

The Role of 24-hour Ambulatory Blood Pressure Monitoring in Hypertensive Patients with Normal-tension Glaucoma

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SUMMARY

Introduction Extreme dippers are patients with a nocturnal fall of blood pressure (BP) of more than 20%, dippers have normal diurnal rhythm and decrease of BP of 10–15%, while patients with a nocturnal BP fall of less than 10% are considered to be non-dippers.

Objective The aim of this study was to compare 24-hour ambulatory BP monitoring results of normal-tension glaucoma (NTG) patients with NTG suspects, as well as to determine whether NTG patients are more prone to daytime/nighttime systemic arterial BP and heart rate oscillations in comparison to NTG suspects.

Methods This was a prospective, cross-sectional and observational study of 57 hypertensive patients (39 female and 18 male), all examined at the Eye and the Cardiology Clinic, Clinical Center of Serbia in Belgrade, between November 2011 and March 2012. Before 24-hour ambulatory BP monitoring, complete ophthalmological examination was performed (intraocular pressure was measured with both Goldmann applanation and dynamic contour tonometer, as well as with computerized perimetry and Heidelberg retinal tomography).

Results There was no statistically significant difference between NTG patients and NTG suspects both in systolic daytime (131.86–141.81 mmHg, SD=±14.92 vs. 129.67–141.83 mmHg, SD=±13; p=0.53) and nighttime measurements (117.1–129.7 mmHg, SD=±18.96 vs. 112.11–127.59 mmHg, SD=±16.53; p=0.53) as well as diastolic daytime (74.55–80.37 mmHg, SD=±8.72 vs. 75.19–82.41 mmHg, SD=±7.72; p=0.58) and nighttime measurements (65.66–71.48 mmHg, SD=±8.73 vs. 67.12–73.78 mmHg, SD=±7.11; p=0.34). There was no statistically significant difference between NTG patients and NTG suspects in heart rate during the day (72.73–76.36 beats per minute [bpm], SD=±5.44 vs. 72.15–76.45 bpm, SD=±4.59; p=0.43) nor during the night (64.4–71.9 bpm, SD=±6.74 vs. 68.02–72.48 bpm, SD=±4.76; p=0.11).

Conclusion No statistically significant difference was found between NTG patients and NTG suspects in regard to their systolic and diastolic BP measured both during daytime and nighttime. NTG patients had lower nocturnal BP fall (both systolic and diastolic) than NTG suspects.

Keywords: normal-tension glaucoma; 24-hour ambulatory blood pressure monitoring; arterial hypertension; dipper and non-dipper

INTRODUCTION

Twenty-four-hour ambulatory blood pressure monitoring (24-hour ABPM), as an important diagnostic procedure in cardiology, could be very helpful with glaucoma as well. In the pathogenesis of glaucomatous optic neuropathy (GON), systemic arterial hypotension, hypertension and altered ocular blood flow play important roles. Impairment in ocular blood flow is usually caused by local and systemic vascular risk factors (vasosclerosis, capillary dropout, vasospasms, etc.).

Nighttime arterial blood pressure (BP) depression (i.e. dipping), hemodynamic crises and extensive hypertensive medication in arterial hypertension play important roles in GON [1-8].

It is already known that intraocular pressure (IOP) fluctuations increase with open-angle glaucoma [9]. Presence of autoregulation dys-

function in glaucoma, with systemic BP variability, leads to ischemic episodes at the optic nerve head and glaucoma progression [3].

Generally speaking, in physiological conditions, BP varies according to the period of the year (it decreases in wintertime), day and night time (lower BP during sleep, also known as a BP dip), and short-time, day-night fluctuations, influenced by individual activities and habits (sports, eating, etc.) [10, 11, 12].

Disturbed diurnal BP variations are strongly connected with an increased risk for cardiovascular diseases in hypertensive patients. Diminished nocturnal BP fall, as that in non-dippers, is a typical subgroup with an abnormal diurnal BP variation associated with higher risk of all main target organs (the brain, heart and kidneys) damage in comparison to dippers (with normal nocturnal BP fall) [11, 13, 14, 15]. A group with significant nocturnal BP fall – extreme dippers – was identified among dippers.

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Reported mostly among elderly hypertensive patients, extreme dippers have a higher risk of cerebrovascular diseases than dippers [16].

OBJECTIVE

The aim of this study was to compare 24-hour ABPM results of normal-tension glaucoma (NTG) patients with NTG suspects, and to try to answer whether NTG patients are more prompt to daytime/nighttime systemic arterial BP and heart rate (HR) oscillations in comparison to NTG suspects.

METHODS

A prospective, cross-sectional, and observational study was conducted on consecutive patients, referred or recruited, attending the outpatient service of the Ophthalmology Department. All patients were examined at the Eye and the Cardiology Clinic of the Clinical Center of Serbia in Belgrade, between November 2011 and March 2012. Patients met inclusion and exclusion criteria.

This study was approved by the Ethics Committee of the University Eye Clinic, Clinical Center of Serbia, and was conducted in accordance with Good Clinical Practice and the tenets of the Declaration of Helsinki. Patients signed an informed consent form before inclusion.

All participants were required to meet the following inclusion criteria: age equal to or higher than 50 years; clinical diagnosis of NTG in early to moderate stage or NTG suspects; IOP equal to or lower than 21 mmHg with or without treatment, depending on the group; postmenopausal status without hormonal replacement therapy (women) and willingness to comply with the investigators and protocol indications.

Patients were excluded if they were positive with the following: type of glaucoma other than NTG; previous treatment with ocular filtering surgery; history of previous refractive surgery; acute myocardial infarction or stroke within previous three months; diabetes; history of progressive retinal or optic nerve disease of any cause; and asthma or any other obstructive pulmonary disease.

We examined 57 hypertensive patients (39 female and 18 male). All 57 patients had arterial hypertension, which was being medically treated. Thirty-seven patients had NTG, treated with topical antiglaucomatous drops. On the day of the examination, 24-hour ABPM found higher BP in 32 NTG patients and 20 NTG suspects. Five NTG patients had compensated BP. Control group consisted of hypertensive patients suspected of having NTG, but without topical antiglaucomatous treatment. The patients' demographic characteristics are summarized in Table 1.

Before 24-hour ABPM, all patients underwent complete ophthalmological examination: visual acuity (Snellen chart), slit lamp (Haag Streit AG, Koeniz, Switzerland) anterior and posterior eye segment exam, gonioscopy (G-1 One-Mirror Glass Trabeculum Lens; Volk Optical Inc.,

Table 1. Demographic data of the studied patients

Characteristics	NTG	NTG suspects	p-value
Number of patients	37	20	
Mean age in years (SD)	65.1 (12.7)	59.3 (13.97)	0.12
Sex, n (%)	Female	14 (70.0)	0.91
	Male	12 (32.4)	6 (30.0)

SD – standard deviation

Mentor, OH, USA), Goldmann applanation tonometry (Goldmann tonometer; Haag Streit AG, Koeniz, Switzerland) and dynamic contour tonometry (PASCAL dynamic contour tonometer; Ziemer Ophthalmic Systems, Port, Switzerland), central corneal thickness with ultrasound pachymetry (Palm Scan AP 2000, ophthalmic ultrasound; Micro Medical Devices, Inc., Clabasco, CA, USA), visual field examination (Model 750; Humphrey-Zeiss, San Leandro, CA, USA) and confocal scanning laser retinal tomography (HRT II; Heidelberg Engineering Inc. Heidelberg, Germany). The IOP measurements of each patient were taken three times on the same day between 08:00 a.m. and 11:00 a.m. by the same ophthalmologist, respectively.

NTG was defined as a glaucomatous optic disc progression, diagnosed clinically, with CVF and with HRT II, with IOP less than 21 mmHg.

Patients with NTG had glaucomatous optic nerve head cupping and glaucomatous visual field defects as defined by the European Glaucoma Society, in the absence of retinal or neurological disease affecting the visual field. Field loss was considered significant when (a) glaucoma hemifield test was abnormal, (b) three points not contiguous with the blind spot were confirmed with $p < 0.05$ probability of being normal (one of which should have $p < 0.01$), or (c) corrected pattern standard deviation was abnormal with $p < 0.05$ [17].

All parameters were confirmed on two consecutive visual fields performed with Humphrey visual field analyzer (full threshold program 24–2).

The IOP was determined three times for each patient, using dynamic contour tonometry and Goldmann applanation tonometry consecutively.

The IOP value above 21 mmHg was neither measured nor had it been documented in the patients' history. At the time of the study, 32 patients with NTG did not receive local IOP-lowering medications. In all, 20 patients were on local IOP-lowering medications (β -blockers, carbonic anhydrase inhibitors, brimonidine, prostaglandins or combinations). None of the control subjects received local treatment.

In all subjects visual acuity was 20/40 or better, and patients with refractive aberrations of more than seven diopters or with diabetes mellitus were excluded from this study. The healthy control subjects had no history of ophthalmological disease. Automatic static white-on-white and short-wavelength automated perimetry did not reveal visual field loss.

Visual field examinations were performed with the Humphrey field analyzer using the white-on-white 24–2 full threshold program. Horizontal and vertical cup-to-disc ratios were measured by the Heidelberg retina tomo-

graph, a confocal laser scanning system for acquisition and analysis of three-dimensional images of the posterior segment of the eye, especially assessment of the glaucomatous optic nerve head. The gathered data served to quantitatively describe the retinal topography and the follow-up topographic changes.

All subjects underwent a detailed ophthalmological examination and patients' histories were explored with special interest on cardiovascular risk factors (i.e. diagnosis of treated hypertension, arterial hypotension, history of cardiovascular events [e.g. myocardial infarction], nicotine abuse, obesity [body mass index value of 426]). Patients with diabetes were excluded from the study. No other systemic diseases were defined as exclusion criteria. The systemic medications were recorded, but only the status of treated arterial hypertension was included in the analysis.

All participants underwent 24-hour ABPM on a usual working day. We measured 24-hour ABPM in hypertensive BP and NTG patients as well as NTG suspects. Variabilities in daytime BP and nighttime BP dip, in systolic, diastolic and mean BP, as well as in data of the HR, were calculated. We measured BP every 30 minutes during the day and every one hour during the night.

Extreme dippers are patients with marked nocturnal fall (more than 20%) in BP. Patients with normal diurnal rhythm and decrease of BP of 10–15% are dippers. Non-dippers are patients with absent (less than 10%) nocturnal fall in BP.

Ambulatory BP monitoring was performed in all subjects included in this prospective study with a SpaceLabs ambulatory BP monitor 90207 (Space Labs Medical Inc., Redmond, WA, USA). Systolic and diastolic BP values were measured, and the mean arterial BP was calculated from each single measurement (diastolic BP $\times 1/3$ [systolic BP - diastolic BP]) [18].

Blood pressure measurements were performed every 30 minutes during the day and night. The obtained values were analyzed separately for the day and for the night. In accordance with the Scientific Committee Document on Non-Invasive Ambulatory Blood Pressure Monitoring [19], daytime was defined from 8:00 a.m. to 8:00 p.m., and nighttime from midnight to 6:00 a.m. Blood pressure measurements between the defined time intervals were excluded from the analysis, in order to obtain a better separation between daytime activities and sleep [20]. All subjects were announced to sleep during the nighttime interval.

The mean systolic, diastolic and mean arterial BP was calculated from all the single measurements for the day and night. A variability index was defined as the standard deviation of all single BP measurements during the day and the night [21]. Nighttime BP dip was also determined (i.e. (mean BP during the day, mean BP during the night) / mean BP during the day). The patients were defined as dippers (nighttime BP depression of 10–15%) and non-dippers (nighttime BP depression of 10%) [22].

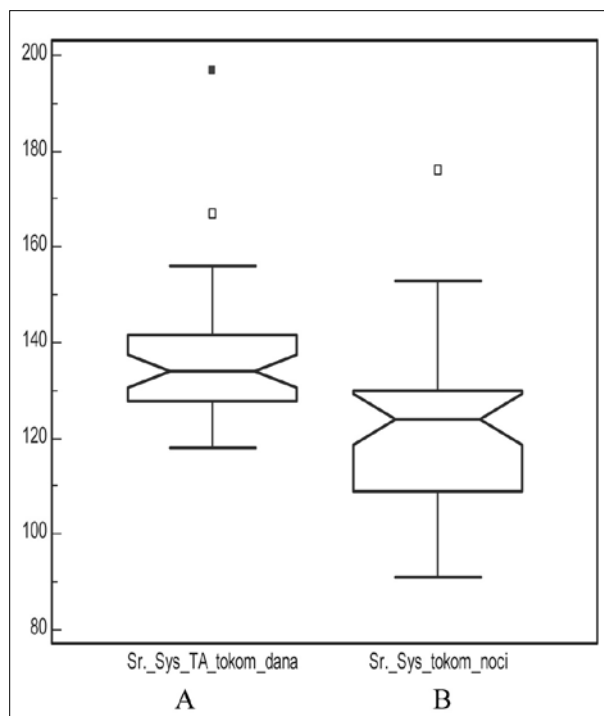
Statistical analysis was performed using MedCalc 11.5.1.0 software package (MedCalc Software, Mariakerke, Belgium). For the statistical analysis of this study, one eye of each subject was randomly chosen. Blood pressure

values and clinical data were compared with analysis of variance (ANOVA) as computed with StatView software (SAS institute Inc., Cary, NC, USA). Descriptive statistics (mean \pm standard deviation) and 95% confidence intervals (95% CIs) were used to report demographic and ocular baseline characteristics. The data were tested for normal distribution using the Kolmogorov–Smirnov test. As data were normally distributed, the two-tailed, paired Student's t-test was used to evaluate IOP and hemodynamic parameters by intragroup comparisons made between the values obtained under baseline conditions and treatment conditions. Findings of probability of a type error less than 0.05 were considered to be statistically significant.

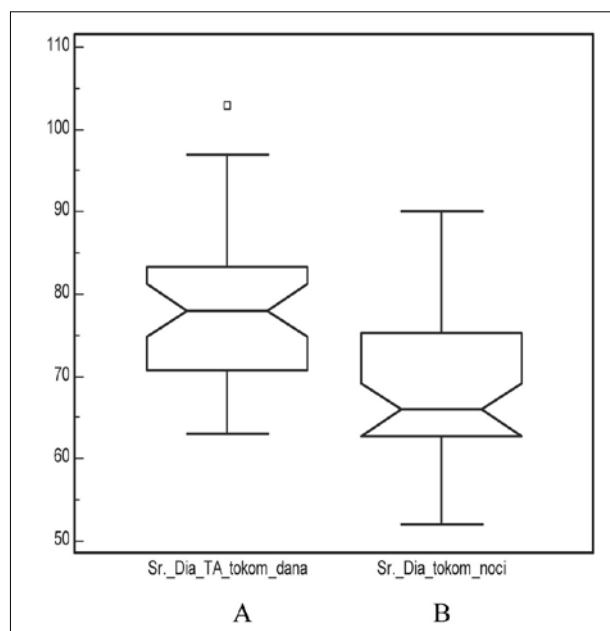
RESULTS

Among NTG patients, average systolic BP data during the day were 95% CI for the mean (131.9–141.8); SD= \pm 14.9; $p < 0.0001$; and during the night 95% CI for the mean (117.1–129.7); SD= \pm 18.96; $p < 0.0001$ (Graph 1). Average diastolic BP data during the day were 95% CI for the mean (74.6–80.4); SD= \pm 8.7; $p < 0.0001$; and during the night 95% CI for the mean (65.7–71.5); SD= \pm 8.7; $p < 0.0001$ (Graph 2). Average HR data during the day were 95% CI for the mean (72.7–76.4); SD= \pm 5.4; $p < 0.0001$; but 95% CI for the mean (67.4–71.9); SD= \pm 6.7; $p < 0.0001$, during the night (Graph 3).

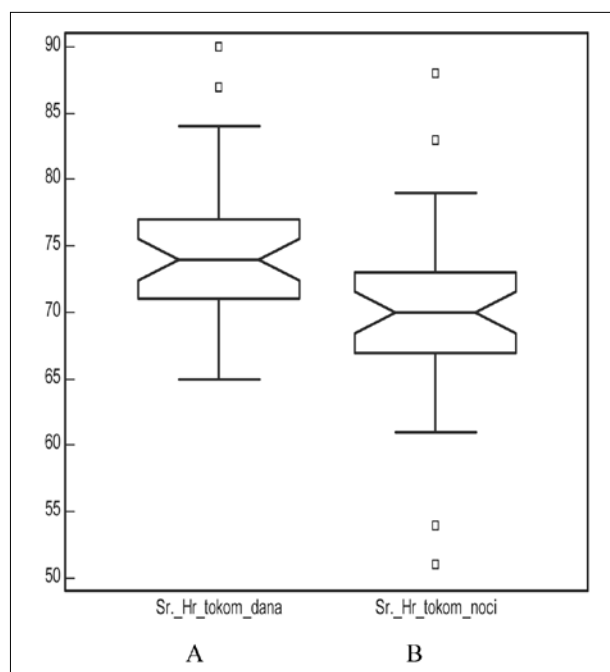
Among NTG suspects, average systolic BP data during the day were 95% CI for the mean (129.7–141.8); SD= \pm 13; $p < 0.0001$; and during the night 95% CI for the mean (112.1–127.6); SD= \pm 16.5; $p < 0.0001$ (Graph 4). Average diastolic BP data during the day were 95% CI for the mean (75.2–82.4); SD= \pm 7.7; $p < 0.0001$; and during the



Graph 1. Average systolic blood pressure data during the day (A) and night (B)



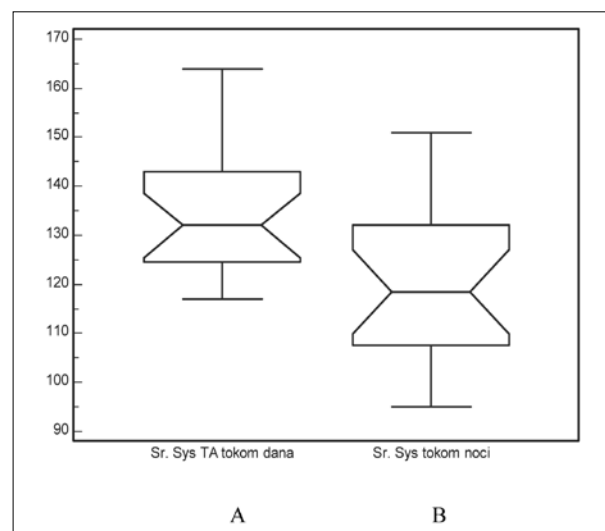
Graph 2. Average diastolic blood pressure data during the day (A) and night (B)



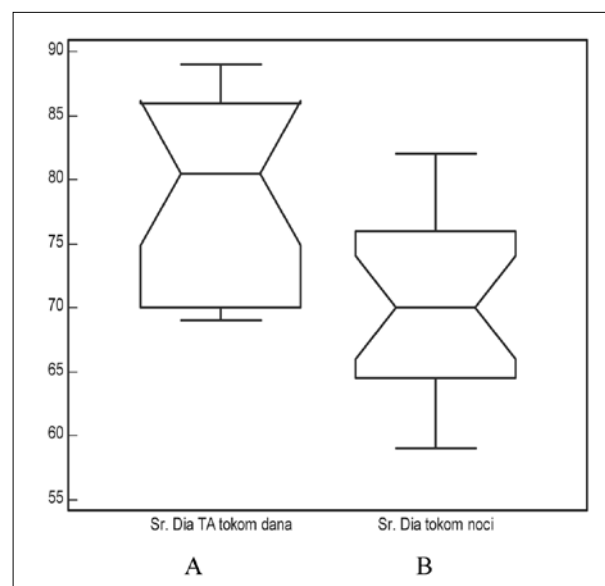
Graph 3. Average data of the heart rate during the day (A) and night (B)

night 95% CI for the mean (67.1–73.8); $SD=\pm 7.1$; $p<0.0001$ (Graph 5). Average HR data during the day were 95% CI for the mean (72.2–76.4); $SD=\pm 4.6$; $p<0.0001$; but 95% CI for the mean (68–72.5); $SD=\pm 4.8$; $p<0.0001$, during the night (Graph 6).

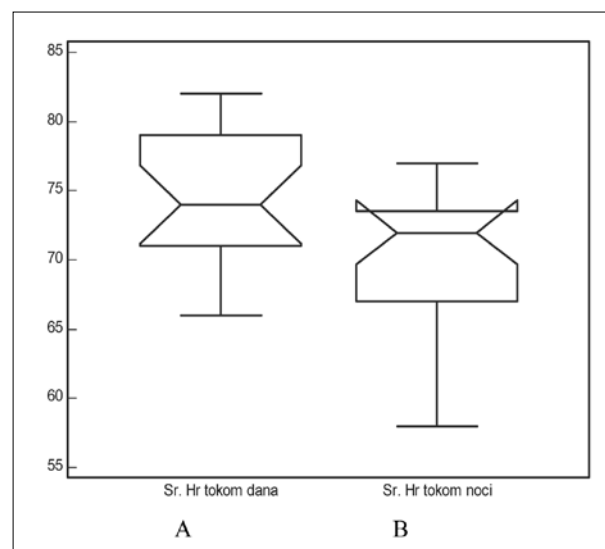
Physiologically average systolic and diastolic BPs were higher during the daytime, but there was no statistically significant difference between NTG patients and NTG suspects in either systolic daytime (131.86–141.81 mmHg, $SD=\pm 14.92$ vs. 129.67–141.83 mmHg, $SD=\pm 13$; $p=0.53$) or nighttime measurements (117.1–129.7 mmHg, $SD=\pm 18.96$ vs. 112.11–127.59 mmHg, $SD=\pm 16.53$; $p=0.53$), nor diastol-



Graph 4. Average systolic blood pressure data during the day (A) and night (B)



Graph 5. Average diastolic blood pressure data during the day (A) and night (B)



Graph 6. Average data of the heart rate during the day (A) and night (B)

ic daytime (74.55–80.37 mmHg, SD=±8.72 vs. 75.19–82.41 mmHg, SD=±7.72; p=0.58) or nighttime measurements (65.66–71.48 mmHg, SD=±8.73 vs. 67.12–73.78 mmHg, SD=±7.11; p=0.34). During nighttime HR physiologically decreased. There was no statistically significant difference between NTG patients and NTG suspects in HR during the day (72.73–76.36 bpm, SD=±5.44 vs 72.15–76.45 bpm, SD=±4.59; p=0.43) nor during the night (64.4–71.9 bpm, SD=±6.74 vs 68.02–72.48 bpm, SD=±4.76; p=0.11).

Among NTG patients (37) there were 21 dippers, 13 non-dippers and three extreme dippers. Among NTG suspects (20) there were two non-dippers and 18 dippers.

DISCUSSION

Decreased ocular blood flow is a significant factor in GON [23]. Significant is an influence of BP on ocular perfusion and therefore its impact on GON. Literature shows that arterial hypertension [2, 3, 6] and hypotension [1, 4, 5] have their impact on GON (both NTG and primary open angle glaucoma [POAG]), but usually have no effect on control subjects [24, 25], similar to our results. Interesting fact is that diastolic perfusion pressure (PP) below 30 mmHg indicates six times higher risk for glaucoma than higher PP [26].

Similar to our study results, numerous studies reported that night time BP dip increased in NTG [7, 8] and POAG [24, 25] patients. Opposite to these findings, smaller dips than those in control subjects were reported in progressive GON [27]. All the studies agreed that the nighttime BP dip is significant in physiological range (10–20% of daytime values) [7, 11, 24, 25]. Increased BP variability in progressive NTG was reported by Kashiwagi et al. [27], while Bechettoille et al. [1] showed higher systolic BP variability in focal ischemic glaucoma compared to POAG, and they detected arterial hypotension as one of the components of the vascular factor, during the examination of a patient with NTG. This is one element in preserving the best possible perfusion of the optic nerve.

In our study, average systolic and diastolic BP was higher during daytime, due to physiological conditions, but there was no statistically significant difference between

NTG patients and NTG suspects. During nighttime HR physiologically decreases, without statistically significant difference between NTG patients and NTG suspects.

Arterial hypertension, as a systemic disease, also involves small vessels, with vasosclerosis, leads to end-organ damage (increased peripheral vascular resistance), usually combined with other cardiovascular risk factors. Optic nerve head is also an end-organ, and arterial hypertension impacts it with decreased perfusion [5].

Perfusion pressure is crucial in pathogenesis of GON. Blood flow depends on peripheral vascular resistance and PP [18]. Hypotension, hypertension, night time BP depression, BP and intraocular pressure fluctuations affect PP. If the autoregulatory capacity of the optic nerve head is low, increased BP fluctuations affect higher PP variability and may lead to ocular tissues ischemia in GON [25, 27]. Also, nighttime BP fluctuations lead to ocular PP deficit. Ocular PP is also linked with diurnal intraocular pressure IOP fluctuations. Higher diurnal IOP fluctuations during the daytime are already well known in GON [28]. Body position (supine) during the day and nighttime does not influence IOP variations in glaucoma patients and control subjects [28].

According to Plange [29], nighttime BP fluctuations could be a relevant factor in the pathogenesis of NTG. This study could not confirm a reduced BP level in NTG patients. In contrast, BP was increased at night in the presented NTG subjects [29].

Systemic risk factors (arterial hypertension and cardiovascular risk factors) are reported to be similar to both NTG patients and control subjects [29]. In our study all the patients were hypertensive.

CONCLUSION

In our study there were more NTG patients who were dippers (with three extreme dippers) than those who were NTG suspects. There was no statistically significant difference between NTG patients and NTG suspects in both systolic and diastolic daytime and nighttime BP values. NTG patients had lower nocturnal BP fall (both systolic and diastolic) than NTG suspects.

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Улога двадесетчетворчасовног амбулантног праћења крвног притиска код особа с хипертензијом и нормотензивним глаукомом

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КРАТАК САДРЖАЈ

Увод „Екстремни дипери“ (енгл. *dippers*) су особе којима се током ноћи крвни притисак смањује за више од 20%. „Дипери“ имају нормалан дневни ритам, а снижење њиховог крвног притиска је за 10–15%. Особе код којих ноћни крвни притисак пада за мање од 10% зову се „нондипери“ (енгл. *non-dippers*).

Циљ рада Циљ истраживања је био да се упореде резултати 24-часовног амбулантног мерења крвног притиска код пацијената с нормотензивним глаукомом и пацијената за које се сумња да болују од њега. Покушало се да одговори на питање да ли су пацијенти с нормотензивним глаукомом осетљивији на дневно-ноћне осцилације у системском артеријском крвном притиску и срчаном пулсу од пацијената за које се сумња да болују од нормотензивног глаукома.

Методе рада Ово проспективно унакрсно истраживање обухватило је 57 испитаника (39 жена и 18 мушкараца) с хипертензијом. Болесници су прегледани од новембра 2011. до марта 2012. године на Клиници за очне болести и Клиници за кардиологију Клиничког центра Србије. Пре 24-часовног амбулантног мерења крвног притиска сви испитаници су подвргнути офталмолошком прегледу, при којем је интраокуларни притисак мерен и Голдмановим (*Goldmann*) апланационим и динамичким контурним тонометром, те током којег су примењене и компјутеризована периметрија и Хајделберг ретинална томографија.

Резултати Нису утврђене статистички значајне разлике између испитаника с нормотензивним глаукомом и испитаника за које се сумња да болују од њега, ни у систолном притиску током дана (131,86–141,81 mm Hg, SD=±14,92, према 129,67–141,83 mm Hg, SD=±13; p=0,53) и током ноћи (117,1–129,7 mm Hg, SD=±18,96, према 112,11–127,59 mm Hg, SD=±16,53; p=0,53), као ни у дијастолном притиску током дана (74,55–80,37 mm Hg, SD=±8,72, према 75,19–82,41 mm Hg, SD=±7,72; p=0,58) и током ноћи (65,66–71,48 mm Hg, SD=±8,73, према 67,12–73,78 mm Hg, SD=±7,11; p=0,34). Статистички значајна разлика није утврђена ни у вредности срчаног пулса између испитаника с нормотензивним глаукомом и испитаника за које се сумњало да болују од њега, како ни током дана (72,73–76,36 b/min, SD=±5,44, према 72,15–76,45 b/min, SD=±4,59; p=0,43), тако ни током ноћи (64,4–71,9 b/min, SD=±6,74, према 68,02–72,48 b/min, SD=±4,76; p=0,11).

Закључак Није забележена статистички значајна разлика у систолном и дијастолном крвном притиску између болесника с нормотензивним глаукомом и оних за које се сумњало да болују од њега ни преко дана, ни током ноћи. Код испитаника с нормотензивним глаукомом установљен је мањи пад крвног притиска током ноћи (и систолног, и дијастолног) у односу на испитанике за које се сумњало да болују од ове врсте глаукома.

Кључне речи: нормотензивни глауком; двадесетчетворчасовно амбулантно мерење крвног притиска; артеријска хипертензија; дипери и нондипери