, methodology, and patient inclusion and exclusion criteria had been described previously. In particular, patients with systolic BP (SBP) >110 mm Hg or diastolic BP (DBP) >110 mm Hg on repeated measurements before study entry were excluded. According to the baseline BP, patients were grouped into initial hypertensives (SBP ≥140 mm Hg or DBP ≥90 mm Hg) and normotensives. The distributions of demographic and clinical factors, disease and medication histories, and the computed tomography (CT) signs of these 2 post hoc groups were compared, and homogeneity in treatment assignment, gender, and age were shown (Table 1). Initial stroke severity on the Scandinavian Stroke Scale (SSS) and time from onset to treatment were also comparable. Body weight was significantly higher in initial hypertensives than in normotensives (P<0.0001). With respect to disease and medication histories, hypertension history was more frequent in initial hypertensives (P<0.0001).

Initial hypertensives seemed to have more frequent previous infarct signs on the CT, with a marginal statistical significance of P=0.032. Supine BP was measured in the hemiparetic arm using a standard mercury sphygmomanometer. BP was measured on admission, every 2 hours within the first 20 hours, and then every 4 hours, up to 72 hours. Although, in practice, some noncompliance with the examination protocol occurred, and measurements between any 2 protocol time points were ascribed to the later time point for the present analysis.

Stroke outcome was assessed on the modified Rankin Scale (mRS) 90±7 days after treatment. Unfavorable outcome (including death within the first 90 days as the worst outcome) was defined as mRS score ≥2 and favorable outcome (no or negligible impairment) as mRS score ≤1.

Treatment assignment, gender, age, baseline body weight, onset to treatment interval, initial stroke severity on SSS, specific disease histories such as atrial fibrillation, previous stroke, transient ischemic attack, hypertension, coronary heart disease, valvular disease, and diabetes mellitus, on acetylsalicylic acid (ASA) medication at baseline, and findings on baseline CT were considered potential confounders of outcome.

Statistical Analysis

Summary parameters used to describe individual patient BP profiles were baseline BP, 0- to 72-hour maximum, 0- to 72-hour minimum, 0- to 72-hour average (mean level), and successive variation (SV) to represent variability of an individual 0- to 72-hour profile that consists of n=24 readings, Xi, X2, ..., Xn, according to protocol such that

\[ SV = \sqrt{\frac{1}{n-1} \sum_{i=1}^{n-1} (X_i - \bar{X})^2} \]

SV of a patient’s BP profile is the average squared difference between any 2 successive BP measurements. In contrast with the widely known sample SD, the SV addresses the time sequence of measurements.

χ² tests were used for the categorical variables and 2-sided nonparametric Wilcoxon U tests for the continuous variables in the univariate analyses. Two binomial logistic regression models for the prediction of favorable 90-day outcome (mRS score ≤1) were considered. In the first, the characteristics of SBP and DBP profiles and the aforementioned potential predictors were included respectively in a single model. Second, the significant predictors were included step by step according to Akaike’s information criterion to obtain a final model. Results were presented as adjusted odds ratios (ORs) with 95% CIs.

Regression analysis of predictors and plotting were performed with S-Plus® version 5.1 release for AIX 4.3.1, and all other data analyses were performed with the Statistical Analysis System® of version 6.12 for AIX 4.3.1.

Results

Among the total of 615 intention-to-treat patients, 493 (80.2%) had elevated initial BP, and 592 (96.3%) patients had complete BP measurements within the first 72 hours after admission.
Sample Mean Profiles of BP Among Favorable and Unfavorable Outcomes

The 0- to 72-hour profiles of sample means of SBP and DBP in patients assigned to 1.1 mg/kg rt-PA IV or to placebo were calculated separately for 2 retrospectively formed subgroups, according to favorable and unfavorable outcome on the mRS after 90 days (Figures 1 and 2). The sample means of SBP and DBP decreased gradually with time in all subgroups.

Association of SBP Profiles and Favorable Outcome on mRS

In the univariate comparison of individual SBP profile characteristics between favorable and unfavorable outcomes in the rt-PA and the placebo-assigned patients, within-patient 0- to 72-hour maximum and average BP values showed significant differences in favorable and unfavorable outcome in the placebo group, whereas association of within-patient 0- to 72-hour maximum and SV were suggested in the rt-PA group (Table 2).

In the multivariate logistic regression analysis, only lower within-patient 0- to 72-hour average SBP value (adjusted OR, 0.74; 95% CI, 0.61 to 0.90 per 10 mm Hg) had an independent overall effect on the probability of favorable outcome at 90 days, as well as treatment with rt-PA (adjusted OR, 1.81; 95% CI, 1.18 to 2.77), and higher initial SSS score (adjusted OR, 2.62; 95% CI, 2.02 to 3.39), smaller hypodensity extent on CT (adjusted OR, 0.37; 95% CI, 0.23 to 0.60), and higher baseline SBP (adjusted OR, 1.22; 95% CI, 1.01 to 1.49 per 10 mm Hg; Table 3).

Association of DBP Profiles and Favorable Outcome on mRS

In the univariate comparison of individual DBP profile characteristics between favorable and unfavorable outcomes in the rt-PA and the placebo-assigned patients, within-patient 0- to 72-hour SV of DBP profile is the single factor significantly associated with 90-day outcome in placebo and rt-PA group (Table 2).

In the multivariate logistic regression analysis, lower within-patient 0- to 72-hour average DBP value (adjusted OR, 0.61; 95% CI, 0.41 to 0.90 per 10 mm Hg) and smaller SV of 0- to 72-hour DBP profile (adjusted OR, 0.58; 95% CI,
0.39 to 0.85 per 5 mm Hg) had independent effect on the probability of favorable outcome at 90 days, as well as treatment with rt-PA (adjusted OR, 1.82; 95% CI, 1.19 to 2.79), younger patient (age in decade; adjusted OR, 0.77; 95% CI, 0.64 to 0.92), higher initial SSS score (adjusted OR, 2.60; 95% CI, 2.02 to 3.34), smaller hypodensity extent on CT (adjusted OR, 0.47; 95% CI, 0.27 to 0.80), and higher baseline DBP (adjusted OR, 1.22; 95% CI, 1.01 to 1.49 per 10 mm Hg; Table 4).

**Discussion**

The main objective of the present study was to examine the effect of patient BP profiles in the acute phase of stroke, in particular within-patient 0- to 72-hour average BP levels and 0- to 72-hour BP variabilities on long-term disability outcome. The available data on patient demographics, initial severity of stroke, disease histories, and CT examinations provided sufficient information in terms of potential confounders to be adjusted for. Good compliance with an examination protocol of repeated measurements of BP at fixed intervals made it possible to analyze the effects of patient average 0- to 72-hour levels and within-patient variabilities of BP values on the 90-day outcome.

The cerebral blood flow in the penumbra depends on the systemic BP and collaterals until the occluded artery is recanalized. Autoregulation is impaired after an ischemic insult. Hence, changes, especially the successive changes of systemic BP, may have important influence on the cerebral perfusion. Various measures of variability of individual BP profile have been used to investigate their association with stroke outcome. The most common measures of variations are the extreme values, such as maximum, minimum, or range (difference between maximum and minimum), SD (root of mean squared differences from the total mean), or coefficient of variation (SD over mean). The adopted measure of within-patient variability in the present analysis is the SV, which was initially suggested previously. This parameter takes the serial variation on the time sequence into account, whereas other measures, such as SD and coefficient of variation, ignore the sequential nature of the data; profile
patterns of a substantially different clinical meaning may then yield the same value of SD or coefficient of variation. Hence, such time-invariant measures could result in misleading predictions on the outcome and provide less information in terms of BP management in practice.

The present analysis aims to estimate the prognostic value of the actual level of BP on the long-term outcome, irrespective of antihypertensive therapy. This was done for 3 reasons. First, antihypertensive medications could be a meaningful surrogate when only the admission (baseline) BP levels are taken into account. Second, as long as a pharmacological interaction between antihypertensive agents and rt-PA is unknown, the profile of BP would be the cause of any effects that were attributed to an antihypertensive medication. And finally, randomization and double blinding in the trial design should ascertain the comparability of prescription of antihypertensive agents between rt-PA and placebo groups.

Our findings implied that decreased SV of DBP is an independent predictor of 90-day favorable outcome. How ever, the successive variability of SBP was not an independent predictor of 90-day functional outcome. This finding was consistent in placebo patients or patients treated with rt-PA. The association between low BP variability and outcome in the present study is supported by observations of Dawson et al\textsuperscript{15} and Robinson et al.\textsuperscript{16} Dawson et al\textsuperscript{15} compared the different measures of beat-to-beat BP and variability on early outcome. They used SD as measure of variability of beat-to-beat BP and reported that higher DBP and mean arterial pressure variability were significantly associated with death or dependent outcome at 30 days, although SBP did not, after the adjustment for age and stroke type. Robinson et al\textsuperscript{16} examined the association between higher BP variability and the occurrence of acute stroke patients in a matched controlled setting, using either SD or SV. To our knowledge, our study is the first to determine the prognostic value of BP variability after adjustment for age, neurological severity, and baseline CT findings.

Our study demonstrated that a higher baseline BP, either SBP or DBP, is an independent predictor of favorable outcome at 90 days, which is corroborated with some other findings.\textsuperscript{17,19} Oliveira-Filho et al\textsuperscript{17} have shown that patients

\begin{table}[h]
\centering
\caption{Characteristics of Within-Patient SBP and DBP Profiles According to 90-Day Outcome and Treatment Assignment, Means (SD) in mm Hg}
\begin{tabular}{llllll}
\hline
 & \multicolumn{2}{c}{Placebo} & & \multicolumn{2}{c}{rt-PA} \\
 & \textit{mRS} 0–1 & \textit{mRS} 2–6 & \textit{P} & \textit{mRS} 0–1 & \textit{mRS} 2–6 & \textit{P} \\
\hline
Baseline SBP & 156.7 (21.3) & 152.7 (23.0) & 0.15 & 157.7 (24.9) & 154.0 (22.7) & 0.19 \\
0- to 72-hour SBP maximum & 173.1 (22.5) & 180.2 (23.7) & 0.03 & 174.6 (24.5) & 182.6 (26.1) & 0.02 \\
0- to 72-hour SBP minimum & 117.4 (14.7) & 121.6 (18.3) & 0.07 & 118.8 (17.4) & 118.9 (19.6) & 0.87 \\
0- to 72-hour SBP mean & 142.8 (16.8) & 149.8 (15.2) & 0.006 & 145.4 (18.8) & 149.4 (19.3) & 0.16 \\
Baseline DBP & 90.2 (12.7) & 86.7 (12.4) & 0.06 & 87.8 (13.0) & 86.9 (12.2) & 0.38 \\
0- to 72-hour DBP maximum & 101.7 (12.6) & 102.6 (12.7) & 0.67 & 100.8 (13.4) & 102.5 (13.4) & 0.20 \\
0- to 72-hour DBP minimum & 68.2 (10.6) & 65.6 (11.9) & 0.15 & 65.2 (10.3) & 64.0 (12.7) & 0.60 \\
0- to 72-hour DBP mean & 84.3 (9.3) & 84.0 (9.6) & 0.78 & 81.4 (8.7) & 83.2 (10.3) & 0.14 \\
0- to 72-hour DBP SV & 15.9 (4.8) & 17.4 (5.8) & 0.053 & 16.4 (6.1) & 18.6 (7.6) & 0.018 \\
Baseline DBP & 90.2 (12.7) & 86.7 (12.4) & 0.06 & 87.8 (13.0) & 86.9 (12.2) & 0.38 \\
0- to 72-hour DBP maximum & 101.7 (12.6) & 102.6 (12.7) & 0.67 & 100.8 (13.4) & 102.5 (13.4) & 0.20 \\
0- to 72-hour DBP minimum & 68.2 (10.6) & 65.6 (11.9) & 0.15 & 65.2 (10.3) & 64.0 (12.7) & 0.60 \\
0- to 72-hour DBP mean & 84.3 (9.3) & 84.0 (9.6) & 0.78 & 81.4 (8.7) & 83.2 (10.3) & 0.14 \\
0- to 72-hour DBP SV & 15.9 (4.8) & 17.4 (5.8) & 0.053 & 16.4 (6.1) & 18.6 (7.6) & 0.018 \\
\hline
\end{tabular}
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\begin{table}[h]
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\caption{Multifactorial Logistic Regression Model Assessing the Independent Association of Within-Patient SBP Profile Within 72 Hours After Admission on 90-Day Functional Outcome (mRS score 0, 1 vs 2, 3, 4, 5, and 6)}
\begin{tabular}{llll}
\hline
Characteristics & OR & 95% CI \\
\hline
Treatment & 1.82 & 1.19–2.79 \\
Age decade & 0.77 & 0.64–0.92 \\
Initial SSS score & 2.60 & 2.02–3.34 \\
HMCA sign & 0.54 & 0.27–1.10 \\
Hypodensity on CT & 0.47 & 0.27–0.80 \\
Focal swelling & 0.58 & 0.29–1.14 \\
Baseline DBP per 10 mm Hg & 1.22 & 1.01–1.49 \\
0- to 72-hour DBP mean per 10 mm Hg & 1.35 & 0.91–2.00 \\
Baseline SBP per 10 mm Hg & 0.86 & 0.71–1.05 \\
0- to 72-hour SBP SV per 5 mm Hg & 0.58 & 0.39–0.85 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{1}HMCA indicates hyperdense middle cerebral artery.
with good outcome had higher admission mean DBP of 96 mm Hg (SD 19) compared with those with poor outcome, who had mean DBP of 89 mm Hg (SD 13), with a significant difference univariately. However, the definition of poor outcome was not identical with the present study. Osaki et al. suggested a statistical significant relationship between hypertension on admission with neurological recovery, in a fairly small sample of 28 nonembolic patients. Semplicini et al. had found that the patients with the best neurological outcome had the highest BP during the first 24 hours and the neurological outcome was dependent on the higher admission BP and better initial neurological condition. To be noted, their results are only comparable with the placebo-treated patients in the present study. In addition, noninterventional studies might have higher BP levels at entry. In ECASS patients with a BP >180 mm Hg could not be included. In contrast, a negative association has been implied in several studies. An analysis by Brown et al. from the National Institute of Neurological Disorders and Stroke study population did not indicate the BP at baseline, calculated with mean arterial pressure, to be significantly associated with major neurological outcome did not indicate the BP at baseline, calculated with mean arterial pressure, to be significantly associated with major neurological improvement within 24 hours. Our findings are not comparable with the U-shaped relationship between outcome and initial BP,23–25 because our results, based on a logistic model, can only be interpreted as an averaged effect. An underestimation of the association in the present study has to be considered. Patients with SBP >185 mm Hg or DBP >110 mm Hg on repeated measurements before study entry were excluded. And 81% patients in the rt-PA group and 79% in the placebo group had elevated BP. This agrees well with common observation that 80% of patients were expected to have elevated BP after acute stroke.26–27

The present study has limitations attributable to its post hoc nature because the ECASS trial had not been initiated and designed for the hypothesis underlying the present analysis. Hence, the potential bias has to be considered. Among the 5 randomized, placebo-controlled, multicenter trials that demonstrated the efficacy and safety of rt-PA that convinced the approval, none of them had been stratified according to BP at the randomization. Random sampling can assure the homogeneity of known and unknown confounders between the compared groups in statistical theory. In clinical trial settings, if randomization is not feasible, comparability of test and control groups is an important principle, which is in accordance of standard practice. The study sample may not be representative of the target patient population. Patients who have only minor stroke symptoms or who show rapid improvement of the symptoms at the time of randomization have been excluded. Patients with presumed vertebrobasilar stroke, including isolated hemianopia or isolated ataxia, known active seizure disorder or a first seizure within 6 hours before initiation of study drug administration, previous cerebral infarct within 3 months or any other disabling stroke, previous known intracranial hemorrhage, intracranial neoplasm, subarachnoid hemorrhage, arteriovenous malformation, or aneurysm in their history were not eligible.

The present study raised again the question whether it is beneficial to reduce the initial BP in acute ischemic stroke, especially in moderate hypertension. Mattle et al. showed that BP goes down when the occluded artery is recanalized but would not if there is inadequate recanalization. In placebo-treated patients in the present study, lower 0- to 72-hour mean BP (Table 2) and faster decrease (Figure 1) in patients with favorable outcome support the idea that the occluded arteries have spontaneously recanalized, and there was no more need for higher BP levels to ensure perfusion pressure in ischemic areas. Multifactorial analyses have confirmed again their independent impact (Tables 3 and 4). We do not know the state of the arteries in the ECASS trial cohort, but our results tally with those of Mattle et al. and suggest that it may not be appropriate to reduce BP without knowing the state of the arteries. That this is the case is also suggested by the results of Lindsberg et al. and that of Brott et al., in which active reduction of BP as recommended by the present guidelines for thrombolysis issued by the American Heart Association and the European Stroke Initiative was associated with poorer outcome. The findings of the present study suggest that it may be beneficial to keep the BP at a reasonable lower overall level and less variable over time in the early phase after acute stroke. In clinical practice, this means that drugs potentially resulting in a sudden drop of BP or drugs with a short half-life and therefore variable efficacy should be avoided. Despite statistical significance, the magnitude of the effect of overall mean and successive variability is minor. Association of lower variability of DBP during the first 24 hours with favorable outcome in the present study may reflect the state of autoregulation and BP control. If they function well, the outcome of a patient will be better than if they are functioning less well, which possibly can jeopardize cerebral blood flow further in ischemic penumbra, asking for more robust corrections (ie, wider variability of BP). The clinical relevance of BP level and variability for the BP management in acute stroke still requires further investigations. In conclusion, our results, as well as those of Mattle et al. and Lindsberg et al., suggest that the present guidelines for BP treatment in acute stroke may need some revisions, and also the state of arteries should be taken in consideration.

References


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