Supine blood pressure normalised by daytime series values is independently associated with ischaemic wake-up stroke

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ABSTRACT

Purpose: Wake-up stroke constitutes up to 1/4 of all ischaemic strokes; however, its pathomechanisms remain largely unknown. Although low nocturnal blood flow may be the underlying cause, little is known about blood pressure (BP) characteristic of wake-up stroke patients. The aim of our study was to look for differences in BP variables between wake-up stroke and known-onset stroke patients and to seek BP indices which could distinguish wake-up stroke patients from other stroke patients.

Materials and Methods: In the study, we included ischaemic stroke patients in whom office BP measurement and Ambulatory BP monitoring (ABPM) were recorded at day 7, after acute hypertensive response. The daytime period was defined as the interval from 6 a.m. to 10 p.m. From ABPM, we obtained parameters of BP variability. Additionally, we calculated the BP percentage differences defined as (supine office BP-average daytime BP)/average daytime BP for systolic, diastolic, and mean blood pressure. We calculated analogous indices for night-time. The univariate and multivariate relationships between BP variables and wake-up stroke were analysed.

Results: Among the recruited 120 patients (aged 61.6 ± 12.3; 88 [73%] males; the baseline National Institutes of Health stroke scale score 4 [3–8]), 36 (30%) had wake-up stroke. In a univariate analysis, the systolic and mean daytime and night-time BP differences were significantly lower in patients with wake-up stroke ([−1.92 (−11.55 to 3.95) vs 4.12 (−2.48 to 11.31), \( p = 0.006 \) and −6.20 (−12.32 to 7.42) vs 2.00 (−6.86 to 11.65), \( p = 0.029 \) for daytime, respectively; 0.00 (−9.79 to 11.82) vs 9.84 (0.00 to 18.25), \( p = 0.003 \) and 0.51 (−8.49 to 12.08) vs 7.82 (−2.47 to 20.39), \( p = 0.026 \), for night-time, respectively). After adjustment for possible confounders, the systolic BP difference remained significantly associated with wake-up stroke (odds ratio = 0.96, 95% confidence interval = 0.92–1.00, \( p = 0.039 \)).

Conclusion: The subacute office-ambulatory BP difference including the dynamic (systolic BP), but not static BP component was independently associated with wake-up stroke.

Introduction

Patients with wake-up stroke are those who fall asleep healthy and wake up with stroke symptoms. Wake-up strokes account for 8–28% of all acute ischaemic strokes [1,2] and approximately 36% of morning-onset ischaemic strokes [2]. The relatively high number of wake-up strokes is caused by circadian morning predominance of stroke [3]. The underlying pathomechanism is not fully known, but several factors play an important role; they include a rise in blood pressure in the morning (‘morning surge’), increased platelet aggregation, and raised level of prothrombic factors, such as lipoprotein (a) or fibrinogen [3]. Recently, interest in wake-up stroke has grown due to the possibility of specific stroke treatment with thrombolysis [4] or mechanical thrombectomy [5,6] in such patients. Little is known about differences between wake-up strokes and known-onset ischaemic strokes. Several studies of wake-up strokes showed that patients with wake-up stroke were older [1], had higher National Institutes of Health Stroke Scale score [1], higher blood pressure [7], were more likely to be female [8], and were less likely to have atrial fibrillation [9], whereas others did not showed such differences [1,7–12]. The aim of this study was to compare certain blood pressure (BP) parameters between...
patients with wake-up stroke and patients with known-onset stroke as well as to try to find a BP index (especially comparing temporary BP with average BP over a longer period, i.e. a reactivity index) which could distinguish wake-up stroke subgroup from the remaining ischaemic stroke patients.

Methods

Patients

In our study, we enrolled adult patients hospitalised between November 2007 and June 2015 in the Department of Adult Neurology, Stroke Unit, Medical University of Gdańsk, Poland, within 24 h after ischaemic stroke onset. The diagnosis of ischaemic stroke was confirmed by a head computed tomography and/or magnetic resonance imaging. Patients with atrial fibrillation and pre-stroke disability (i.e. a modified Rankin scale score > 1 point) were not included in the study. The informed consent was obtained from all subjects. The study was conducted in accordance with the Declaration of Helsinki and approved by the Independent Bioethics Commission for Research of Medical University of Gdańsk.

Basic characteristics

In all subjects, we obtained basic clinical data, such as age, sex, stroke severity according to the National Institutes of Health Stroke Scale score at baseline and at day 7, weight, and height. The patients were divided into two groups: with wake-up stroke and known-onset stroke. Wake-up stroke was defined as stroke which symptoms were found by the patient or their family after waking up from sleep. The patients’ functional outcome was assessed at day 7 using the modified Rankin scale score and we distinguished three subgroups: patients able to look after their own affairs without assistance (i.e. no or slight disability, preserved ability to walking without assistance, a modified Rankin scale score of 0–2 points), patient requiring some external help but able to walk without assistance (a modified Rankin scale score of 3 points), and patients unable to walk and look after their own affairs without assistance (a modified Rankin scale score of 4–5 points).

Blood pressure measurements

In the subacute phase of ischaemic stroke (at day 7), we recorded office blood pressure and ambulatory blood pressure monitoring (ABPM). We choose day 7 to omit bias associated with acute hypertensive response. Office blood pressure was taken three times after at least a 10-minute rest in the supine position using the Omron 705 C oscillometric device. The two latter measurements were averaged and considered in further analyses. Office BP was taken during assessment of pulse wave velocity using applanation tonometry (not considered in the present study). ABPM was performed with the SpaceLabs 90207 device. The daytime period was defined as the interval between 6 a.m. and 10 p.m., while the nighttime, as the interval between 10 p.m. and 6 a.m. The following parameters were obtained: minimal, mean, and maximal systolic BP, diastolic BP, mean BP as well as heart rate during a 24-h period, during the day, and during the night; the standard deviation and coefficient of variation of 24-h, day, and night systolic BP, diastolic BP, mean BP, and heart rate.

Based on a nocturnal systolic BP fall, patients were divided into four dipping groups: extreme dippers (a nocturnal BP fall of >20%), dippers (a BP fall of >10% and <20%), non-dippers (a BP fall of ≥0% and <10%), and risers (a nocturnal increase in systolic BP).

In addition, for a more complex assessment of BP reactivity, we defined the following office-ambulatory

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\begin{align*}
\text{supine office systolic BP} - \text{ABPM average daytime systolic BP} \times 100\% \quad \text{(the daytime systolic BP difference)} \\
\text{supine office diastolic BP} - \text{ABPM average daytime diastolic BP} \times 100\% \quad \text{(the daytime diastolic BP difference)} \\
\text{supine office mean BP} - \text{ABPM average daytime mean BP} \times 100\% \quad \text{(the daytime mean BP difference)} \\
\text{supine office systolic BP} - \text{ABPM average night-time systolic BP} \times 100\% \quad \text{(the night – time systolic BP difference)} \\
\text{supine office diastolic BP} - \text{ABPM average night-time diastolic BP} \times 100\% \quad \text{(the night – time diastolic BP difference)} \\
\text{supine office mean BP} - \text{ABPM average night-time mean BP} \times 100\% \quad \text{(the night – time mean BP difference)}
\end{align*}
\]
blood pressure indices taking into account the temporary BP parameter in relation to the average value of the same BP parameter over the day and night:

**Statistical analysis**

Data were expressed as the mean ± standard deviation or median (interquartile range), as appropriate. The subgroups were compared using the Student’s t test, Mann-Whitney U test, Kruskal–Wallis analysis of variance, or Chi-squared test, as appropriate. The univariate and multivariate association between BP variables and wake-up stroke were calculated using logistic regression analysis and expressed as the odds ratio and 95% confidence interval. The p value <0.05 was considered as statistically significant. The statistical analysis was carried out with Dell Statistica software (Dell Inc.), version 13.

**Results**

**Baseline characteristics**

We enrolled 120 patients with acute ischaemic stroke, aged 61.6 ± 12.3 years, 88 (73%) of whom were males, with the baseline National Institutes of Health Stroke Scale score of 4 (3–8) points. Among participants, 36 patients (30%) had wake-up stroke. Baseline characteristics of the study population are given in Table 1. The study groups did not differ, except for the rate of treatment with intravenous recombinant tissue plasminogen activator and admission glucose.

ABPM parameters were not different in wake-up stroke and known-onset stroke; however, there was a trend towards higher daytime maximal heart rate in wake-up stroke. The standard deviation and coefficient of variation values were comparable in these two groups (Table 2 and Supplementary Table 1).

Office BP parameters did not differ significantly between wake-up stroke and known-onset stroke groups; however, systolic BP and mean BP tended to be lower in wake-up stroke (Table 2).

Among non-wake-up stroke patients, 1% were extreme dippers, 20% were dippers, 58% were non-dippers, and 21% were risers; among wake-up stroke patients, 0% were extreme dippers, 11% were dippers, 61% were non-dippers, and 28% were risers. Dipper status was not associated with wake-up stroke (p = 0.464).

In a univariate analysis, the daytime systolic and mean BP differences were significantly lower in patients with wake-up stroke compared to patients with known-onset stroke [−1.92 (−11.55 to 3.95) vs 4.12 (−2.48 to 11.31), p = 0.006 and −6.20 (−12.32 to 7.42) vs 2.00 (−6.86 to11.65), p = 0.029, respectively]; the office-ambulatory daytime diastolic BP difference did not differ between analysed groups. Regarding the night-time differences, also the systolic and mean BP differences were lower in patients with wake-up stroke [0.00 (−9.79 to 11.82) vs 9.84 (0.00 to 18.25), p = 0.003 and 0.51 (−8.49 to 12.08) vs 7.82 (−2.47 to 20.39), p = 0.026, respectively]; the night-time diastolic BP difference did not differ between the subgroups (Table 3).

In a multivariate logistic regression analysis, only the daytime systolic BP difference remained significantly associated with wake-up stroke after adjustment for possible confounders, such as age, sex, the baseline National Institutes of Health Stroke Scale.

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**Table 1.** Baseline characteristics of the study participants.

| Parameter                                      | Overall          | Wake-up stroke  | Known-onset stroke | p  |
|------------------------------------------------|------------------|-----------------|--------------------|----|
| Age, years                                     | 61 (56–69)       | 63 (56–69)      | 62 (56–70)         | 0.879 |
| Male sex, n (%)                                | 88 (73%)         | 28 (77%)        | 60 (71%)           | 0.471 |
| Admission National Institutes of Health Stroke Scale score | 4 (3–8)         | 4 (3–7)         | 5 (3–9)            | 0.993 |
| National Institutes of Health Stroke Scale score at day 7 | 2 (1–4)         | 2 (1–3)         | 2 (1–4)            | 0.231 |
| Use of recombinant tissue plasminogen activator, n (%) | 36 (30%)        | 2 (5%)          | 34 (41%)           | <0.001 |
| Previous stroke, n (%)                         | 14 (12%)         | 5 (14%)         | 9 (11%)            | 0.906 |
| Hypertension, n (%)                            | 76 (63%)         | 25 (69%)        | 51 (61%)           | 0.649 |
| Smoking status, n (%)                          | 43 (36%)         | 12 (33%)        | 31 (37%)           | 0.436 |
| Body mass index, kg/m²                         | 28 (24–30)       | 29 (24–30)      | 28 (24–30)         | 0.581 |
| Prehospital antihypertensives, n (%)           | 60 (50%)         | 18 (50%)        | 42 (50%)           | 0.602 |
| In-hospital antihypertensives, n (%)           | 79 (66%)         | 25 (69%)        | 54 (64%)           | 0.789 |
| Admission glucose, mg/dL                       | 116 (102–152)    | 108 (97–119)    | 121 (107–158)      | 0.001 |
| Pulse wave velocity, m/s                       | 9.6 (8.0–12.3)   | 9.3 (7.8–10.7)  | 9.9 (8.1–12.6)     | 0.105 |
| Augmentation index normalised for heart rate of 75 bpm, % | 26.2 ± 11.5     | 23.4 ± 10.9     | 27.3 ± 11.7        | 0.329 |
| Total cholesterol, mg/dL                       | 196.9 ± 45.1     | 196.9 ± 40.3    | 196.9 ± 47.3       | 0.996 |
| Triglycerides, mg/dL                           | 118.0 (83.0–176.0) | 121.0 (83.0–161.0) | 115.0 (82.5–184.5) | 0.796 |
| High-density lipoprotein, mg/dL                | 39.0 (34.0–47.0) | 37.0 (33.0–44.0) | 39.0 (34.0–48.0)   | 0.544 |
| Low-density lipoprotein, mg/dL                 | 130.0 ± 39.4     | 133.2 ± 36.5    | 128.3 ± 40.7       | 0.577 |
| Brain natriuretic peptide, pg/mL               | 64.0 (32.0–122.0) | 49.0 (43.0–104.0) | 67.0 (28.0–128.5)  | 0.598 |
| Modified Rankin scale score, points            | 2.0 (1.0–2.0)    | 2.0 (1.0–2.0)   | 2.0 (1.0–2.0)      | 0.344 |

Values are expressed as the mean ± standard deviation or median (interquartile range) unless otherwise indicated.
score, admission glucose, daytime maximal heart rate, the use of recombinant tissue plasminogen activator, and the use of antihypertensives during hospitalisation (Table 4). Similar results were found when considering the National Institutes of Health Stroke Scale score obtained at the time of BP measurements (Supplementary Table 2).

Other office-ambulatory BP indices lost their predictive value after adjustment for confounders.

A comparison of BP parameters between subgroups distinguished based on mobility in participants with known-onset and wake-up stroke is shown in Supplementary Table 3. In the wake-up stroke group, systolic, diastolic, and mean BP did not differ between subgroups; however, patients with a modified Rankin scale score of 3 points had higher mean heart rate in all periods (24-h, daytime, and night-time) and higher minimal night-time heart rate. In contrast, patients with a modified Rankin scale score of 3 points in known-onset stroke group had higher minimal 24-h systolic, diastolic, and mean BP, minimal night-time diastolic and mean BP as well as the lower 24-h heart rate standard deviation and coefficient of variation than patients with a modified Rankin scale score of 0–2 points.

A comparison of patients who received thrombolytic treatment and who did not receive such a treatment showed no difference in ABPM parameters in the wake-up stroke group; however, in patients with known-onset stroke, the use of recombinant tissue plasminogen activator was associated with lower 24-h systolic and diastolic BP as well as the lower 24-h heart rate standard deviation and coefficient of variation than patients with a modified Rankin scale score of 0–2 points.

**Discussion**

In our study, we assessed detailed BP parameters in patients who woke up with ischaemic stroke, including not only blood pressure, but also ABPM and

### Table 2. BP parameters in ischaemic stroke patients.

| Parameter                        | Overall     | Known-onset stroke | Wake-up stroke | p   |
|----------------------------------|-------------|--------------------|----------------|-----|
| **Supine office BP parameters**  |             |                    |                |     |
| Systolic BP, mm Hg               | 134.0 (123.0–153.0) | 136.5 (125.5–155.5) | 129.0 (118.5–149.0) | 0.077 |
| Diastolic BP, mm Hg              | 79.8 ± 12.8 | 80.9 ± 13.3        | 76.9 ± 11.3    | 0.130 |
| Mean BP, mm Hg                   | 99.0 (89.0–109.0) | 102.0 (93.0–110.0) | 96.0 (85.5–106.0) | 0.098 |
| Pulse pressure, mm Hg            | 57 (47.0–70.0) | 59.0 (48.0–70.0)   | 51.0 (47.0–67.0) | 0.396 |
| Heart rate, bpm                  | 66.0 ± 11.5 | 67.0 ± 11.8        | 63.6 ± 10.4    | 0.152 |
| **ABPM parameters**              |             |                    |                |     |
| Mean 24-h systolic BP, mm Hg     | 132.0 (122.0–143.0) | 130.0 (121.0–143.0) | 133.5 (125.0–144.5) | 0.584 |
| Mean 24-h diastolic BP, mm Hg    | 77.0 (71.0–84.0) | 76.0 (71.0–84.0)   | 77.0 (70.5–84.5) | 0.935 |
| Mean daytime systolic BP, mm Hg  | 134.0 (125.0–145.5) | 133.5 (125.0–145.5) | 137.0 (125.0–145.0) | 0.614 |
| Mean daytime diastolic BP, mm Hg | 79.0 (72.5–86.0) | 79.0 (72.5–85.0)   | 78.5 (72.0–88.0) | 0.879 |
| Mean night-time systolic BP, mm Hg| 128.0 (117.0–141.0) | 126.0 (117.0–142.0) | 128.0 (118.5–140.5) | 0.538 |
| Mean night-time diastolic BP, mm Hg| 74.3 ± 11.1 | 74.0 ± 10.8        | 75.0 ± 11.8    | 0.657 |

ABPM: ambulatory blood pressure monitoring; BP: blood pressure. Values are expressed as the mean ± standard deviation or median (interquartile range).

### Table 3. Office-ambulatory BP differences among wake-up stroke versus non-wake-up stroke patients.

| Parameter                                      | Known-onset stroke | Wake-up stroke | p     |
|------------------------------------------------|--------------------|----------------|-------|
| Systolic daytime BP difference                 | 4.12 (−2.48 to 11.31) | −1.92 (−11.55 to 3.95) | 0.006 |
| Diastolic daytime BP difference                | 1.27 (−7.46 to 10.67) | −6.33 (−15.63 to 8.70) | 0.068 |
| Mean daytime BP difference                     | 2.00 (−6.86 to 11.65) | −6.20 (−12.32 to 4.72) | 0.029 |
| Systolic night-time BP difference               | 9.84 (0.00 to 18.25)  | 0.00 (−9.79 to 11.82)  | 0.003 |
| Diastolic night-time BP difference              | 8.81 (−0.57 to 17.69) | 0.00 (−9.21 to 12.05) | 0.061 |
| Mean night-time BP difference                   | 7.82 (−2.47 to 20.39) | 0.51 (−8.49 to 12.08) | 0.026 |

Values are expressed as the median (interquartile range).

### Table 4. Results of a multinominal logistic regression for distinguishing between wake-up stroke and known-onset stroke.

| Parameter                              | Odds ratio | 95% confidence interval | p     |
|----------------------------------------|------------|-------------------------|-------|
| Sex                                    | 1.84       | 0.56–6.02               | 0.317 |
| Age, years                             | 1.02       | 0.98–1.06               | 0.440 |
| Baseline National Institutes of Health Stroke Scale score | 1.00       | 0.90–1.11               | 0.993 |
| Admission glucose, mg/dL               | 0.99       | 0.98–1.01               | 0.308 |
| Use of recombinant tissue plasminogen activator | 0.10       | 0.02–0.46               | 0.003 |
| Office-ambulatory systolic BP difference, % | 0.96       | 0.92–1.00               | 0.039 |
| Maximal daytime heart rate, bpm         | 0.97       | 0.94–1.00               | 0.085 |
| Use of antihypertensives during hospitalisation | 0.90       | 0.27–2.97               | 0.860 |
blood pressure variability. The most important finding from this study is that the indices of blood pressure reactivity, the systolic and mean daytime and night-time BP differences, were substantially lower in wake-up stroke. Although basic BP parameters individually were not significantly associated with wake-up stroke, the differences including both office systolic BP and mean systolic BP from the whole day or night were related to wake-up stroke. The office-ambulatory systolic daytime BP difference remained statistically significant after adjustment to confounding factors, such as age, sex, admission glucose, the use of recombinant tissue plasminogen activator, daytime maximal hear rate, the National Institutes of Health Stroke Scale score (both at baseline and at day 7, separately), and in-hospital use of hypotensives. It is worth noting that these analyses showed statistically more frequent use of fibrinolysis in patients with known-onset stroke, which was associated with guidelines for the management of acute ischaemic stroke valid at the time of patient enrolment.

The explanation of the underlying cause of the lower office-ambulatory BP difference in wake-up stroke patients is unknown. One of the potential causes could be reduced reactivity to a stressor (blood pressure measurement by a doctor/nurse) associated with reduced state of consciousness; however, in our study both patient subgroups had similar neurological deficit as measured by the National Institutes of Health Stroke Scale score. The participants also did not differ in their mobility (their modified Rankin scale scores were comparable).

Interestingly, the difference in the systolic BP difference between wake-up stroke and known-onset stroke was not accompanied by differences in office BP. A study by Nadeau et al. showed that patients with wake-up stroke had higher systolic BP (160 mm Hg vs 157 mm Hg) [7]. However, it included not only ischaemic stroke, but also intracerebral haemorrhage, subarachnoid haemorrhage, cerebral venous sinus thrombosis, and transient ischaemic attack; thus, no reasonable conclusions regarding blood pressure in ischaemic stroke can be drawn from this paper. Another studies demonstrated no difference in number of ischaemic stroke patients with systolic BP > 185 mm Hg or diastolic BP > 110 mm Hg [1] and no difference in arterial pressure at admission [8,12,13].

We also did not observe any significant differences in BP values in ABPM between participant with wake-up and known-onset stroke which is in-line with another studies [14,15]. As far as blood pressure variability is concerned, we did not find any differences in the standard deviation and coefficient of variation in ABPM. A study by Lundholm et al. revealed that wake-up stroke patients had greater nocturnal blood pressure variability based on ABPM carried out within 24 h after admission [15]. The possible reason why our study did not confirm this result is that blood pressure variability was calculated for day 7 after admission when BP in ischaemic stroke patients is completely different, associated with, among others, partial or complete regression of acute hypertensive response observed early after stroke onset [16].

Intriguingly, ABPM parameters differed in the wake-up and known-onset stroke groups after taking mobility into account. Patients with wake-up stroke and a modified Rankin scale score of 3 points (requiring some help but able to walk without assistance) had higher mean heart rate, whereas patients with non-wake-up stroke and a modified Rankin scale score of 3 points had higher some minimal BP values and lower heart rate variability. These observations are not consistent with the literature, as physical activity temporarily increases mean BP [17], so patients with lower Rankin scale scores might be expected to have higher mean BP. This inconsistency may be, at least partially, caused by a small number of patients in the subgroups.

The analysis of ABPM demonstrated that thrombolysis was associated with lower mean 24-h, daytime, and night-time diastolic BP as well as lower 24-h and night-time average mean BP. This result is basically in line with the literature which showed that systolic, diastolic, and mean BP decrease after thrombolysis and that this decline was greater in patients with adequate vessel recanalization [18]. It should be mentioned that we did not assess the degree of vessel recanalization in our patients.

Our study has several important limitations. Firstly, our conclusions were based on a post-hoc analysis. Therefore, future prospective research is needed to confirm our results. Secondly, ABPM was divided into daytime and night-time hours in a fixed manner which may not reflect a real time of patients’ awakening and falling asleep. Thirdly, activity of participants in our study may differ depending on a degree of their motor impairment which may affect BP. Fourthly, because office BP was measured during pulse wave velocity assessment, patients with atrial fibrillation were excluded (a contraindication to applanation tonometry) which could impact on BP parameters.
In conclusion, the lower differences between office and ambulatory blood pressure including the dynamic BP component (systolic BP) was independently associated with wake-up stroke. In the future, an in-depth knowledge of BP specificity in wake-up stroke may allow a better understanding of its pathophysiology and triggers as well as its prevention. However, further study is needed.

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