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ORIGINAL ARTICLE

Elevated Neuropeptide Y Plasma Concentration in Non-dippers With Essential Hypertension

Podwyższone stężenie neuropeptydu Y we krwi u chorych z nadciśnieniem tętniczym pierwotnym i brakiem nocnego obniżenia ciśnienia tętniczego

Streszczenie

Wstęp Brak nocnego obniżenia ciśnienia tętniczego prowadzi do zwiększonej częstości powikłań narządowych nadciśnienia tętniczego, a jego przyczyny pozostają niejasne. Celem pracy była ocena zależności między biochemicznymi wykładnikami aktywności współczulnej a rytmem dobowym ciśnienia u chorych z pierwotnym nadciśnieniem tętniczym.

Materiał i metody Do badania zakwalifikowano 68 chorych z nadciśnieniem tętniczym w średnim wieku 40 ± 1 lat (20 K, 48 M). Do grupy kontrolnej włączono 25 zdrowych ochotników w średnim wieku 38 ± 1 lat (8 K i 17 M). U badanych wykonywano 24-godzinny pomiar ciśnienia (*SpaceLabs* 90207) oraz oznaczano we krwi stężenie katecholamin i neuropeptydu Y. Całodobowo prowadzono zbiórkę moczu w celu oznaczenia wydalania katecholamin.

Wyniki U chorych z nadciśnieniem tętniczym stężenie neuropeptydu Y było wyższe niż u osób zdrowych. Stężenie katecholamin w surowicy i ich wydalanie z moczem były w obu grupach podobne. Chorych z nadciśnieniem podzielono na dwie grupy zależnie od obecności — *dippers* (46 chorych) — lub braku nocnego obniżenia ciśnienia — *non-dippers* (22 chorych). Stężenie neuropeptydu Y było istotnie wyższe w grupie *non-dippers* niż w grupie *dippers* (10,6 ± 1 *vs.* 8,6 ± 1 fmol/ml, $p < 0,05$). Nie stwierdzono między grupami różnic w zakresie stężenia katecholamin w surowicy i katecholamin wydalanych z moczem. W obu grupach wydalanie katecholamin w czasie nocy było istotnie niższe aniżeli w ciągu dnia. Nocne i dzienne wydalanie katecholamin było podobne w grupie *dippers* i *non-dippers*.

Wnioski Uzyskane wyniki wskazują, że neuropeptyd Y może wpływać na zaburzenie rytmu dobowego ciśnienia tętniczego u chorych z nadciśnieniem i brakiem nocnego obniżenia ciśnienia. Prawdopodobnie katecholaminy nie wpływają na dobowy rytm ciśnienia tętniczego.

słowa kluczowe: neuropeptyd Y, katecholaminy, 24-godzinny ambulatoryjny pomiar ciśnienia tętniczego, *dippers*, *non-dippers*

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Introduction

Ambulatory blood pressure monitoring (ABPM) has allowed the presence of a diurnal rhythm of blood pressure (BP) and heart rate (HR) to be demonstrated [1]. It has been established that the circadian pattern of BP and HR is characterised by low values during sleep and higher values during wakefulness. Data based on 24-hour ABPM have demonstrated that the nocturnal decline of BP may be diminished or even

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absent in some subjects called non-dippers [2, 3]. In contrast, patients with preserved circadian rhythm are described as dippers. Non-dippers have come to be arbitrarily identified as patients whose nocturnal reduction in BP is more than 10% of the diurnal BP values. ABPM has shown that repeated BP recordings better represent the mean blood pressure of an individual subject and better correlate with several indices of hypertension-related end-organ damage than office blood pressure [4]. Non-dippers were characterised as associated with increased frequency of end-organ damage and poorer prognosis for cardiovascular events, as compared to dippers [4]. The reasons why BP and HR have a circadian rhythm with nocturnal blood pressure decline remain unclear. Some data indicate that circadian rhythm is influenced by extrinsic factors like the mental and physical activity of investigated subjects [5]. Other data point to intrinsic, i.e. physiological and pathophysiological, factors [6]. While most evidence favours the theory of extrinsic factors, clinical studies show that some hormonal disorders, like hyperaldosteronism or excessive production of glucocorticoids, can lead to blunting or absence of nocturnal fall in blood pressure [7, 8]. Also some data point to a relationship between the circadian rhythm of BP and the sympathetic nervous system activity.

The present study was designed to determine the relationship between hormonal indices of the sympathetic activity (catecholamines, neuropeptide Y) and disturbances in diurnal blood pressure rhythm in hypertensive patients.

Material and methods

The study group consisted of 68 patients (20 women, 48 men), mean age 40 ± 1 years. All patients had newly diagnosed mild to moderate hypertension or they had not received any antihypertensive medication for at least 14 days before the study. Ambulatory blood pressure was higher than: systolic 134 mm Hg and/or diastolic 90 mm Hg in all hypertensives. Before the study secondary forms of hypertension were excluded in all investigated subjects. The control group consisted of 28 healthy normotensive volunteers (8 women, 20 men), mean age 38 ± 1 years. ABPM was performed using a SpaceLabs 90207 device (SpaceLabs Inc. Redmond, Washington, USA). The device was programmed to measure BP every 15 minutes during the daytime (6.00 AM to 10.00 PM) and every 20 minutes during the night (10.00 PM to 6.00 AM). Urine collections for norepinephrine (NE), epinephrine (E) and dopamine (D) were performed separately between 6.00 AM and 10.00 PM and then from 10.00 PM to 6.00 AM. Urine NE and E were measured by the fluorometric method. A venous blood sample was taken at 08.00 AM after participants had been resting in a supine position for 30 minutes. Blood samples were collected into ice-cold tubes containing sodium EDTA (1 mg/ml) and aprotinin (500 U/ml) for NPY, and EDTA glutatione for catecholamines. All samples were immediately centrifuged at +4°C, 2000 g for 30 min and aliquots of plasma were frozen at –20°C until assayed. Plasma NPY concentration was determined by radioimmunoassay using Peninsula antibodies (RAS 7172), standard (7172) and Amersham iodinated NPY (IM 170). The intra- and interassay coefficients of variation were 8% and 14%, respectively. The catecholamine plasma concentration was determined by the radioenzymatic method using a commercial kit (Upjohn). The intra-assay coefficient of variation was 3,1% for E and 4,2% for NE. The interassay coefficient of variation was 6,6% for E and 7,4% for NE.

The protocol of the study was reviewed and approved by the Ethical Committee of the Medical Academy. All study parameters are expressed as a mean value followed by standard error (mean ± SE). Statistical analysis was performed using Student's t-test and the Mann-Whitney test. Differences with a value of $p < 0,05$ were considered to be significant.

Results

We investigated 68 hypertensives (20 females, 48 males) and 25 normotensive (8 females, 17 males) volunteers. Subjects did not differ from healthy patients with regard to age (40 ± 1 *vs.* 38 ± 1 yrs) and body mass index — BMI (28 ± 3 *vs.* 26 ± 3 kg/m^2, respectively). There were significant differences in office systolic (159 ± 2 *vs.* 121 ± 2 mm Hg, $p < 0,01$) and diastolic (104 ± 1 *vs.* 78 ± 2 mm Hg, $p < 0,01$) BP, while no differences were found in HR (72 ± 1 *vs.* 64 ± 2 beats/min) between the groups. In accordance with 10% diurnal — nocturnal difference as a cut-off point, hypertensive patients (68) were divided into two groups: dippers (D — 46) and non-dippers (ND — 22). No differences in age (40 ± 1 *vs.* 40 ± 1 yrs), BMI (28 ± 3 *vs.* 28 ± 3 kg/m^2), basal systolic BP (155 ± ± 2 *vs.* 161 ± 2 mm Hg), diastolic BP (102 ± 2 *vs.* 106 ± ± 2 mm Hg) and HR (72 ± 2 *vs.* 70 ± 1, respectively) were found between dippers and non-dippers.

Mean systolic and diastolic BP values during 24 h, daytime and night-time were significantly higher in hypertensive patients as compared to controls (Table I). Heart rate during 24 h, daytime and night-

Table I. Mean systolic, diastolic blood pressure, heart rate during 24 h, day and night and nocturnal fall in systolic and diastolic blood pressure and heart rate in investigated groups

Tabela I. Średnie ciśnienie tętnicze skurczowe (SBP), rozkurczowe (DBP) i częstotliwość serca (HR) w ciągu 24 h, z dnia i nocy oraz nocny spadek ciśnienia skurczowego i rozkurczowego oraz częstoliwość serca w badanych grupach

	Hypertensives	Controls	Non-dippers	Dippers
SBP 24 h [mm Hg]	146 ± 2*	118 ± 1	149 ± 2	144 ± 1
DBP 24 h [mm Hg]	94 ± 1*	73 ± 1	97 ± 1	94 ± 1
HR 24 h [b/min]	75 ± 2	73 ± 2	72 ± 2	76 ± 2
SBP day [mm Hg]	150 ± 2*	123 ± 1	151 ± 2	150 ± 2
DBP day [mm Hg]	99 ± 1*	76 ± 1	99 ± 1	98 ± 1
HR day [b/min]	79 ± 1	78 ± 2	75 ± 2	80 ± 2
SBP night [mm Hg]	138 ± 2*	108 ± 1	147 ± 2**	134 ± 1
DBP night [mm Hg]	88 ± 1*	64 ± 1	95 ± 1**	84 ± 1
HR night [b/min]	68 ± 1	62 ± 2	67 ± 2***	68 ± 2****
ΔSBP [mm Hg]	15 ± 1	14 ± 1	7 ± 1**	19 ± 1
ΔDBP [mm Hg]	13 ± 1	11 ± 1	6 ± 1**	17 ± 1
ΔHR [b/min]	11 ± 1*	16 ± 1	8 ± 1**	12 ± 1
Night MBP fall (%)	11 ± 1	13 ± 1	4 ± 1**	15 ± 1

Values are means ± SEM, *p < 0,01 — hypertensives *vs.* control, **p < 0,001 — non-dippers *vs.* dippers, ***p < 0,01 — HRn *vs.* HRd non-dippers, ****p < 0,001 — HRn *vs.* HRd dippers
ΔSBP, ΔDBP, ΔHR — differences between: day and night systolic, diastolic blood pressure and heart rate

time was similar in both groups (Table I). Dippers and non-dippers had similar mean systolic and diastolic BP during 24 h and daytime. Night-time systolic and diastolic BP were significantly lower in dippers than in non-dippers (Table I). HR during 24 h, daytime and night-time was similar in dippers and non-dippers, but in both groups significantly lower during the night than during the day (Table I).

Nocturnal systolic and diastolic BP fall (ΔSBP and ΔDBP) and mean night blood pressure (MBP) fall were similar in hypertensive patients and in control subjects, while nocturnal HR decline (ΔHR) was significantly higher in controls (Table I). Non-dippers had a significantly lower nocturnal fall in systolic and diastolic BP and in HR than dippers (Table I). Night mean BP fall was significantly higher in dippers as compared to non-dippers (Table I).

Plasma NE, E and D concentrations were similar in hypertensives and controls (NE 359 ± 16 *vs.* 348 ± ± 26 pg/mL, E 86 ± 4 *vs.* 85 ± 6 pg/mL and D 120 ± ± 9 *vs.* 94 ± 10 pg/mL, respectively. Also no differences were observed between non-dippers and dippers with regard to plasma catecholamine concentrations (NE 369 ± 16 *vs.* 354 ± 20 pg/mL, E 79 ± 5 *vs.* 89 ± 7 pg/mL and D 109 ± 9 *vs.* 126 ± 10 pg/mL, respectively). Plasma NPY concentration was significantly higher in hypertensive patients as compared to controls (NPY 9,2 ± 1 *vs.* 6.8 ± 1 fmol/mL, p < 0,05) and in non-dippers as compared to dippers and to controls (10,6 ± 1 *vs.* 8,6 ± 1 — p < 0,05 and *vs.* 6,8 ± 1 fmol/mL — p < 0,001) (Fig. 1).

Urine catecholamine excretion during 24 h was similar in hypertensive patients and in controls (NE 15,7 ± 0,5 *vs.* 18,1 ± 1,7 ug/24 h, E 2,7 ± 0,5 *vs.* 3,0 ± ± 0,3 ug/24 h and D 139 ± 8 *vs.* 143 ± 19 ug/24 h, respectively). There were no significant differences between non-dippers and dippers with regard to urine catecholamine excretion during the daytime and night-time (Table II). Also no differences were found between groups when hormone excretion was recalculated as rate per one hour (non-dippers *vs.* dippers NE day: 0,82 ± 0,04 *vs.* 0,84 ± 0,03 mg/h, NE night 0,31 ± 0,04 *vs.* 0,39 ± 0,03 mg/h, E day 0,15 ± 0,02 *vs.* 0,15 ± 0,01 mg/h, E night 0,04 ± ± 0,01 *vs.* 0,04 ± 0,01 mg/h, D day 5,24 ± 0,47 *vs.* 6,26 ± 0,48 mg/h and D night 4,77 ± 0,38 *vs.* 6,16 ± ± 0,5 mg/h). Urine NE excretion per hour during the night, but not urine E and D excretion, was significantly lower in non-dippers than in controls (0,31 ± ± 0,04 *vs.* 0,61 ± 0,1 mg/h, p < 0,05). No such difference was found between dippers and controls.

One-hour urine NE and E excretion was significantly lower during the night-time than during the daytime in non-dippers and dippers (Table III).

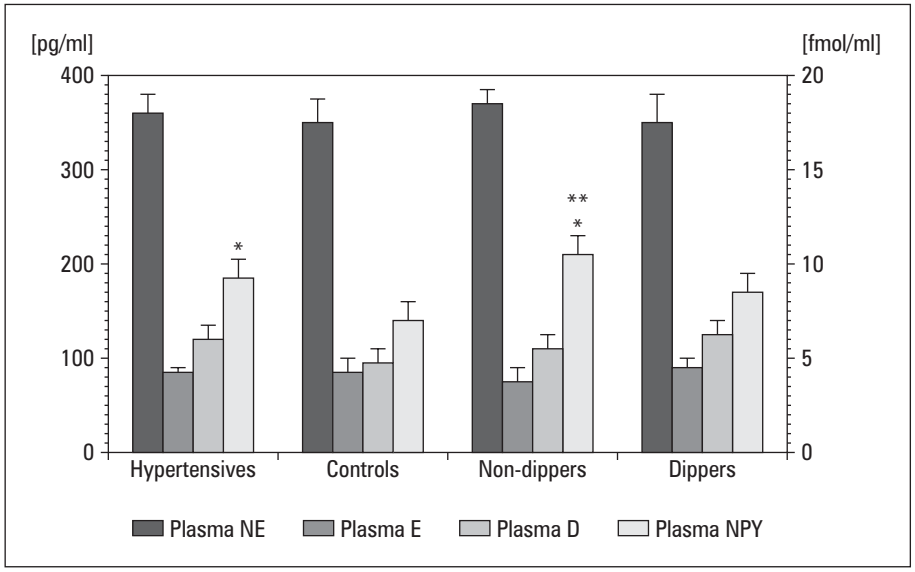

Figure 1. Plasma norepinephrine, epinephrine, dopamine and NPY concentrations in investigated groups. *p < 0,05 — hypertensives *vs.* controls and non-dippers *vs.* dippers, **p < 0,001 — non-dippers *vs.* controls

Rycina 1. Stężenie noradrenaliny, adrenaliny, dopaminy i NPY w badanych grupach. *p < 0,05 — chorzy z nadciśnieniem *vs.* grupa kontrolna i chorzy *non-dippers vs.* chorzy *dippers*, **p < 0,001 — chorzy *non-dippers vs.* grupa kontrolna

Table II. Urine catecholamine excretion in non-dippers, dippers and control group (mean ± SE)

Tabela II. Wydalanie katecholamin z moczem u chorych *non-dippers*, *dippers* i w grupie kontrolnej (średnia ± SE)

	Non-dippers	Dippers	Controls
uNEd [mg/16 h]	11,7 ± 0,7	12,6 ± 0,6	13,9 ± 1,0
uNEn [mg/8 h]	3,0 ± 0,2*	3,67 ± 0,3	4,5 ± 1,0
uEd [mg/16 h]	2,0 ± 0,2	2,4 ± 0,2	2,6 ± 0,2
uEn [mg/8 h]	0,41 ± 0,1	0,43 ± 0,05**	0,87 ± 0,2
uDd [mg/16 h]	75 ± 8	89 ± 8	109 ± 14
uDn [mg/8 h]	46 ± 4	57 ± 5	73 ± 8

uNEd — day urine norepinephrine excretion, uNEn — night urine norepinephrine excretion, uEd — day urine epinephrine excretion, uEn — night urine norepinephrine excretion, uDd — day urine dopamine excretion, uDn — night urine dopamine excretion
*p < 0,05 — uNEn in non-dippers *vs.* controls, **p < 0,05 — uEn in dippers *vs.* controls

Table III. Day and night-time urine catecholamine excretion in non-dippers and dippers

Tabela III. Dzienne i nocne wydzielanie katecholamin z moczem u chorych *non-dippers* i *dippers*

Group	Non-dippers		Dippers	
Time	Day	Night	Day	Night
uNE [mg/h]	0,82 ± 0,04	0,31 ± 0,04 *	0,84 ± 0,03	0,39 ± 0,04 *
uE [mg/h]	0,15 ± 0,002	0,04 ± 0,01 *	0,15 ± 0,01	0,04 ± 0,01 *
uD [mg/h]	5,2 ± 0,47	4,7 ± 0,38	6,26 ± 0,48	6,16 ± 0,5

uNE — urine norepinephrine excretion, uE — urine epinephrine excretion, uD — urine dopamine excretion
values are means ± SEM, *p < 0,001 day *vs.* night in dippers and non-dippers

Urine D excretion was similar during both periods in hypertensives with and without nocturnal BP decline (Table III). Nocturnal decline in urine NE and E excretion was similar in non-dippers and dippers.

It was observed that night urine NE excretion was significantly lower in non-dippers than in controls while dippers have significantly lower night urine E excretion as compared to controls (Table II).

Discussion

It is well known that sympathetic nervous system plays a central role in cardiovascular regulation in both health and disease. Many experimental and clinical data show that sympathetic activation may be implicated in the pathogenesis of coronary artery disease, heart failure or cardiac arrhythmias [9–12]. Evidence for increased sympathetic drive is particularly strong in hypertension. Many effective antihypertensive agents were found to work by interfering with sympathetic neurotransmission, blocking cardiac or vascular adrenoceptors and confirming adrenergic mechanisms in the hypertensive process [13]. Sympathetic activity disorders were also suggested as playing an important role in the regulation of abnormal circadian BP pattern. In our study we investigated hormonal indicators of sympathetic activity in hypertensive subjects with normal and disturbed circadian BP rhythm. Similar plasma and urine catecholamines in both healthy and hypertensive subjects were found. Data concerning plasma and urine catecholamines in hypertensives and controls are not homogeneous. Some authors revealed higher plasma and urine norepinephrine in hypertensive subjects than in healthy controls [14–17]. Higher plasma catecholamines were especially found in young patients with borderline hypertension [15, 16]. Other data showed no differences in catecholamines between hypertensives and controls. The above observations reflect the heterogeneity of subjects with essential hypertension in respect to sympathetic activity.

When patients were divided into dippers and non-dippers, our data showed no differences in plasma and urine catecholamines between the two groups. Similar plasma catecholamines in dippers and non-dippers were also observed by Schmieder *et al.* [18]. Kohara *et al.* [19] reported higher plasma NE in non-dippers as compared to dippers, while plasma E and urine catecholamines were similar in both groups [19]. It is established that sympathetic activity is reduced during sleep. Many data showed that plasma catecholamine concentration during nighttime was lower than during daytime. Also nocturnal urine excretion of catecholamines was lower than that observed during the day [20, 21]. Our data support the above observations. Urine catecholamine excretion was significantly lower during the night as compared to day excretion in healthy subjects. Also hypertensive dippers and non-dippers had lower urine catecholamine excretion during the night than during the day. When dippers and non-dippers were compared, no differences in day and night urine catecholamines were found between the two groups. Lack of differences in nocturnal urine catecholamine excretion between these groups may support the suggestion that night BP elevation in non-dippers is not a result of sympathetic enhancement. The above observations have at least one significant limitation. Although measurements of plasma and urine catecholamines provide useful information, this does not reflect precisely the „overall" sympathetic activity. In addition to the level of sympathetic neural outflow, plasma catecholamine concentration is influenced by prejunctional modulation of neurotransmitter release, the clearance, metabolism and uptake of the hormone from the circulation. Therefore new methods, such as microneurography and heart rate variability, were employed to investigate sympathetic activity [22, 23]. Interestingly Hojo *et al.* [24] showed lower sympathetic activity during 24 hours in non-dippers than in dippers, however in non-dippers sympathetic activity was not lowered during the night as it was in dippers. Kohara *et al.* [19], using spectral analysis of heart rate variability, reported higher sympathetic activity during the night than during the daytime in non-dippers. Other authors reported higher sympathetic activity measured with spectral analysis of BP and HR variability during all phases of sleep in non-dippers as compared to dippers [25]. According to presented data non-dippers are characterised by elevated sympathetic activity during the night. Our results did not confirm the above observations and even showed lower urine catecholamine excretion during the night in non-dippers as compared to controls. These observations may suggest the contribution of other factors than catecholamines in circadian BP regulation.

Apart from catecholamines, neuropeptide Y is a mediator of the sympatho-adrenomedullary system. Many data show that NPY is a potent, long-acting vasoconstrictor, which exerts direct action and modulates the effects of other mediators, such as norepinephrine, serotonin or angiotensin II [26]. The contribution of NPY in the pathogenesis of hypertension was shown elsewhere [27–29]. In the present study we found higher plasma NPY concentration in hyperten-

sive patients than in controls. Similar results were found by other authors [27, 29]. When hypertensives were divided into non-dippers and dippers, plasma NPY concentration was significantly higher in the former group. Plasma NPY was significantly higher in non-dippers than in controls, while no such difference was found between dippers and the control group. Simultaneously our data showed a decrease of urine catecholamine excretion during the night in non-dippers similar to that in dippers. Interestingly, urine NE excretion was significantly more decreased in non-dippers than in controls. One can speculate that the inhibition of NE excretion may be caused by NPY, via an activation of presynaptic NPY receptors [30]. Although we observed decreased nocturnal NE excretion in non-dippers, its influence on BP and HR was not reduced. Possibly high plasma NPY may enhance the influence of NE on night BP.

As was shown before, urine and plasma NE were similar in non-dippers and dippers, while plasma NPY was different in both groups. However it is well known that co-stored NPY and NE are simultaneously excreted in answer to different stimuli. We did not observe such parallel changes in NPY and NE in our patients. This observation may be related to the mechanism mentioned above, i.e. to the inhibition of NE excretion by higher plasma NPY via an activation of presynaptic NPY receptor. Another explanation is that NPY and NE interplay is affected by other active hormones which may play a role in diurnal BP changes.

Some other confirmations of the role of NPY in non-dipper phenomenon exist. It was previously described that NPY is a vasoconstrictor with no influence on HR [31]. Other data revealed that NPY may influence the presynaptic inhibition of acetylocholine release from parasympathetic nerve endings [32, 33]. We found that non-dippers are characterised by significant night HR decrease while their BP was not decreased. Kohara *et al.* [19] showed in non-dippers that night HR was decreased despite higher nocturnal sympathetic activity. One can speculate that NPY may generate lower nocturnal parasympathetic activity and therefore influence HR decline at normal at even increased sympathetic activity.

In conclusion, a suggestion can be made that NPY modulate the influence of the sympathetic nervous system on the cardiovascular system in hypertensive subjects with a lack of nocturnal blood pressure decline. The findings of this study need to be confirmed by circadian cycle of NPY in healthy and hypertensive subjects. The lack of diurnal NPY rhythm is a limitation of our study. However, to our knowledge there have been no such investigations until now.

Summary

Background The aim of the study was to investigate the relationship between biochemical indices of sympathetic activity and diurnal blood pressure rhythm in patients with essential hypertension.

Material and methods The study included 68 patients with mild-to-moderate essential hypertension (EH) (mean age 40 ± 1 yrs; 20 F, 48 M). The control group consisted of 25 healthy normotensive volunteers (C) (mean age 38 ± 1 yrs; 8F, 17M). Twenty-four hour ambulatory blood pressure monitoring was obtained using the SpaceLabs 90207. Blood samples for NPY and catecholamines were taken. Urine for catecholamines determination was collected.

Results In patients with EH NPY, plasma concentration was significantly higher as compared to C. Plasma catecholamine and urine catecholamine excretion was similar in patients with EH and in C. Patients with EH were divided into two groups: dippers (46 pts) and non-dippers (22 pts). In EH, the NPY plasma concentration was significantly higher in non-dippers than in dippers (10,6 ± 1 *vs.* 8,6 ± ± 1 fmol/mL, respectively, $p < 0,05$). No differences in plasma catecholamine and urine catecholamine excretion were found between dippers and non-dippers. Urine catecholamine excretion during night-time was significantly lower as compared to day-time excretion in dippers and non-dippers. No differences between the groups were found with regard to day-time and night-time catecholamine excretion.

Conclusion NPY may play a role in diurnal blood pressure rhythm disturbances in non-dippers with EH. Catecholamines appear not to influence non-dipper phenomenon.

key words: NPY, catecholamines, 24-h ambulatory blood pressure monitoring, dippers, non-dippers

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