Recanalization Modulates Association Between Blood Pressure and Functional Outcome in Acute Ischemic Stroke

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Background and Purpose—Historical stroke cohorts reported a U- or J-shaped relationship between blood pressure (BP) and clinical outcome. However, these studies predated current revascularization strategies, disregarding the recanalization state of the affected arterial territory. We aimed to investigate the relationship between BP in the first 24 hours after ischemic stroke and clinical outcome in patients submitted to intravenous or intra-arterial recanalization treatments.

Methods—Consecutive patients with acute stroke treated with intravenous thrombolysis or intra-arterial therapies were enrolled in a retrospective cohort study. BP was measured on regular intervals throughout day and night during the first 24 hours after stroke onset. The mean systolic BP and diastolic BP during the first 24 hours post stroke were calculated. Recanalization was assessed at 6 hours by transcranial color-coded Doppler, angiography, or angio–computed tomography. Functional outcome was assessed at 3 months by modified Rankin Scale. Linear and quadratic multivariate regression models were performed to determine associations between BP and functional outcome for the whole population and recanalized and nonrecanalized patients.

Results—We included 674 patients; mean age was 73.28 (SD, 11.50) years. Arterial recanalization was documented in 355 (52.70%) patients. In multivariate analyses, systolic BP and diastolic BP in the first 24 hours post stroke show a J-shaped relationship with functional outcome in the total population and in the nonrecanalized patients. Recanalized patients show a linear association with functional outcome (systolic BP: odds ratio, 1.015; 95% confidence interval, 1.007–1.024; P=0.001; R² change=0.001; P=0.412 and diastolic BP: odds ratio, 1.019; 95% confidence interval, 1.004–1.033; P=0.012; R² change<0.001; P=0.635).

Conclusions—Systemic BP in the first 24 hours after ischemic stroke influences 3-month clinical outcome. This association is dependent on the recanalization status. (Stroke. 2016;47:1571-1576. DOI: 10.1161/STROKEAHA.115.012544.)

Key Words: acute stroke □ blood pressure □ hemodynamics □ neurosonology □ stroke □ thrombectomy □ ultrasonography

Optimal management of blood pressure (BP) during the acute stage of patients with ischemic stroke is a medical challenge with potential clinical effect. However, knowledge of the precise hemodynamic physiological and pathological responses is still scarce. Moreover, the transient focal disruption of cerebral autoregulation renders perfusion of the ischemic tissue directly dependent on systemic BP.¹

Classically, the relationship between systolic BP (SBP) and clinical outcome was described as U- or J shaped, with both high and low values of BP being independent prognostic factors for poor outcome.² ³ Nonetheless, these studies did not consider the recanalization state of the affected arterial territory, which may directly influence the hemodynamic response.

The main objective of this study is to determine the relationship between BP during the first 24 hours after ischemic stroke and clinical outcome in patients submitted to intravenous or intra-arterial recanalization treatments.

Methods

Study Population

We included consecutive patients with acute ischemic stroke from July 2009 to June 2015, treated with intravenous thrombolysis (IVrtPA) or intra-arterial therapies in our tertiary, university hospital in Portugal. The exclusion criteria were as follows: patients who had insufficient BP data (ie, incomplete BP readings in the first 24 hours poststroke due to patient death or early hospital transfer); unavailable information...
about recanalization state; and unfavorable previous functional status, defined by a previous modified Rankin Scale (mRS) score >2. The algorithm for study inclusion is presented in Figure 1.

Vascular risk factors were collected from a standardized local clinical registry. Considering the observational and retrospective design of the study, signed informed consent specific for this study was not obtained. All patients received oral and written information on collection of observational data for clinical studies and were free to withdraw consent. The study was approved by the institutional ethics committee of our hospital.

**BP Measurements**

In our institution, all patients submitted to intravenous or intra-arterial treatment for acute ischemic stroke are admitted at the local stroke unit. According to this unit’s protocol, all vital signs are measured at predetermined time intervals. BP readings were performed automatically every 2 hours during daytime and every 3 hours during nighttime. Diurnal measurements were obtained between 8 am and 11 pm and nocturnal measurements between 11 pm and 8 am. Baseline measurements were obtained before reperfusion therapies in all patients. All the measurements were obtained by certified and trained nurses, using Phillips Agilent NBP equipment, model M1008B, validated annually (last validation in October 2015).

The mean SBP and diastolic BP (DBP) during the first 24 hours post stroke were calculated.

**Data Collection**

We collected data on vascular risk factors from a prospectively defined clinical registry: age, sex, alcohol consumption (>80 g per day at least in the previous year), smoking (present or past), hypertension (defined as SBP ≥140 or DBP ≥90 mmHg before stroke or history of antihypertensive medication), diabetes mellitus (previously diagnosed or by fasting glucose superior to 126 mg/dL or 200 mg/dL or greater for those nonfasting), dyslipidemia (current or history of antihypertensive medication), diabetes mellitus (previously diagnosed or by fasting glucose superior to 126 mg/dL or 200 mg/dL or greater for those nonfasting), dyslipidemia (current or history of abnormal plasma high-/low-density cholesterol or triglycerides values), coronary artery disease (history of angina pectoris or acute myocardial infarction, or evidence from coronary artery catheterization), peripheral artery disease (history of intermittent claudication, ischemic ulcers or gangrene, or evidence of peripheral artery narrowing on ultrasound examination), atrial fibrillation (paroxysmal, permanent, or persistent episodes of atrial fibrillation), and heart failure (previous history with or without recent exacerbation).

**Neurological, Hemodynamic, and Imagiological Assessment**

To assess impairment at admission, we used the National Institute of Health Stroke Scale. For the 3-month functional outcome, we used the mRS obtained from the follow-up appointment registry or, when possible, the mRS obtained from the follow-up appointment registry or, when

**Table 1. Baseline Characteristics of the Study, Univariate Linear Regression for Predictors of SBP at 24 Hours, and Univariate Binary Logistic Regression for Predictors of Early Recanalization**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Population, n=674 Patients</th>
<th>Univariate Association With SBP, β (95% CI)</th>
<th>PValue</th>
<th>Univariate Association With Recanalization, OR (95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>73.28±11.50</td>
<td>0.442 (0.307 to 0.577)</td>
<td>&lt;0.001</td>
<td>0.980 (0.967 to 0.993)</td>
<td>0.003</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>363 (53.90)</td>
<td>1.037 (−2.167 to 4.240)</td>
<td>0.525</td>
<td>1.393 (1.027 to 1.888)</td>
<td>0.033</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>67 (10.00)</td>
<td>−0.013 (−0.037 to 0.011)</td>
<td>0.298</td>
<td>0.999 (0.997 to 1.002)</td>
<td>0.522</td>
</tr>
<tr>
<td>Alcoholism, n (%)</td>
<td>45 (6.70)</td>
<td>−2.787 (−5.874 to 0.301)</td>
<td>0.077</td>
<td>0.904 (0.675 to 1.211)</td>
<td>0.498</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>541 (80.40)</td>
<td>12.398 (8.480 to 16.315)</td>
<td>&lt;0.001</td>
<td>0.986 (0.674 to 1.444)</td>
<td>0.942</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>166 (24.60)</td>
<td>6.485 (2.835 to 10.136)</td>
<td>&lt;0.001</td>
<td>0.772 (0.545 to 1.093)</td>
<td>0.144</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>353 (52.70)</td>
<td>−1.625 (−4.833 to 1.583)</td>
<td>0.320</td>
<td>1.335 (0.985 to 1.810)</td>
<td>0.063</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>329 (48.90)</td>
<td>1.438 (−1.760 to 4.636)</td>
<td>0.378</td>
<td>0.596 (0.440 to 0.809)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>90 (13.0)</td>
<td>0.007 (−0.011 to 0.026)</td>
<td>0.431</td>
<td>0.999 (0.998 to 1.001)</td>
<td>0.568</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>62 (9.40)</td>
<td>5.275 (−0.271 to 10.820)</td>
<td>0.062</td>
<td>0.834 (0.494 to 1.407)</td>
<td>0.497</td>
</tr>
<tr>
<td>Previous mRS, mean±SD</td>
<td>0.31±0.60</td>
<td>1.395 (−2.657 to 3.446)</td>
<td>0.800</td>
<td>0.911 (0.681 to 1.218)</td>
<td>0.527</td>
</tr>
<tr>
<td>NIHSS at admission, mean±SD</td>
<td>15.29±7.01</td>
<td>0.447 (0.221 to 0.674)</td>
<td>&lt;0.001</td>
<td>0.891 (0.868 to 0.914)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinolysis (IV), n (%)</td>
<td>663 (98.40)</td>
<td>4.664 (−7.939 to 17.267)</td>
<td>0.468</td>
<td>1.342 (0.406 to 4.440)</td>
<td>0.630</td>
</tr>
<tr>
<td>Endovascular treatment, n (%)</td>
<td>52 (7.70)</td>
<td>−6.010 (−11.980 to −0.041)</td>
<td>0.048</td>
<td>0.754 (0.427 to 1.329)</td>
<td>0.328</td>
</tr>
<tr>
<td>Time to treatment, min, mean±SD</td>
<td>150.25±55.27</td>
<td>0.012 (−0.017 to 0.041)</td>
<td>0.405</td>
<td>0.999 (0.996 to 1.002)</td>
<td>0.441</td>
</tr>
</tbody>
</table>

Dichotomous variables are presented as frequency (%). CI indicates confidence interval; IV, intravenous; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; and SBP, systolic blood pressure.
missing, by telephone contact with the patient or relative. Time to treatment was defined as minutes from stroke onset to beginning of IIVtPA or arterial puncture in the cases of isolated intra-arterial treatment. Stroke onset was determined as the time of symptomatic installation or last seen well.

Arterial recanalization was assessed by the angiographic pattern at the end of intra-arterial treatment, transcranial color-coded Doppler, or computed tomographic angiography of intracranial arteries performed at 6 hours after stroke. We considered recanalization as grade 2b or 3 from the modified Thrombolysis in Cerebral Infarction score in patients under intra-arterial treatment, grades 4 or 5 from the thrombolysis in brain ischemia classification using transcranial color-coded Doppler, or visualization of contrast perfusion in all symptomatic vessels by computed tomographic angiography.

Symptomatic intracerebral hemorrhage (sICH) was defined by the presence of local or remote parenchymal hemorrhage temporally and causally related to deterioration of the patient’s clinical condition in the judgment of the clinical investigator.

Statistical Analysis
Baseline characteristics are presented as frequency (percentage) for dichotomous variables and mean±SD for quantitative variables. Univariate associations with SBP of the first 24 hours were assessed with a linear regression and presented as $\beta$ (95% confidence interval). Univariate associations with recanalization at 6 hours were assessed with a binary logistic regression and presented as odds ratio (95% confidence interval). For inclusion in the regression model, the ordinal variable (previous mRS) was dichotomized into patients with and without symptoms.

Independent predictors of 3-month functional outcome were determined using a linear regression. The variables included in the multivariate model were the mean SBP and DBP of each patient in the first 24 hours post ischemic stroke and variables with statistically significant univariate association with either SBP of the first 24 hours or recanalization. In short, the quadratic values of SBP and DBP were included in a separate block of the regression model software. A nonlinear association was determined whenever the quadratic variable produced a statistically significant $R^2$ change. Variables with both linear and nonlinear associations were defined as having a J-shaped relationship.

The independent association of SBP and DBP with sICH was determined using a binary logistic regression adjusting for recanalization status and variables with univariate association with SBP of the first 24 hours or early recanalization.

Table 2. Linear and Quadratic Regressions Analyzing Relationship Between 24 Hours Post Ischemic Stroke BP Values and 3-Month Clinical Outcome in Total Population and in Nonrecanalyzed and Recanalyzed Patients

| Variable | OR (95% CI) | $P$ Value | $R^2$ | $P$ Value
|----------|-------------|-----------|-------|--------
| 24-h SBP | Total population | 1.016 (1.009–1.022) | <0.001 | 0.006 | 0.012
| | Recanalyzed at 6 h | 1.015 (1.007–1.024) | 0.001 | 0.001 | 0.412
| | Nonrecanalyzed at 6 h | 1.013 (1.005–1.021) | 0.001 | 0.011 | 0.033
| 24-h DBP | Total population | 1.019 (1.009–1.029) | <0.001 | 0.006 | 0.010
| | Recanalyzed at 6 h | 1.019 (1.004–1.033) | 0.012 | <0.001 | 0.635
| | Nonrecanalyzed at 6 h | 1.018 (1.004–1.031) | 0.009 | 0.020 | 0.004

OR (95% CI) and associated $P$ values represent the results of linear regression. $R^2$ change associated with quadratic regression and its statistical significance is presented in the right columns. All models are adjusted for age, baseline National Institute of Health Stroke Scale, hypertension, diabetes mellitus, endovascular treatment, atrial fibrillation and sex. CI indicates confidence interval; OR, odds ratio; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Statistical significance was set for $P<0.05$. All the statistical analyses were made in IBM SPSS Statistics software, version 22.

Results
During the study period, a total of 748 patients received acute recanalization treatment for ischemic stroke. For our analysis, we included 674 patients; mean age was 73.28±11.50 years, and 363 (53.90%) were men. Baseline features and univariate associations with 24-hour SBP and early recanalization are presented in Table 1. A total of 663 patients underwent IIVtPA and 52 endovascular procedures (11 of which isolated). Recanalization was assessed by transcranial color-coded Doppler in 615 patients (91.20%), angiography in 52 (7.70%),

Figure 2. Relationship between blood pressure (BP) in the first 24 hours post ischemic stroke and functional outcome at 3 months (through modified Rankin Scale [mRS]). A and B, Total population included in this study. Error bars represent the 95% confidence interval for mean.
and computed tomographic angiography in 7 (1.10%). Timings of recanalization assessment by angiography and computed tomographic angiography are presented in Table I in the online-only Data Supplement.

Recanalization was obtained in 355 patients (52.70%); 331 (53.22%) of those were treated with IVrtPA alone and 24 (46.15%) of those were submitted to endovascular treatments.

In multivariate analyses, applying quadratic regression and after adjusting for age, hypertension, diabetes mellitus, baseline National Institute of Health Stroke Scale, endovascular treatment, atrial fibrillation, and sex, we determined a J-shaped relationship between 3-month mRS score and SBP or DBP in the first 24 hours post stroke in the total population and in the nonrecanalyzed patients group, with the highest and the lowest values of BP being associated with a worst outcome. In the recanalyzed patient group, the relationship is linear, with lower values of BP being related to a better functional outcome at 3 months (Table 2; Figures 2 and 3).

In our population, sICH was observed in 42 patients (6.20%). SBP and DBP were independent predictors of sICH (odds ratio, 1.032; 95% confidence interval, 1.014–1.049; P<0.001 and odds ratio, 1.033; 95% confidence interval, 1.006–1.061; P=0.017; Figure 4).

Discussion

The main finding of our study is that recanalization status influences the association between BP values in the first 24 hours after ischemic stroke and functional outcome at 3 months. In the nonrecanalyzed group, the highest and the lowest BP values are related to a worst clinical outcome, with a J-shaped association. Patients with early recanalization show a linear relationship with functional outcome. These findings have significant potential effect in acute stroke care, promoting the need to assess arterial permeability and to adjust hemodynamic status accordingly.

The clinical characteristics of our study sample are similar to other published acute stroke cohorts. More than 3 quarters of the patients were diagnosed with hypertension, and about half of the population showed dyslipidemia or atrial fibrillation, which are all well-known risk factors for cerebrovascular diseases. Higher SBP was associated with older age,

Figure 3. Relationship between blood pressure (BP) in the first 24 hours post ischemic stroke and functional outcome at 3 months (through modified Rankin Scale [mRS]). A and B, Nonrecanalyzed patients. C and D, Recanalyzed patients. Error bars represent the 95% confidence interval for mean.
hypertension, diabetes mellitus, higher baseline National Institute of Health Stroke Scale score, and the absence of endovascular treatment. All these associations were expected and in line with previous reports of BP in acute stroke, particularly considering the acute hypertensive response in patients with severe strokes and sustained arterial occlusions. Atrial fibrillation, older age, higher baseline National Institute of Health Stroke Scale, and women were associated with decreased odds of recanalization. Cardiac emboli have been previously linked to lower recanalization rates, probably because of the association with more severe strokes, larger thrombi, and older age, making them more resistant to recanalization. Several studies have shown that women have worse outcomes in ischemic stroke, with a growing body of evidence relating these data to an enhanced resistance to IVrtPA in women.

The relative frequencies of recanalyzed and nonrecanalized patients and sICH after IVrtPA are similar to other study reports. The relatively low frequency of recanalization in endovascular therapies is likely related to the study period, where many patients were treated with intra-arterial fibrinolysis.

In the setting of acute ischemic stroke, over two thirds of the patients show an acute elevation of BP. This acute hypertensive response has many possible causes: pain, stress, and dehydration related to the pathological situation, ischemia in strategic brain locations, elevated serum catecholamine levels arising from ischemic areas, and impaired baroreceptor sensitivity. BP values tend to return to prestroke levels within 10 days.

Early recanalization has been described as one of the most important predictors of good clinical outcome. Previous studies suggested that in large-artery occlusions, local hemodynamics is altered in result of vasoparalysis caused by ischemic tissue lactic acidosis, inhibiting normal autoregulatory function. In fact, cerebral autoregulation has been shown to be transiently impaired in the first 5 to 10 days after an unsuccessful IVrtPA treatment. This mechanism is especially relevant when there is a sustained occlusion, making collateral circulation even more important and dependent on systemic BP. During this autoregulatory failure, the brain tissue becomes particularly vulnerable to BP changes through its direct effects on cerebral perfusion. These facts support our finding of deleterious effect of low BP in the nonrecanalized patients. The improved functional outcome obtained with lower BP values in patients with early recanalization is likely related to decreased hemodynamic stress in this setting.

In our study, patients with higher BP values in the first 24 hours post ischemic stroke had a worse clinical outcome. This fact is probably related to the increased risk of cerebral edema and hemorrhagic transformation, which was documented in our study (Figure 4) and has been previously reported for high BP in the acute stage. This association was registered for all patients regardless of the presence of early recanalization, thus confirming the ubiquitous harmful effect of extremely high BP as can be seen in Figure 4.

The previous studies on BP in acute ischemic stroke did not take the hemodynamic effect of reperfusion therapies under consideration. A J- or U-shaped association between BP values and outcome was described, but no information on recanalization was reported. Our study was able to evaluate the independent association between BP in the first 24 hours post ischemic stroke and functional outcome, which is dependent on the recanalization state. This information is of particular importance in current stroke unit care, particularly with the widespread use of intravenous and intra-arterial reperfusion therapies. Furthermore, our findings suggest that in future trials, addressing BP management in acute stroke recanalization status should be taken under consideration.

Figure 4. Percentage of symptomatic intracerebral hemorrhage (sICH) for each systolic and diastolic blood pressure (BP) class. Black bars represent nonrecanalized patients. Gray bars represent recanalized patients at 6 hours post ischemic stroke. A, Systolic BP. B, Diastolic BP.
This study has several limitations, including its retrospective nature, raising the possibility of classification and measurement bias. Nonetheless, the analyzed variables are objective and registered prospectively, which reduces a possible effect in the results. As a single-centered study, the results could reflect a local feature. The demographic and baseline characteristics of the study population were similar to other large stroke cohorts, supporting the external validity of this study; however, larger multicenter studies would further support these findings. Another limitation was the heterogeneous method used to grade recanalization. Nonetheless, all the methods have been previously validated, with high inter-rater agreement, and the dichotomous classification used reduces variability between examinations. Functional outcome at 3 months was assessed by a clinician who previously knew the patient and was aware of the baseline treatment, which can be a potential source of bias. Furthermore, we did not evaluate data on early recurrence, which has also been shown to have a J- or U-shaped association with admission BP. However, considering the hard clinical end point analyzed at a subacute stage (mRS score at 3 months), these factors are unlikely to have significantly impaired the study conclusions.

In acute stroke, BP fluctuations are frequently observed, particularly during the night time. For our study, we chose to analyze the mean 24-hour BP to increase validity and applicability. It is also likely that any major night time fluctuation would be reflected in the mean 24-hour BP, thus reducing a possible confounding effect.

Conclusions
Systemic BP in the first 24 hours after ischemic stroke influences functional outcome in patients with acute stroke depending on the recanalization state. In the nonrecanlayzed group, a J-shaped association is observed. However, in the recanalized group, the association is linear, and low BP is associated with the best outcome.

Acknowledgments
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Disclosures
J. Sargento-Freitas received a speaking fee from Bioportugal in Symposium on the subject “Blood pressure in acute stroke: from physiopathology to clinical impact.” The other authors report no conflicts.

References
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Supplemental Table I - Timing of recanalization assessment (minutes) for angiography and CT angiography. All transcranial color coded Doppler were performed at bedside within the first 6 hours.

<table>
<thead>
<tr>
<th>Method</th>
<th>Angiography</th>
<th>CT Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time +/- SD to recanalization assessment (min)</td>
<td>285.73 +-58.04</td>
<td>134.14 +-33.90</td>
</tr>
</tbody>
</table>