Nocturnal blood pressure dipping in acute ischemic stroke

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Objectives – We aim to assess the impact of early nocturnal blood pressure (BP) variation in the functional outcome of patients after an acute ischemic stroke. **Materials and methods** – We included consecutive stroke patients treated with intravenous thrombolysis (IVrtPA) in a tertiary stroke center. BP measurements were performed at regular intervals throughout day and night during the first 48 h after stroke onset, and subjects were divided into four dipping categories (extreme dippers, dippers, non-dippers, and reverse dippers). Recanalization was assessed by transcranial color-coded Doppler and/or angiographic CT. Hemorrhagic transformation was evaluated at 24 h follow-up CT scan. Functional outcome was evaluated at 3 months after stroke using the modified Rankin Scale.

Results – A total of 304 patients were included, mean age 72.80 ± 11.10 years. After 24 h of systolic BP monitoring, 30.59% were classified as reverse dippers, 39.14% as non-dippers, 19.10% as dippers, and 11.18% as extreme dippers. Multivariate analysis did not show an independent association of any dipping class with 3-month functional outcome. Hemorrhagic transformation was not uniform between dipping classes: 25.81% for reverse dippers, 14.29% for non-dippers, 15.52% for dippers, and 5.88% for extreme dippers, $P = 0.033$. **Conclusions** – Nocturnal BP dipping pattern is not associated with functional outcome at 3 months in acute stroke patients treated with IVrtPA. Hemorrhagic transformation was more frequent in reverse dippers.

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Introduction

Recanalization of the occluded arterial territory remains the mainstay of acute ischemic stroke treatment (1, 2). Nevertheless, medical care in the first hours after acute stroke can significantly influence clinical outcome. Specifically, optimal blood pressure (BP) management in this setting is still a matter of debate (3). This is emphasized by the transient ipsilateral disruption of cerebral autoregulation in the first days after stroke, making perfusion of the ischemic tissue directly dependent on systemic BP (4, 5). Moreover, BP follows circadian changes including a nocturnal dipping (6). Despite the recognized beneficial effect of nocturnal dipping in physiological circumstances, in the context of acute stroke, with autoregulation impairment,

the clinical consequences of these fluctuations are still undetermined.

The main objective of this study was to investigate the clinical impact of different dipping profiles in the context of acute ischemic stroke.

Materials and methods

Study population

We included consecutive patients with acute ischemic stroke, treated with IV thrombolysis (IVrtPA) and admitted at the Neurology Department of the Coimbra University and Hospital Centre from July 2009 to May 2013. The exclusion criteria were as follows: patients that underwent intra-arterial treatments (in addition to IVrtPA); had insufficient

BP data (i.e., incomplete post-stroke first 24 h BP readings due to patient death or early hospital transfer); an unfavorable prior functional status, defined by a previous modified Rankin Scale (mRS) (7) score >2 ; and administration of continuous intravenous BP drug treatment, including labetalol and amines. The algorithm for study inclusion is presented in Fig. 1.

Vascular risk factors were collected from a prospectively defined local clinical registry. The study was approved by the institutional ethics committee of the Coimbra University and Hospital Centre. Signed informed consent was obtained from all patients or their legal representatives.

Blood pressure measurements

In our institution, all patients treated with IVrtPA 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 h during daytime and every 3 h during nighttime. Diurnal measurements were obtained between 8 am and 11 pm and nocturnal measurements between 11 pm and 8 am.

The mean diurnal and nocturnal systolic BP (SBP) and diastolic BP (DBP) during the first 24 h post-stroke were calculated. To determine the nocturnal BP percent fall, we applied the following formula: $100 \times [1 - (\text{mean nocturnal SBP} / \text{mean diurnal SBP})]$ (8). Finally, patients were categorized as reverse dippers if dipping $<0\%$ (that is, a rise in mean nocturnal SBP as compared to mean diurnal SBP), non-dippers if

fall ≥ 0 and $<10\%$, dippers if ≥ 10 and $<20\%$, and extreme dippers if decrease $\geq 20\%$.

Additional classifications of dipping classes were performed using the same formula, but considering the diastolic instead of systolic BP and for the BP measurements during the second day of admission (at 48 h).

Neurological assessment, hemorrhagic transformation, and artery recanalization

To assess functional status at admission, we used the National Institute of Health Stroke Scale (NIHSS). For the 3-month functional outcome, we used the mRS (7). This information was obtained from the follow-up appointment registry or, when missing, by telephone contact with the patient or relative (9). The 3-month mRS data were then dichotomized into favorable (for patients functionally independent at 3 months; $\text{mRS} \leq 2$) or unfavorable outcome (for dependency or death; $\text{mRS} > 2$). Time to treatment was defined as minutes from stroke onset to beginning of IVrtPA and hour of stroke as the time at symptomatic installation/last seen well.

Arterial recanalization was assessed by transcranial color-coded Doppler (TCCD) or computerized tomography (CT) angiography of intracranial arteries performed 2 h after IVrtPA perfusion. We considered recanalization as grades 4 or 5 from the thrombolysis in brain ischemia (TIBI) classification using TCCD (10) or visualization of contrast perfusion in all symptomatic vessels by CT angiography 2 h after IVrtPA.

Hemorrhagic transformation was graded in the 24 h follow-up CT scan according to the European Cooperative Acute Stroke Study (ECASS) scoring system (11). Only parenchymal hemorrhages (PH), grades 1 or 2, were considered as hemorrhagic transformation. 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 (12).

Statistical analysis

Primary outcome was functional outcome at 3 months. We performed univariate analyses comparing the four dipping classes with baseline characteristics, hemorrhagic transformation and SICH using chi-square test or *t*-test where appropriate. Dippers were used as the reference category and were separately compared with extreme dippers, non-dippers, and reverse dippers. Independent

Figure 1. Algorithm for patient inclusion and dipping classes according to circadian systolic blood pressure variations are represented. All exclusion criteria and the respective number of patients are listed as well as the absolute and relative frequencies of each dipping class. AIS: acute ischemic stroke; BP: blood pressure; IA: intra-arterial; IVrtPA: intravenous thrombolysis; mRS: modified Rankin scale.

predictors of 3-month functional outcome were determined using a binary logistic regression. The variables included in the multivariate model were BP dipping category (defined as a categorical variable, with dippers as the reference category) and established independent functional stroke outcome predictors, namely age, NIHSS at admission, and arterial recanalization (Regression Model A). No other risk factor was included considering the results of the univariate analysis (Table S1). We performed additional comparisons adding hour of stroke onset, SBP at admission, and SICH to the already-mentioned variables. Subsequently, we reran Regression Model A restricting the population to those without effective arterial recanalization post-thrombolysis. Finally, we reran the regression models but using different BP dipping definitions considering systolic BP variability in the 48 h post-stroke and using diastolic BP other than systolic. We considered statistically significant two-sided *P*-values <0.05.

Results

During the study period, a total of 360 patients were treated with IVrtPA for acute ischemic stroke. For our analysis, we included 304 patients, mean age 72.80 ± 11.10 years (Table 1). The analysis of blood pressure variation in the first 24 h identified 93 (30.59%) patients as reverse dippers, 119 (39.14%) as non-dippers, 58 (19.10%) as dippers, and 34 (11.18%) as extreme dippers (Fig. 1). Considering the diastolic BP definition for dipping profile, 93 (30.6%) were reverse dippers, 101 (33.2%) non-dippers, 68 (22.4%) dippers, and 42 (13.8%) extreme dippers. The circadian systolic blood pressure analysis at 48 h was available for 276 (90.8%) patients: 91 (33.0%) reverse dippers, 120 (43.5%) non-dippers, 57 (20.7%) dippers, and 8 (2.9%) extreme dippers.

Univariate analysis of first 24 h systolic dipping classes for all baseline variables did not show any statistically significant changes (Table S1).

In multivariate analysis, after adjusting for age, baseline stroke severity, and recanalization, no 24 h dipping class was associated with the 3-month functional outcome (Table 2). Additional regression models with the inclusion of hour of stroke onset, admission systolic blood pressure, and SICH showed no differences between dipping classes (Table 2). These results were similar when analyzing only non-recanalized patients. The use of different dipping definitions, namely dipping of diastolic pressure in the first 24 h (Table 3) and dipping of systolic blood pressure at 48 h (Table S2), did not significantly change the results.

Table 1 Baseline characteristics of the study population

Variable	Total population (<i>n</i> = 304)
Age	72.80 $\pm$ 11.10
Male gender	162 (53.29%)
Alcoholism	29 (9.54%)
Smoking	32 (10.53%)
Hypertension	237 (77.96%)
Diabetes Mellitus	77 (25.33%)
Dyslipidemia	125 (41.12%)
Coronary artery disease	>31 (10.20%)
Peripheral artery disease	6 (1.97%)
Atrial fibrillation	143 (47.04%)
Heart failure	26 (8.55%)
Previous BP medication	221 (72.7%)
Previous mRS	0.31 (0.60)
NIHSS at admission	15.11 $\pm$ 6.96
Time to treatment	157.63 $\pm$ 53.59
Recanalization	170 (55.92%)

Categorical variables are presented as frequency (percentage) and continuous variables as mean $\pm$ standard deviation. Age is expressed in years and time to treatment in minutes. mRS, modified Rankin Scale, NIHSS, National Institute of Health Stroke Scale; BP, blood pressure.

The rate of SICH was not statistically different between dipping classes (Fig. 2C.). Hemorrhagic transformation was not uniform between dipping classes: 25.81% for reverse dippers, 14.29% for non-dippers, 15.52% for dippers, and 5.88% for extreme dippers, *P* = 0.033 (Fig. 2D.).

Discussion

The main findings of our study are that blood pressure dipping profile in the setting of acute stroke care does not seem to influence functional prognosis, although reverse dipping is associated with more frequent hemorrhagic transformation.

The relative frequencies of dipping classes in our study were different from reports in non-stroke and chronic stroke populations, specifically with a decrease in dippers and increase in all other classes, more pronounced in reverse and extreme dippers. These data confirm an impairment of circadian BP control in acute ischemic stroke (6, 8, 13–15). Notably, baseline characteristic was similar across the different dipping profiles (Table S1).

Up to three quarters of patients with acute ischemic stroke have elevated BP at presentation, of which only half have a previous history of hypertension. Over the course of the first week, most will spontaneously return to prestroke levels (16–18). Many factors may concur to this acute rise in BP; nonetheless, it is recognized, at least to some extent, as an adaptive mechanism to maintain cerebral perfusion. In fact, persistent arterial occlusion has been associated with longer

Table 2 Dipping profile of systolic blood pressure in the first 24 h and 3-month functional outcome

Regression model	Dippers	Reverse dippers		Non-dippers		Extreme dippers	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Univariate	Ref.	0.96 (0.50–1.86)	0.906	1.34 (0.71–2.54)	0.372	0.53 (0.23–1.25)	0.147
Multivariate A	Ref.	1.05 (0.47–2.34)	0.914	1.82 (0.82–4.01)	0.140	0.60 (0.21–1.69)	0.333
Multivariate A + Hour of stroke	Ref.	1.01 (0.45–2.29)	0.973	1.81 (0.82–4.01)	0.141	0.60 (0.21–1.70)	0.341
Multivariate A + admission SBP	Ref.	1.21 (0.53–2.79)	0.643	1.98 (0.88–4.46)	0.099	0.54 (0.19–1.57)	0.260
Multivariate A + SICH	Ref.	0.95 (0.41–2.18)	0.899	1.78 (0.79–4.02)	0.164	0.60 (0.21–1.74)	0.345
Multivariate A for non-reanalyzed	Ref.	1.29 (0.37–4.44)	0.686	1.69 (0.49–5.77)	0.404	0.47 (0.09–2.37)	0.358

Multivariate A includes adjustment for age, baseline NIHSS, and recanalization. SBP, systolic blood pressure, SICH, symptomatic intracerebral hemorrhage.

Table 3 Dipping profile of diastolic blood pressure in the first 24 h and 3-month functional outcome

Regression model	Dippers	Reverse dippers		Non-dippers		Extreme dippers	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Univariate	Ref.	1.23 (0.66–2.31)	0.518	1.41 (0.76–2.63)	0.276	1.08 (0.50–2.33)	0.852
Multivariate A	Ref.	1.43 (0.67–3.09)	0.358	1.32 (0.62–2.80)	0.475	0.86 (0.32–2.28)	0.862
Multivariate A + Hour of stroke	Ref.	1.41 (0.65–3.06)	0.379	1.32 (0.62–2.81)	0.470	0.87 (0.33–2.30)	0.778
Multivariate A + admission DBP	Ref.	1.37 (0.63–2.98)	0.429	1.25 (0.58–2.69)	0.571	0.86 (0.32–2.28)	0.759
Multivariate A + SICH	Ref.	1.23 (0.55–2.71)	0.616	1.37 (0.63–2.95)	0.426	0.81 (0.30–2.20)	0.677
Multivariate A for non-reanalyzed	Ref.	1.08 (0.28–4.23)	0.909	0.72 (0.21–2.46)	0.600	0.88 (0.29–3.94)	0.864

Multivariate A includes adjustment for age, baseline NIHSS, and recanalization. DBP, diastolic blood pressure, SICH, symptomatic intracerebral hemorrhage.

periods of elevated SBP in the subacute stage (19). Moreover, cerebral autoregulation has been demonstrated to be transiently impaired in the first 5 days after an unsuccessful IVrtPA treatment (5). This is especially the case of patients with persistent occlusions, mostly dependent on adequate collateral circulation and particularly vulnerable to systemic BP fluctuations. Considering a possible simple early dampening effect of BP, we adjusted our model for baseline BP with consistent findings. In the absence of autoregulation, extreme dippers could be at a particular risk of supplementary ischemia; nevertheless, these subjects do not have different functional prognosis. It is noteworthy that in Fig. 2B, the relationship of recanalization with good outcome is especially true in extreme dippers, and in Table S1, this dipping class shows a trend for association with higher recanalization rates, suggesting again that a significant decrease in BP will mostly be due to a physiological response to recanalization. Altogether, these data seem to suggest that the circadian BP variation may predominantly be an adaptive response to the vascular status of a certain patient. It is noticeable that our findings were replicated considering different definitions of BP dipping and at distinct timepoints. Another possible interpretation would be that the clinical impact of autoregulation impairment may not be universal. Nevertheless, it should be noted that autoregulation was not assessed in this study.

Recanalization has been recognized as one of the strongest predictors of good clinical outcome (20). However, as shown in Fig. 2B, this does not seem to be absolutely true for reverse dippers that show a wide variability of functional outcome. This appears to be explained by the higher rates of hemorrhagic transformation in reverse dippers (Fig. 2D). This result is substantiated by previous studies indicating that blunted nocturnal BP dip is more frequent in patients with hemorrhagic stroke (21). Additionally, reperfusion is a well-established predictor of hemorrhagic transformation, blood–brain barrier dysfunction, and thus loss of autoregulatory mechanisms (22, 23). Put together, these data suggest that reverse dipping in the acute stage might be related to reperfusion injury in reanalyzed patients. Whether nocturnal rise of BP acts as a promoter or simply a marker of this injury is not possible to conclude; nonetheless, it is an information with potential therapeutical implications.

The few previous studies on circadian BP in the acute stroke setting have been mainly descriptive or comparing stroke etiologies (6, 15). Two small studies on BP dipping in acute stroke showed contradictory univariate comparisons of functional outcome, unaccounting for clinical prognostic indicators, acute stroke treatment, or arterial recanalization (8, 14). Our study was able to evaluate the independent association of

Figure 2. (A) Boxplot representing the functional outcome at 3 months between 24 h systolic dipping classes. (B) The same data are presented and clustered for reanalyzed (light gray) and non-reanalyzed patients (dark gray). (C) and (D) show bar graphs with percentage of SICH (C) and hemorrhagic transformation (D). Abbreviations: mRS: modified Rankin Scale; SICH: symptomatic intracerebral hemorrhage; ns: not significant; * $p < 0.05$.

dipping profile with clinical outcome in a large cohort of acute stroke patients, assessing possible pathophysiological mechanisms.

A few limitations to our study require consideration in its analysis. First, it was a single-centered study. However, the patients enrolled in our study were similar to other stroke cohorts supporting the external validity of the study. Moreover, the retrospective nature of the study design raises the possibility of classification and measurement bias. Nonetheless, considering the objective variables analyzed, this is unlikely to have significantly influenced the results. Also, there is no consensus on the ideal BP dipping definition, and therefore, we chose the most widespread and user-friendly concepts, repeating our analysis for each definition with consistent results. Lastly, despite being a moderately large stroke population, some individual dipping

classes did not have many patients. Considering the small confidence intervals obtained, it is unlikely that an even greater number would render statistical significance, although a larger multicenter study would definitely increase confidence and applicability of these results.

In conclusion, early BP nocturnal dipping profile was not related to functional outcome in acute stroke patients submitted to IVrtPA. Nonetheless, nocturnal BP variation should be interpreted in light of the patient's vascular status, particularly reverse dipping which may be a sign of reperfusion injury with hemorrhagic transformation.

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Conflicts of interest/sources of funding

Nothing to declare.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Univariate comparison of baseline characteristics of study population between dipping classes.

Table S2. Dipping profile of systolic blood pressure at 48 h and 3 months functional outcome.

References

1. JAUCH EC, SAVER JL, ADAMS HP JR et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2013;**44**:870–947.
2. Anonymous. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;**25**:457–507.
3. BATH PM, KRISHNAN K. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev* 2014;**10**:CD000039.
4. REINHARD M, RUTSCH S, LAMBECK J et al. Dynamic cerebral autoregulation associates with infarct size and outcome after ischemic stroke. *Acta Neurol Scand* 2012;**125**:156–62.
5. REINHARD M, WIHLE C, ROTH M et al. Cerebral autoregulation dynamics in acute ischemic stroke after rtPA thrombolysis. *Cerebrovasc Dis* 2008;**26**:147–55.
6. JAIN S, NAMBOODRI KK, KUMARI S, PRABHAKAR S. Loss of circadian rhythm of blood pressure following acute stroke. *BMC Neurol* 2004;**4**:1.
7. VAN SWIETEN JC, KOUDSTAAL PJ, VISSER MC, SCHOUTEN HJ, VAN GIJN J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;**19**:604–7.
8. PANDIAN JD, WONG AA, LINCOLN DJ et al. Circadian blood pressure variation after acute stroke. *J Clin Neurosci* 2006;**13**:558–62.
9. JANSSEN PM, VISSER NA, DORHOUT MEES SM, KLIJN CJ, ALGRA A, RINKEL GJ. Comparison of telephone and face-to-face assessment of the modified Rankin Scale. *Cerebrovasc Dis* 2010;**29**:137–9.
10. DEMCHUK AM, BURGINS WS, CHRISTOU I et al. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke* 2001;**32**:89–93.
11. FIORELLI M, BASTIANELLO S, VON KUMMER R et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke* 1999;**30**:2280–4.
12. Anonymous. Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-PA stroke study group. *N Engl J Med* 1995;**333**:1581–7.
13. HAJJAR I, ZHAO P, ALSOP D et al. Association of blood pressure elevation and nocturnal dipping with brain atrophy, perfusion and functional measures in stroke and nonstroke individuals. *Am J Hypertens* 2010;**23**:17–23.
14. ALI K, LEONG KM, HOULDER S, GETOV S, LEE R, RAJKUMAR C. The relationship between dipping profile in blood pressure and neurologic deficit in early acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2011;**20**:10–5.
15. CASTILLA-GUERRA L, ESPINO-MONTORO A, FERNANDEZ-MORENO MC, LOPEZ-CHOZAS JM. Abnormal blood pressure circadian rhythm in acute ischaemic stroke: are lacunar strokes really different? *Int J Stroke* 2009;**4**:257–61.
16. BRITTON M, CARLSSON A, DE FAIRE U. Blood pressure course in patients with acute stroke and matched controls. *Stroke* 1986;**17**:861–4.
17. BACK C, THIESEN KL, SKOVGAARD K et al. RAAS and stress markers in acute ischemic stroke: preliminary findings. *Acta Neurol Scand* 2014;**131**:132–9.
18. STRBIAN D, ATULA S, MERETOJA A, KASTE M, TATLISUMAK T. Outcome of ischemic stroke patients with serious post-thrombolysis neurological deficits. *Acta Neurol Scand* 2013;**127**:221–6.
19. MATTLE HP, KAPPELER L, ARNOLD M et al. Blood pressure and vessel recanalization in the first hours after ischemic stroke. *Stroke* 2005;**36**:264–8.
20. MOLINA CA, SAVER JL. Extending reperfusion therapy for acute ischemic stroke: emerging pharmacological, mechanical, and imaging strategies. *Stroke* 2005;**36**:2311–20.
21. TSIVGOULIS G, VEMMOS KN, ZAKOPOULOS N et al. Association of blunted nocturnal blood pressure dip with intracerebral hemorrhage. *Blood Press Monit* 2005;**10**:189–95.
22. KHATRI R, MCKINNEY AM, SWENSON B, JANARDHAN V. Blood-brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke. *Neurology* 2012;**79**:S52–7.
23. WARACH S, LATOUR LL. Evidence of reperfusion injury, exacerbated by thrombolytic therapy, in human focal brain ischemia using a novel imaging marker of early blood-brain barrier disruption. *Stroke* 2004;**35**:2659–61.