

From Clinical Considerations to Theory - Blood Pressure Variability Profiles and Patterns

Cristina JAPIE^a; Emma WEISS^{a,b}; Magda BUNEA^b; Sabina FRUNZA^a;
Ana Maria DARABAN^{a,b}; Daniela BARTOS^{a,b}; Elisabeta BADILA^{a,b}

^a Clinic of Internal Medicine, Emergency Clinical Hospital Bucharest, Romania

^b "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Background: Blood pressure variability (BPV) has recently been associated with adverse cardiovascular (CV) events, endothelial dysfunction as well as both CV and non-CV morbidity and mortality. Different BPV indicators have been associated with increased CV risk.

Methods: We included 744 hypertensive patients referred to our clinic for uncontrolled arterial hypertension (HTN) between 2012 and 2014, with a minimum of 40 successful daytime and 8 successful nighttime readings on automatic blood pressure monitoring (ABPM Meditech-05 device, recordings at 15-20 minutes intervals during daytime and 20-30 minutes intervals during nighttime). Exclusion criteria were presence of secondary HTN, significant CV disease and estimated glomerular filtration rate <30 ml/min/1.73 m². BPV was expressed as dipping pattern, BP load, SD of 24-hour mean BP, average weighted SD and average real variability (ARV).

Results: All patients were known hypertensives, however their average blood pressure (BP) values on 24-hour ABPM were below 135/85 mmHg. The average dipping was higher in dippers ($p < 0.01$) and nighttime systolic BP (SBP) load was increased among the non-dippers group ($p < 0.01$). Mean diastolic BP (DBP) was slightly increased in dippers vs. non-dippers (75.82 ± 10.28 mmHg vs. 71.42 ± 10.17 mmHg, $p < 0.01$). Of the total of 407 dippers, 31.2% displayed an extreme dipping pattern, whereas 29.67% of the 337 non-dippers were risers. In our study, average SBP, daytime and nighttime SBP SD and ARV did not differ significantly between the two extreme groups, as opposed to classical indicators such as SBP load ($p < 0.01$) and weighted SD ($p = 0.02$).

Conclusion: In the emergency hospital setting, hypertensive patients can have normal mean BP values, but still can display a very high variability and in most cases abnormal dipping profiles, requiring a strictly controlled drug therapy that is able to match each individual's chronobiology.

Keywords: arterial hypertension, blood pressure variability, dipping profile, standard deviation, average real variability

Address for correspondence:

Elisabeta Badila, Clinic of Internal Medicine, Emergency Clinical Hospital, 8th Floreasca Avenue, zip code 014461, 1st District, Bucharest, Romania.

E-mail: elisabeta.badila@gmail.com

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BACKGROUND

Blood pressure variability (BPV) – the degree of variation between BP readings – has recently been shown to be responsible for adverse cardiovascular (CV) events, development and progression of renal disease, endothelial dysfunction as well as both CV and non-CV morbidity and mortality (1,2).

Blood pressure (BP) is a continuous, not a static variable. As a consequence, BPV is characterized by short-term fluctuations within 24 hours (beat-to-beat, minute-to-minute, hour-to-hour and day-to-night changes) and long-term fluctuations within a larger period of time (days, weeks, months, seasons and years) (3). Patients with similar office or home BP values can display different daytime and nighttime average values depending on extrinsic factors (environmental or behavioral) or intrinsic CV regulatory mechanisms (central neural mechanisms, neural reflexes, humoral factors) (3).

BP normally follows a circadian pattern characterized by a decline of 10-20% in mean BP levels from day to night, a physiological phenomenon known as the dipping profile. Alterations in these intrinsic circadian rhythms can result in a non-dipping profile (BP decline during nighttime less than 10%). Hypertensive patients who demonstrate an exaggerated circadian BP rhythm (more than 20%) are known as extreme dippers, while patients with an increase of nocturnal BP values are known as risers (reverse or inverted dippers).

Different BPV indicators have been proven to correlate with an increased risk of CV events even in patients with controlled hypertension (4), however none, except for dipping profile, has become a standard of measure well enough to enter the guidelines. Average real variability (ARV) of daytime systolic BP and not high standard deviation (SD) has been recently proposed as a more reliable representation of BP variability than SD (5).

The aim of our study was to underline the significance of novel BPV indicators beyond the dipping pattern on the 24-hour ABPM evaluation of uncontrolled hypertensive patients referred to an emergency hospital.

METHODS

We included 744 hypertensive patients referred to our clinic for uncontrolled HTN

between 2012 and 2014. For each patient we recorded demographic data, 24-hour automatic BP monitoring (ABPM) data and BPV indices.

All ABPM recordings had a minimum of 40 successful daytime and 8 successful nighttime readings on ABPM (Meditech-05 device) with BP recordings programmed at 15-20 minutes intervals during daytime (6 AM to 22 PM) and 20-30 minutes intervals during nighttime (22 PM to 6 AM). During monitoring, each subject maintained a diary, listing the time they went to bed at night, woke up in the morning, took the medication, ate meals, performed physical activity, experienced events or emotional states that might have affected BP.

Exclusion criteria were presence of secondary HTN, significant CV disease and estimated glomerular filtration rate (eGFR) CKD-EPI <30 ml/min/1.73 m².

BPV was expressed as dipping pattern, BP load, standard deviation (SD) of 24-hour mean BP, average weighted SD and ARV.

The BP load was obtained for each profile of ABPM as the percentage of values greater than 135/85 mmHg and 120/70 mmHg during daytime and nighttime, respectively.

Weighted SD (wSD) was defined as the mean of day and night SD values, corrected for the number of hours included in each of these subintervals and was calculated according to the following formula (6):

$wSD = [(day\ SD \times hours\ included\ during\ daytime) + (night\ SD \times hours\ included\ during\ nighttime)] / (hours\ included\ during\ daytime + nighttime).$

ARV expressed the absolute differences of consecutive measurements and was calculated by the following formula (5):

$$ARV = \frac{1}{\sum w} \times \sum_{k=1}^{N-1} w \times |BP_{k+1} - BP_k|$$

where N stands for the number of valid BP readings, k is the order of measurements from each patient monitoring (ranging from 1 to N-1) and w is the time interval between BP_k and BP_{k+1} .

Comparisons were performed by paired-sample z-test. Two-tailed $p < 0.05$ was considered significant.

RESULTS

All patients were known hypertensives. However, their average BP values on 24-hour ABPM were below 135/85 mmHg. Of the whole cohort of 744 patients, 412 (55.38%) were females. Normal dipping profile was observed in 407 cases (54.7%) with no significant difference between genders. Patients with a non-dipping pattern (45.29%) were older than the ones with a dipping one (65.37 ± 11.24 vs. 56.38 ± 14.13 years old, $p < 0.01$) and were predominantly females (62.32% vs. 37.78% males, $p < 0.01$) (see Table 1 and Figure 1). Interestingly, mean diastolic BP (DBP) was slightly increased in dippers vs. non-dippers (75.82 ± 10.28 mmHg vs. 71.42 ± 10.17 mmHg, $p < 0.01$).

Analyzing beyond dipping profiles, major differences between BPV indices in the dippers versus non-dippers groups were observed (see Table 1 and Figure 2). Thus average dipping was considerably higher in dippers ($p < 0.01$) and nighttime SBP load was increased among the non-dippers group ($p < 0.01$) (Figure 3).

Of the total of 407 dippers, 127 patients (31.2%) displayed an extreme dipping pattern, whereas 100 patients (29.67%) of the 337 non-dippers were risers. There was no significant difference in terms of gender distribution between the two groups (Figure 1), however extreme-dippers were younger (54.5 ± 13.2 mmHg vs. 69.29 ± 10.54 mmHg, $p < 0.01$).

In our study, average SBP, daytime and nighttime SBP SD and ARV did not differ significantly between the two extreme groups (see Table 2), as opposed to classical indicators such as SBP load and weighted SD ($p < 0.01$ and $p 0.02$ respectively) (Figure 3 and 4). As expected, risers had an increased mean SBP and DBP during nighttime ($p < 0.01$ for SBP and

$p < 0.05$ for DBP) (Figure 5) and a lower average dipping (-5.81 ± 4.89 mmHg, $p < 0.01$).

DISCUSSION

Hypertension guidelines offer no recommendations on documenting and targeting BPV, even though evermore research has documented its role in residual CV risk in patients with both controlled and uncontrolled HTN.

The introduction of out-of-office BP measurement techniques (home BP monitoring - HBPM, 24-hour ABPM) has improved the management of arterial HTN, providing BP measurements in the patient's natural environment. Nowadays, noninvasive ABPM techniques are widely available and provide BP measurements both during daytime and nighttime when BP levels are known to have the strongest prognostic value (7). However, because these noninvasive techniques require the patient to stop any activity at the time of measurement, this approach does not capture BPV in truly real-life conditions and, thus, the development of devices capable of measuring beat-

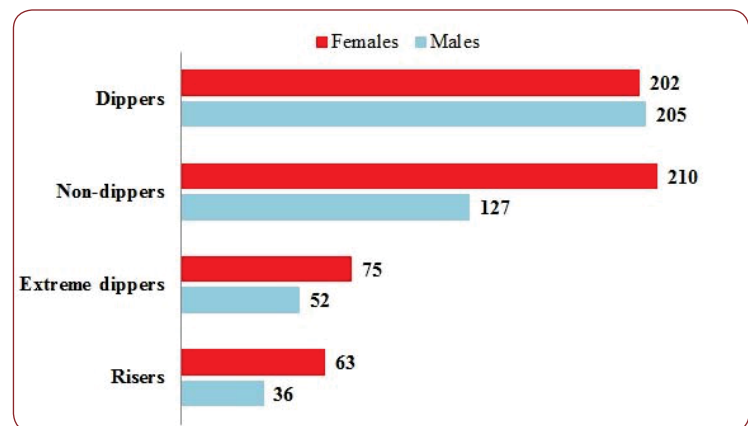


FIGURE 1. Gender distribution between studied groups.

	Dippers	Non-Dippers	Dippers vs. non-dippers (p)
No. pts.	407	337	
Females, no. (%)	202 (49.64%)	210 (62.32%)	<0.01
Age, years	56.38 ± 14.13	65.37 ± 11.24	<0.01
Mean SBP, mmHg	129.82 ± 3.21	128.28 ± 15.27	ns
Mean DBP, mmHg	75.82 ± 10.28	71.42 ± 10.17	<0.01
Daytime SBP SD, mmHg	13.61 ± 3.47	13.24 ± 3.56	<0.01
Nighttime SBP SD, mmHg	11.67 ± 3.74	11.81 ± 4.42	<0.01
Average dipping, mmHg	18.38 ± 6.57	2.31 ± 6.41	<0.01
Daytime SBP load, %	45	34	<0.01
Nighttime SBP load, %	15	31	<0.01
wSD, mmHg	12.38 ± 2.75	11.91 ± 2.93	<0.01

TABLE 1. Dippers versus non-dippers.

DBP = diastolic blood pressure, SBP = systolic blood pressure, SD = standard deviation, wSD = weighted standard deviation.

	Extreme dippers	Risers	Extreme dippers vs. risers (p)
No pts	127	100	
Females, no. (%)	75 (59.06%)	63 (63%)	ns
Age, years	54.5 ± 13.2	69.29 ± 10.54	<0.01
Mean SBP, mmHg	132.72 ± 13.34	131.46 ± 16.92	ns
Daytime SBP, mmHg	138.99 ± 13.7	129.77 ± 16.83	<0.01
Nighttime SBP, mmHg	113.6 ± 13.34	136.58 ± 17.72	<0.01
Mean DBP, mmHg	78.7 ± 11.15	70.74 ± 10.56	<0.01
Daytime DBP, mmHg	83.24 ± 11.82	70.9 ± 10.41	<0.01
Nighttime DBP, mmHg	64.75 ± 10.0	70.93 ± 11.4	<0.05
Mean SBP SD, mmHg	18.09 ± 3.41	14.13 ± 3.98	<0.01
Daytime SBP SD, mmHg	14.73 ± 3.94	13.91 ± 3.94	ns
Nighttime SBP SD, mmHg	12.11 ± 4.36	12.35 ± 6.23	ns
Mean DBP SD, mmHg	13.28 ± 2.5	8.98 ± 2.42	<0.01
Daytime DBP SD, mmHg	10.68 ± 2.99	9.05 ± 2.49	<0.01
Nighttime DBP SD, mmHg	9.12 ± 3.19	7.94 ± 3.58	<0.04
Average dipping, mmHg	26.39 ± 5.27	-5.81 ± 4.89	<0.01
Daytime SBP load, %	56	36	<0.01
Nighttime SBP load, %	12	47	<0.01
wSD, mmHg	13.33 ± 3.09	12.43 ± 3.37	0.02
ARV, mmHg	11.63 ± 2.54	11.71 ± 3.81	ns

TABLE 2. Extreme dippers versus risers.

ARV = average real variability, DBP = diastolic blood pressure, SBP = systolic blood pressure, SD = standard deviation, wSD = weighted standard deviation.

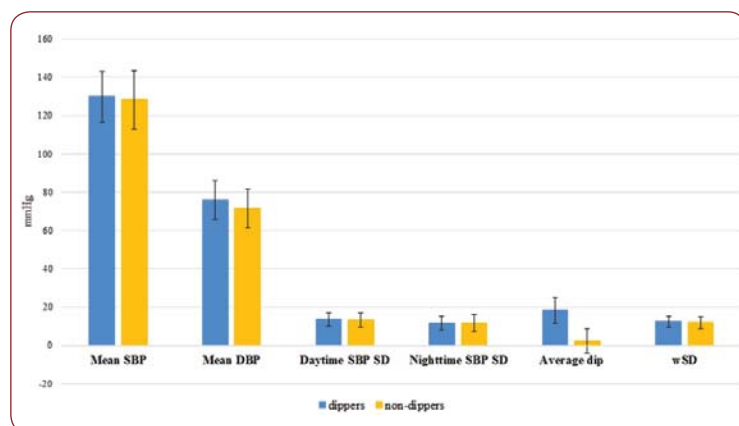


FIGURE 2. Blood pressure variability indicators in dippers and non-dippers.

to-beat ambulatory BP even in long-term studies is strongly required.

Short-term blood pressure variability

Various indices have been used to assess short-term BPV, including 24-hour, daytime and nighttime SD and the coefficient of variation of SBP and DBP (8). It has been questioned whether standard deviation is or is not an appropriate parameter for assessing short-term BPV, considering that SD represents the dispersion of BP values around the mean. SD doesn't take in consideration the order in which BP measurements are obtained, hence being sensitive to the low sampling frequency of ABPM (9). Hence, two subjects with significantly different BP measurements could display the same SD value.

In order to improve the prognostic value of short-term BPV, ARV of daytime and nighttime BP has been introduced, expressing the average of the absolute differences of consecutive measurements. This indicator is sensitive to the individual BP measurement order and less sensitive to low sampling frequency of ABPM (9). Thus, ARV is a more accurate method to assess BPV when compared to SD. In 2005, Mena et al. (5) first compared the impact of BPV evaluated with SD and ARV. Patients were grouped according to tertiles of SD and ARV of daytime SBP, defined as having low, moderate or high BPV and followed-up for 2 years. Results showed that CV risk was not significantly higher in subjects with high BPV evaluated through SD, but in contrast it was significantly higher in those with high BPV according to ARV ($p < 0.02$). Thus, the authors concluded that ARV is a more appropriate index of BPV and is superior to SD in predicting CV events, as subjects with different BP profiles may have the same SD, but different ARV. Also, the results suggested that ARV adds prognostic value to the ABPM and prompts the use of therapeutic measures to control BPV. Recently, Mena et al. (10) concluded that a number of 48 readings is sufficient for an accurate assessment of the ARV and CV risk without any loss of prognostic information.

Short-term BPV is independently associated with target organ damage and rate of CV events in both general population and in hypertensive

patients (11). Studies have shown that BPV indicators are strongly correlated with the prevalence and severity of target organ damage (left ventricular hypertrophy, carotid intima-media thickness) (12), CV events and mortality (13). Other studies determined a positive relationship between short-term BPV and arterial stiffness in diabetic hypertensives (14). By using ABPM, daytime SBP was proven to correlate with renal vascular resistance, while nighttime SBP was associated with intima-media thickness (15). Furthermore, nighttime SBP variability is independently associated with large arch plaque suggesting that excessive fluctuations of BP could contribute to the formation and progression aortic arch atherosclerosis (16).

Data from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study showed that the risk of CV death is inversely related to day-night DBP decrease (17). Also, diastolic BPV seems to be a better outcome predictor than systolic BPV (18). In normal conditions, SBP and DBP both change in the same manner in response to physiological stimuli. However, in subjects with arterial stiffness, usually, when SBP increases, DBP increases less or even falls, thus being responsible for a greater variability (19).

Increased short-term BPV is associated with increased risk of stent restenosis after percutaneous coronary intervention in normotensive patients (20).

Short-term BPV also involves cerebrovascular damage and decline in cognitive function in hypertensive patients. Increased daytime SBP was associated with cognitive dysfunction in the elderly (21). The impact of aging on BPV is due to impaired baroreceptor sensitivity promoting transient BP fluctuations and to exaggerated pressor response to mental and physical stimuli. Also, advanced age is accompanied by arterial stiffness that decreases baroreceptor function and contributes to increased BPV (22).

Long-term blood pressure variability

BP also displays a long-term variability (day-by-day, visit-to-visit, seasonal BP variations) that has been associated with increased risk of CV disease. Large variation of long-term BPV could be influenced by poor BP control in treated patients, incorrect dosing and titration of antihypertensive medication, poor patient adherence to prescribed treatment as dose

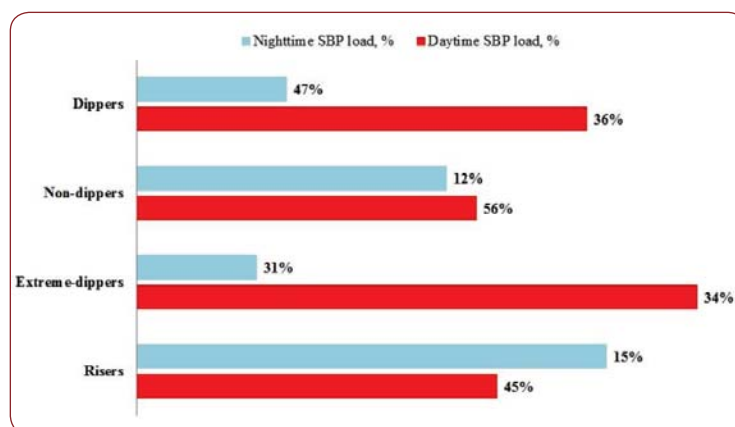


FIGURE 3. Daytime and nighttime systolic blood pressure load between studied groups.

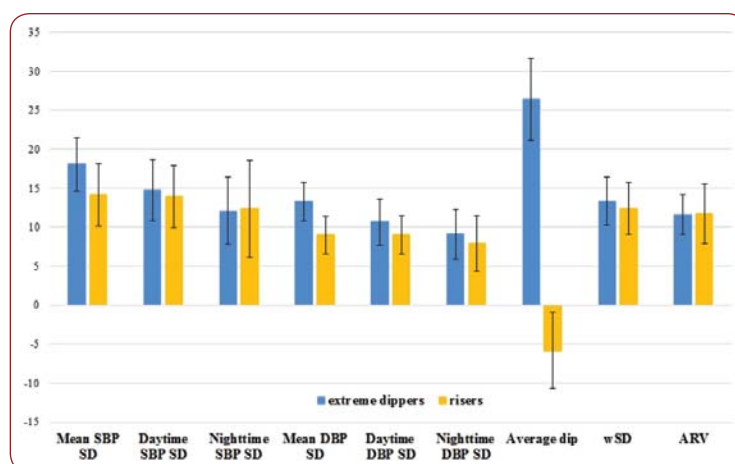


FIGURE 4. Blood pressure variability indicators in extreme dippers and risers.

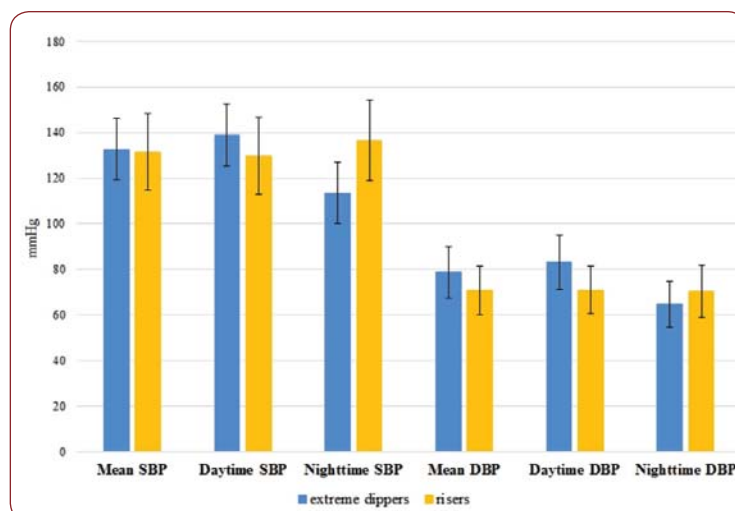


FIGURE 5. Mean, daytime and nighttime blood pressure in extreme dippers and risers.

omission or delay in drug intake during the follow-up period may contribute to an increased day-by-day and visit-to-visit BPV.

Day-to-day BPV is situated between short-term BPV (within the 24 hours) and visit-to-visit BPV (within weeks, months or years). Measurement of day-to-day BPV can be performed by using ABPM over consecutive days (i.e. 48 hours) or by HBPM, even if the latter does not provide the same extensive information as ABPM. Home BP measurement seems a more appropriate BP measurement technique for long-term assessment of BPV and BP control than repeated office or ambulatory BP monitoring.

In clinical practice, visit-to-visit BPV assessment is rather difficult to obtain. Office BP measurement cannot provide information regarding BP values within long periods of time, whereas ABPM cannot be repeated routinely even though it provides extensive information on BP values. Thus, probably the best method to assess long-term BPV could be HBPM (23).

Visit-to-visit BPV is associated with endothelial dysfunction, cognitive dysfunction, cerebral (white matter lesions, cerebral infarctions) (24), cardiac (diastolic dysfunction), microvascular (development of micro- and macroalbuminuria and renal vascular atherosclerosis) and macrovascular (increased intima-media thickness and arterial stiffness) (25) complications in diabetic hypertensives. Thus, visit-to-visit BPV could be considered a risk factor for the development and progression of diabetic nephropathy in diabetic patients.

Visit-to-visit BPV contributes to target organ damage and CV events in patients with chronic kidney disease or under hemodialysis. Studies have demonstrated that SD and the coefficient of variation of office SBP measured at 12 consecutive visits were strongly associated with deterioration of renal function in patients with nondiabetic chronic kidney disease (26). A cohort study including 1088 patients under hemodialysis which were followed-up for 5 years showed that long-term BPV is a predictor of CV mortality in patients with end-stage renal disease under hemodialysis (27).

Therapeutic implications

In recent years, evidence from clinical trials show the effect of antihypertensive medication on both short- and long-term BPV. Anglo Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BLPA) revealed that when compared to the atenolol group, pa-

tients treated with amlodipine had a lower SBP-SD, mainly due to lower visit-to-visit variability, and a lower risk of stroke and coronary events (28). The Medical Research Council (MRC) trial showed that SD of within-individual visit-to-visit systolic BPV and the risk of stroke were increased in the atenolol group compared with placebo and the diuretic groups during initial follow-up (29), while a recent review found that systolic BPV is increased more by non-selective beta-blockers than by selective beta1-blockers (30). Consequently, antihypertensive drugs need to reduce mean BP values and its short- and long-term variability in order to prevent cerebrovascular events.

Webb et al. studied the effect of antihypertensive drugs on inter-individual BPV. Thus, they revealed that the most effective therapeutic class in reducing BPV was represented by the calcium antagonists and that angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, thiazide-type diuretics and beta-blockers were less effective and showed neutral effects in comparison with placebo (31). Furthermore, adding calcium antagonist to any another antihypertensive drug significantly reduced visit-to-visit BPV.

The NatriX SR versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study compared the effect of candesartan, indapamide sustained release and amlodipine on BPV assessed by SD of 24-hour ABPM. The study revealed that amlodipine had the greater effect on short-term BPV indicators ameliorating daytime, nighttime and 24-hour SBP-SD and ARV, while candesartan showed neutral effects on short-term BPV and indapamide reduced only daytime and 24-hours systolic BPV (32).

Also, Scholze et al. (33) studied the effect of fixed-dose combination of 10 mg lercanidipine hydrochloride and 20 mg enalapril maleate by using ABPM, office and self-measured BP. After a three months follow-up, this fixed-dose combination improved pulse pressure, BPV indicators and microalbuminuria and significantly reduced 24-hour and nighttime BPV.

STUDY LIMITATIONS

The present study must be interpreted within the context of its limitations as we applied intermittent techniques of 24-hour ABPM,

which compared with intra-arterial recordings or continuous recordings of the arterial signal, is a less precise technique to capture short-term BPV. The study analysed the patterns and profiles of BPV during one visit and did not include follow-up. Also it did not evaluate the patients' CV risk profile and did not collect information on antihypertensive medication or target organ damage.

CONCLUSION

In an emergency hospital setting, hypertensive patients can have normal mean BP values, but still can display a very high variability and in most cases abnormal dipping profiles, thus re-

quiring a strictly controlled drug therapy that is able to match each individual's chronobiology.

Our study highlights the importance of 24-hour ABPM and the utility of BP indicators, although it doesn't reflect a complete 24-hour BP variability profile. New parameters such as ARV may overcome the deficiencies of the classically used BP indices, although it still has a questionable value in our study as it did not differ significantly between the studied groups. As such, the usefulness of ARV in the clinical setting still remains to be determined.

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REFERENCES

- Rossignol P, Kessler M, Zannad F - Visit-to-visit blood pressure variability and risk for progression of cardiovascular and renal diseases. *Curr Opin Nephrol Hypertens* 2013;22:59-64.
- Yokota K, Fukuda M, Matsui Y, et al. - Impact of visit-to-visit variability of blood pressure on deterioration of renal function in patients with non-diabetic chronic kidney disease. *Hypertens Res* 2013;36:151-157.
- Mancia G - Short- and Long-Term Blood Pressure Variability: present and future. *Hypertension* 2012;60:512-517.
- Pengo MF, Rossitto G, Bisogni V, et al. - Systolic and diastolic short-term blood pressure variability and its determinants in patients with controlled and uncontrolled hypertension: a retrospective cohort study. *Blood Press April* 2015;24:124-9.
- Mena L, Pintos S, Queipo NV, et al - A reliable index for the prognostic significance of blood pressure variability. *J Hypertens* 2005;23:505-511.
- Bilo G, Giglio A, Styczkiewicz K, Caldara G, Maronati A, Kawecka-Jaszcz K, Mancia G, Parati G - A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J Hypertens* 2007;25:2058-2066.
- Clement DL, De Buyzere ML, De Bacquer DA, et al. - Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003;348:2407.
- Parati G, Ochoa JE, Lombardi C, Bilo G - Assessment and management of blood-pressure variability. *Nature Reviews Cardiology* 2013;10:143-155.
- Pierdomenico SD, Di Nicola M, Esposito AL, et al. - Prognostic value of different indices of blood pressure variability in hypertensive patients. *Am J Hypertens* 2009;22:842-847.
- Mena LJ, Maestre GE, Hansen TW, et al. - How many measurements are needed to estimate blood pressure variability without loss of prognostic information? *Am J Hypertens* 2014;27:46-66.
- Madden JM, O'Flynn AM, Dolan E, Fitzgerald AP, Kearney PM - Short-term blood pressure variability over 24h and target organ damage in middle-aged men and women. *Journal of Human Hypertension* 2015;29:719-725.
- Sander D, Kukla C, Klingelhöfer J, Winbeck K, Conrad B - Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis: A 3-year follow-up study. *Circulation* 2000;102:1536-1541.
- Verdecchia P, Angeli F, Gattobigio R, Rapicetta C, Reboldi G - Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. *Am J Hypertens* 2007;20:154-61.
- Fukui M, Ushigome E, Tanaka M, et al. - Home blood pressure variability on one occasion is a novel factor associated with arterial stiffness in patients with type 2 diabetes. *Hypertens Res* 2013;36:219-225.
- Kawai T, Ohishi M, Kamide K, et al. - Differences between daytime and nighttime blood pressure variability regarding systemic atherosclerotic change and renal function. *Hypertens Res* 2013;36:232-239.
- Iwata S, Jin Z, Schwartz JE, et al. - Relationship between ambulatory blood pressure and aortic arch atherosclerosis. *Atherosclerosis* 2012;221:427-431.
- Mancia G, Bombelli M, Facchetti R, et al. - Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007;49:1265-1270.
- Hansen TW, Thijs L, Li Y, et al. - Prognostic Value of Reading-to-Reading Blood Pressure Variability Over 24 Hours in 8938 Subjects From 11 Populations. *Hypertension* 2010;55:1049-57.
- Li Y, Wang JG, Dolan E, et al. - Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. *Hypertension* 2006; 47:359-364.
- Cay S, Cagirci G, Demir AD, et al. - Ambulatory blood pressure variability is associated with restenosis after percutaneous coronary intervention in normotensive patients. *Atherosclerosis* 2011;219:951-957.
- Sakakura K, Ishikawa J, Okuno M, Shimada K, Kario K - Exaggerated ambulatory blood pressure variability is associated with cognitive dysfunction in the very elderly and quality of life in the younger elderly. *Am J Hypertens* 2007;20:720-727.
- Kato T, Kikuya M, Ohkubo T, et al. - Factors associated with day-by-day variability of self-measured blood pressure at home: the Ohasama study. *Am J Hypertens* 2010;23:980-86.
- Stergiou GS, Nasothimiou EG - Home monitoring is the optimal method for assessing blood pressure variability. *Hypertens Res* 2011;34:1246-1248.
- Brickman AM, Reitz C, Luchsinger JA, et al. - Long-term blood pressure

- fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol* 2010;67:564-569
25. **Kilpatrick ES, Rigby AS, Atkin SL** - The role of blood pressure variability in the development of nephropathy in type 1 diabetes. *Diabetes Care* 2010;33:2442-2447
 26. **Yokota K, Fukuda M, Matsui Y, Hoshida S, Shimada K, Kario K** - Impact of visit-to-visit variability of blood pressure on deterioration of renal function in patients with non-diabetic chronic kidney disease. *Hypertens Res* 2013;36:151-157.
 27. **Di Iorio B, Di Micco L, Torraca S, et al.** - Variability of blood pressure in dialysis patients: a new marker of cardiovascular risk. *Journal of Nephrology* 2013;26:173-182.
 28. **Rothwell PM, Howard SC, Dolan E, et al.** - Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol* 2010;9:469-48.
 29. **Hocht C, Bertera FM, Taira CA.** - Importance of blood pressure variability in the assessment of cardiovascular risk and benefits of antihypertensive therapy. *Expert Review of Clinical Pharmacology* 2010;3:617-621.
 30. **Stewart AJ, Fischer U, Rothwell PM.** - Effects of β -blocker selectivity on blood pressure variability and stroke: a systematic review. *Neurology* 2011;77:731-737.
 31. **Webb AJ, Fischer U, Mehta Z, Rothwell PM** - Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and metaanalysis. *Lancet* 2010;375:906-915.
 32. **Zhang Y, Agnoletti D, Safar ME, Blacher J** - Effect of antihypertensive agents on blood pressure variability: the natrilix SR versus candesartan and amlodipine in the reduction of systolic blood pressure in hypertensive patients (X-CELLENT) study. *Hypertension* 2011;58:155-160.
 33. **Scholze J, Bramlage P, Trenkwalder P, Kreutz R** - Efficacy and safety of a fixed-dose combination of lercanidipine and enalapril in daily practice. A comparison of office, selfmeasured and ambulatory blood pressure. *Expert Opinion on Pharmacotherapy* 2011;12:2771-2779.

