

# Blood Pressure Variability in Acute Ischemic Stroke: The Role of Early Recanalization

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## Keywords

Blood pressure fluctuations · Recanalization · Acute stroke

## Abstract

We performed a retrospective study with the aim of investigating the association between blood pressure (BP) variability in the first 24 h after ischemic stroke and functional outcome, regarding arterial recanalization status. A total of 674 patients diagnosed with acute stroke and treated with revascularization therapies were enrolled. Systolic and diastolic BP values of the first 24 h after stroke were collected and their variation quantified through standard deviation. Recanalization state was evaluated at 6 h and clinical outcome at 3 months was assessed by modified Rankin Scale. In multivariate analyses systolic BP variability in the first 24 h post-stroke showed an association with 3 months clinical outcome in the whole population and non-recanalized patients. In recanalized patients, BP variability did not show a significant association with functional outcome.

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## Introduction

Blood pressure (BP) is an independent predictor of functional outcome in acute ischemic stroke setting [1]. It has been consistently reported that higher systolic and diastolic BP values (SBP and DBP) are related to worst outcomes. Spontaneous variations in SBP and DBP in the acute phase after ischemic stroke are common, however their pathological background and clinical impact are still largely undetermined. Previous work suggested that BP variability in the acute phase might be linked to a worst prognosis, by enhancing symptomatic intracerebral hemorrhage, early neurological deterioration, and death rates after treatment with intravenous recombinant tissue plasminogen activator (IVrtPA) [2]. Recent work from our group demonstrated that early recanalization status influences directly the association of 24 h BP and clinical outcome [3]. Nevertheless, studies assessing the effect of acute cerebrovascular hemodynamic status on the clinical impact of spontaneous BP fluctuations are lacking.

**Table 1.** Baseline characteristics of the study, univariate linear regression for predictors of SBP and DBP fluctuations at 24 h

| Variable                              | Total population<br><i>n</i> = 674 patients | Univariate association<br>with SBP SD, B (95% CI) | <i>p</i> value | Univariate association<br>DBP SD, B (95% CI) | <i>p</i> value |
|---------------------------------------|---|---|----------------|--|----------------|
| Age, years, mean $\pm$ SD             | 73.28 $\pm$ 11.50                           | 0.083 (0.030 to 0.136)                            | 0.002          | 0.040 (0.004 to 0.076)                       | 0.029          |
| Gender, male, <i>n</i> (%)            | 363(53.90)                                  | −0.517 (−1.738 to 0.704)                          | 0.406          | −0.286 (−1.120 to 0.548)                     | 0.501          |
| Smoking, <i>n</i> (%)                 | 67 (9.90)                                   | 0.890 (−1.142 to 2.922)                           | 0.390          | 0.718 (−0.675 to 2.110)                      | 0.312          |
| Alcoholism, <i>n</i> (%)              | 45 (6.70)                                   | 0.115 (−1.059 to 1.289)                           | 0.975          | −0.051 (−0.806 to 0.724)                     | 0.876          |
| Hypertension, <i>n</i> (%)            | 541 (80.40)                                 | 1.818 (0.290 to 3.346)                            | 0.020          | 0.751 (−0.296 to 1.798)                      | 0.159          |
| Diabetes mellitus, <i>n</i> (%)       | 166 (24.60)                                 | 1.510 (0.099 to 2.921)                            | 0.006          | 0.867 (−0.113 to 1.847)                      | 0.083          |
| Dyslipidemia, <i>n</i> (%)            | 353 (52.70)                                 | −0.614 (−1.837 to 0.609)                          | 0.324          | −0.465 (−1.301 to 0.370)                     | 0.275          |
| Atrial fibrillation, <i>n</i> (%)     | 329 (48.90)                                 | 0.137 (−1.081 to 1.355)                           | 0.826          | 1.724 (0.902 to 2.546)                       | <0.001         |
| Heart failure, <i>n</i> (%)           | 90 (13.00)                                  | 0.006 (−0.002 to 0.013)                           | 0.406          | 0.003 (−0.002 to 0.007)                      | 0.296          |
| Coronary artery disease, <i>n</i> (%) | 62 (9.40)                                   | 1.763 (−0.343 to 3.868)                           | 0.101          | 0.080 (−1.362 to 1.522)                      | 0.913          |
| Previous mRS, mean $\pm$ SD           | 0.31 $\pm$ 0.60                             | 0.972 (−0.036 to 1.980)                           | 0.059          | 0.351 (−0.339 to 1.041)                      | 0.318          |
| NIHSS at admission, mean SD           | 15.29 $\pm$ 7.01                            | −0.006 (−0.093 to 0.081)                          | 0.893          | 0.011 (−0.049 to 0.070)                      | 0.723          |
| Fibrinolysis (i.v.), <i>n</i> (%)     | 663 (98.40)                                 | 4.399 (−0.394 to 9.193)                           | 0.720          | 0.793 (−2.490 to 4.076)                      | 0.635          |
| Endovascular treatment, <i>n</i> (%)  | 52 (7.70)                                   | −1.957 (−4.234 to 0.320)                          | 0.092          | −0.069 (−1.628 to 1.490)                     | 0.931          |
| Time to treatment, min, mean $\pm$ SD | 150.25 $\pm$ 55.27                          | 0.006 (−0.005 to 0.017)                           | 0.287          | −0.007 (−0.031 to 0.018)                     | 0.605          |

mRS, modified Rankin Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; i.v., intravenous.

The main objective of this study is to evaluate the clinical effect of acute BP variability after ischemic stroke in patients submitted to intravenous and/or intra-arterial recanalization treatments, according to recanalization status.

## Material and Methods

We included consecutive patients with acute ischemic stroke from July 2009 to June 2015, submitted to intravenous thrombolysis (IVrtPA) and/or intra-arterial therapies in our tertiary hospital. Vascular risk factors were collected from a standardized local clinical registry. All patients were admitted to the stroke unit and BP readings were performed by protocol every 2 h during daytime and every 3 h throughout nighttime. Baseline measurements were obtained previous to recanalization therapies. All BP measurements were performed by certified and trained nurses, in Phillips Agilent NBP equipment, model M1008B, validated annually (last validation in January 2017). Standard deviation (SD) of the first 24 h systolic BP (SBP SD) and diastolic BP (DBP SD) values were calculated, in order to assess BP variation in acute phase.

Neurological status at admission was evaluated by using National Institute of Health Stroke Scale (NIHSS). Clinical data from follow-up appointment (modified Rankin Scale [mRS]) or information obtained by telephone contact were used to estimate 3-month clinical outcome. Arterial recanalization was assessed by angiographic pattern at the end of intra-arterial treatment, cerebral CT angiography, or by transcranial color-coded Doppler performed at 6 h 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 [4] classification using TCCD, or visualization of contrast perfusion in all symptomatic vessels by CT angiography.

Our institution's protocol regarding BP values in acute phase post-ischemic stroke follows ASA/AHA guidelines, and BP values are kept <185 mm Hg SBP and <110 mm Hg DBP before intravenous and/or intra-arterial therapies and <180/105 mm Hg for the first 24 h after treatment [5].

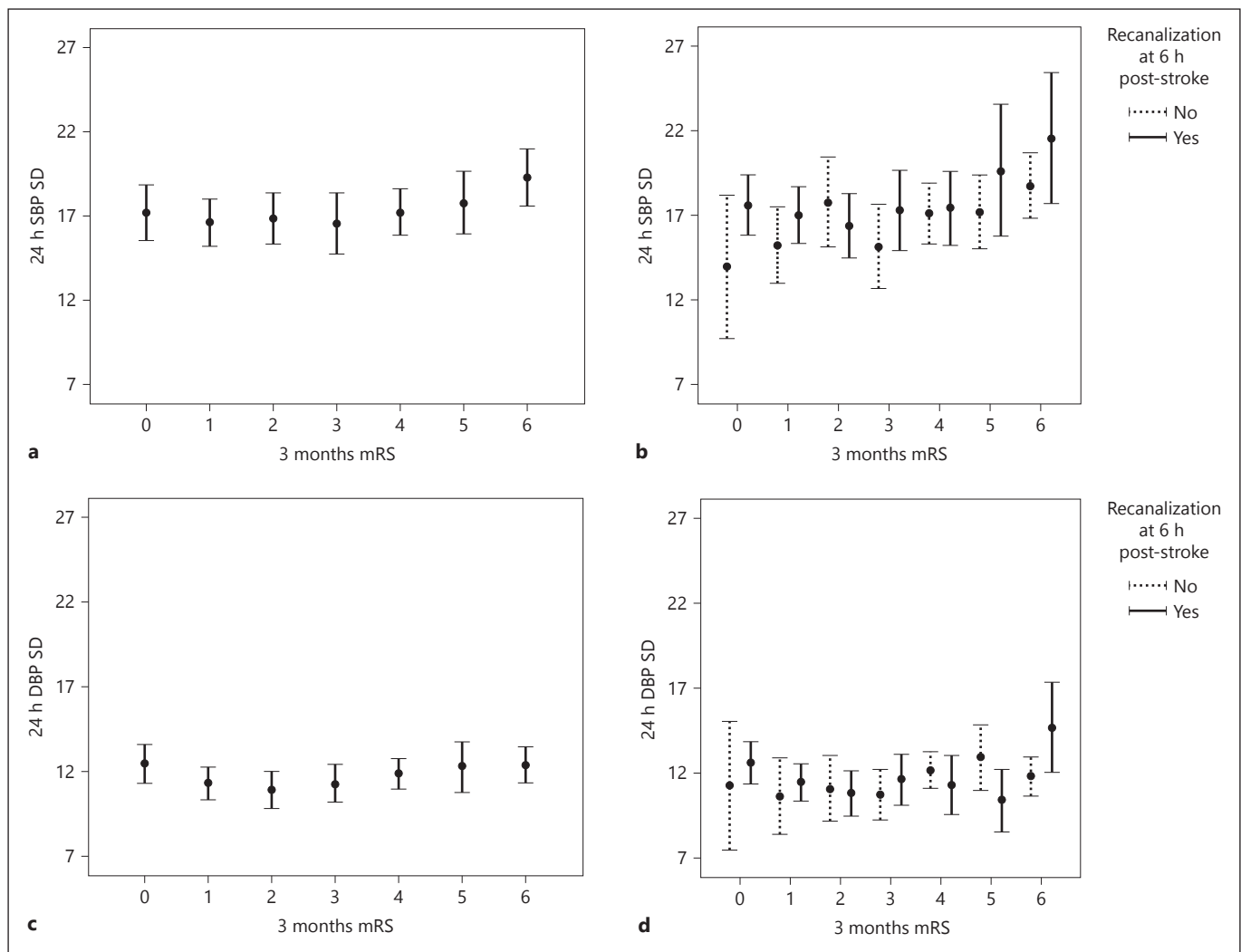
Symptomatic intracerebral hemorrhage (sICH) defined according to NINDS trial criteria was any intracerebral hemorrhage with neurological deterioration (increase of  $\geq 1$  in the NIHSS score) from baseline or death within 36 h [6].

Considering the observational and retrospective design of the study, a specific signed informed consent was not obtained. All patients received oral and written information regarding collection of observational data for clinical studies and were free to withdraw consent. The institutional Ethics Committee of our hospital approved the study.

Univariate associations were performed with 24 h SBP SD, DBP SD, 3 months mRS, and sICH, using a linear regression. Ordinal multivariate regression models identified the relationship between BP SD and functional outcome. The variables included in the multivariate model were SBP and DBP SD, and variables with univariate association with SBP SD and DBP SD (Table 1) and sICH and mRS at 3 months (Table 2).

The relationship between of SBP and DBP fluctuations in the first 24 h post-ischemic stroke and sICH was determined using a binary logistic regression adjusting for recanalization status and variables with univariate association with SBP SD and DBP SD of the first 24 h.

Statistical significance was set for  $p < 0.05$ .



**Fig. 1.** Error bar representing the relationship between blood pressure fluctuations in the first 24 h post-ischemic stroke and functional outcome at 3 months. (a, c) Total population; (b, d) recanalized and non-recanalized patients. mRS, modified Rankin Scale; BP, Blood pressure; SD, standard deviation; error bars represent the 95% confidence interval for mean.

## Results

A total of 748 patients were submitted to acute recanalization treatment for ischemic stroke, during the study period, and 674 were enrolled in this study. From the 74 excluded patients, 55 had a previous mRS ranking higher than 2, and the remaining patients were excluded due to lacking information regarding recanalization status or clinical outcome. Population characteristics are described in Table 1. According to the Oxfordshire Community Stroke Project Classification [7], 442 patients were catalogued as total anterior circulation infarct (TACI), 162 as partial anterior circulation infarct (PACI), 53 as posterior circulation infarct, and 17 as lacunar infarct. Of those, 616

patients had an anterior circulation (carotid) ischemic stroke and 58 were diagnosed with vertebro-basilar circulation ischemic stroke. A total of 663 patients underwent IVrtPA, 52 were submitted to endovascular procedures (11 of which isolated), and recanalization was accomplished in 355 patients (52.70%). Recanalization was assessed by TCCD in 615 patients (91.20%), angiography in 52 (7.70%), and CT angiography in 7 (1.10%). A total of 98 patients (14.50%) received antihypertensive treatment (labetalol) within the first 24 h.

In our population, sICH was observed in 42 patients (6.20%). SBP and DBP variation in the first 24 h was not associated with sICH. (OR 1.023; 95% CI 0.987–1.061;  $p = 0.215$  and OR, 1.005; 95% CI 0.974–1.037;  $p = 0.765$ ).

**Table 2.** Univariate linear regression for predictors of sICH and 3-month mRS

| Variable                | Univariate association with sICH, B (95% CI) | <i>p</i> value | Univariate association with 3 months mRS, B (95% CI) | <i>p</i> value |
|-------------------------|--|----------------|--|----------------|
| Age, years              | 0.001 (−0.001 to 0.002)                      | 0.311          | 0.050 (0.037 to 0.063)                               | <0.001         |
| Gender, male            | 0.026 (−0.011 to 0.063)                      | 0.162          | −0.503 (−0.811 to −0.196)                            | 0.001          |
| Smoking                 | −0.036 (−0.098 to 0.025)                     | 0.244          | −1.194 (−1.703 to −0.684)                            | <0.001         |
| Alcoholism              | −0.010 (−0.045 to 0.026)                     | 0.596          | −0.089 (−0.388 to 0.210)                             | 0.558          |
| Hypertension            | 0.021 (−0.025 to 0.067)                      | 0.372          | 0.559 (0.171 to 0.946)                               | 0.005          |
| Diabetes mellitus       | 0.010 (−0.034 to 0.053)                      | 0.665          | −0.026 (−0.391 to 0.339)                             | 0.890          |
| Dyslipidemia            | −0.049 (−0.085 to −0.012)                    | 0.009          | −0.335 (−0.645 to −0.026)                            | 0.034          |
| Atrial fibrillation     | 0.027 (−0.010 to 0.063)                      | 0.152          | 0.762 (0.458 to 1.066)                               | <0.001         |
| Heart failure           | 0.002 (−0.064 to 0.034)                      | 0.204          | 0.001 (−0.001 to 0.003)                              | 0.322          |
| Coronary artery disease | 0.037 (−0.027 to 0.101)                      | 0.260          | 0.306 (−0.228 to 0.840)                              | 0.261          |
| Previous mRS            | −0.009 (−0.039 to 0.022)                     | 0.582          | 0.831 (0.582 to 1.080)                               | <0.001         |
| NIHSS at admission      | 0.002 (0.000 to 0.005)                       | 0.080          | 0.157 (0.138 to 0.175)                               | <0.001         |
| Fibrinolysis (i.v.)     | 0.063 (−0.081 to 0.208)                      | 0.389          | −0.352 (−1.572 to 0.868)                             | 0.571          |
| Endovascular treatment  | 0.058 (−0.011 to 0.126)                      | 0.100          | 0.758 (0.181 to 1.334)                               | 0.098          |
| Time to treatment       | 0.001 (0.000 to 0.002)                       | 0.062          | 0.009 (0.001 to 0.017)                               | 0.145          |

mRS, modified Rankin Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; i.v., intravenous; sICH, symptomatic intracerebral hemorrhage.

**Table 3.** Multivariate association analyzing the relationship between 24 h post-ischemic stroke blood pressure fluctuations and 3-month mRS in total population, non-recanalized, and recanalized patients

| Variable                           | OR (95% CI)         | <i>p</i> value |
|------------------------------------|---------------------|----------------|
| SBP SD 24 h total population       | 1.023 (1.005–1.040) | 0.010          |
| DBP SD 24 h total population       | 1.008 (0.983–1.033) | 0.533          |
| SBP SD 24 h non-recanalized at 6 h | 1.027 (1.001–1.053) | 0.041          |
| DBP SD 24 h non-recanalized at 6 h | 1.012 (0.779–1.049) | 0.528          |
| SBP SD 24 h recanalized at 6 h     | 1.021 (0.970–1.046) | 0.089          |
| DBP SD 24 h recanalized at 6 h     | 0.904 (0.631–1.027) | 0.600          |

mRS, modified Rankin Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure.

In multivariate analyses, SBP SD in the first 24 h post-stroke was associated with 3 months mRS in total population and in the non-recanalized patients. In the recanalized group, there was no statistically significant association. DBP SD in the first 24 h was not associated with 3 months mRS (Fig. 1; Table 3). A sub-analysis including solely TACI and PACI patients revealed similar results.

## Discussion

The main finding of our study is that recanalization status influences the association between SBP and DBP spontaneous fluctuations in the first 24 h post-ischemic stroke and functional outcome at 3 months. In the non-

recanalized group, the highest SBP SD values were associated with worst clinical outcomes at 3 months. When early recanalization was accomplished, neither SBP SD nor DBP SD values influenced 3 months functional outcome.

BP variability has been identified as an independent risk factor for ischemic and hemorrhagic stroke. However, data on the impact of BP fluctuations in acute ischemic stroke are scarce and conflicting [1, 8], notwithstanding their high frequency in acute phase. Although the pathophysiologic mechanism is still unsettled, changes in the neuroendocrine system (hypothalamic-pituitary-adrenocortical axis and sympathetic nervous system) and malfunction of cardiac baroreceptor reflex have been proposed to be associated with BP changes in acute ischemic stroke [9]. Moreover, known circadian BP changes could have an impact

on clinical outcome. However, the profile of nocturnal BP dipping in acute ischemic stroke did not seem to influence functional prognosis. Nonetheless, reverse dipping – a rise in mean nocturnal SBP as compared to mean diurnal SBP – was associated to more frequent hemorrhagic transformations, probably related to reperfusion injury [10].

Early recanalization has been acknowledged as one of the most important predictors of good clinical outcome [11], influencing the association between BP values in the first 24 h and functional outcome [3]. In our study, SBP fluctuations had a deleterious effect only in the non-recanalized patients, independently from the development of sICH, suggesting an association with the increased hemodynamic stress due to BP variability in patients without early recanalization. Thus, in the non-recanalized patients, penumbra area is rendered with poor autoregulation, remaining directly dependent on collateral circulation. Moreover, when the protective autoregulation mechanisms are malfunctioning, BP changes may result in hyper or hypoperfusion of the ischemic tissue. On the other hand, if early recanalization is accomplished, brain tissue autoregulation is reassured, and BP fluctuations deleterious effects are prevented.

Although spontaneous fluctuations of SBP were associated with functional outcome, DBP SD did not show any association. DBP is related to the relaxing diastolic phase, while SBP is associated to ventricular ejection phase [12], rendering perfusion intensity, which may translate into reperfusion injury. That probably explains why only SBP SD was associated with a poorer prognosis in non-recanalized patients, and DBP SD did not have an association with clinical prognosis.

This novel information is of particular importance in current stroke unit care, especially with the widespread use of intravenous and intra-arterial reperfusion therapies and easy access to regular hemodynamic assessments. Furthermore, our findings reinforce that future trials addressing BP management in acute stroke should take recanalization status under consideration.

This study has some limitations. Though it is retrospective, the studied variables are objective and registered prospectively, reducing a possible influence. Moreover, although it is a single-centered study, the demographic and baseline characteristics of the study population were similar to other large stroke cohorts. Additionally, our study design does not allow identification of the relative contribution of spontaneous vs. therapeutic BP fluctuations, as 14.50% of the included patients received IV BP lowering treatments. Despite recanalization state being graded by heterogeneous procedures, all methods have been previously validated and performed by experienced vascular neurologists and neuroradiologists.

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## Disclosure Statement

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