Circadian rhythm of blood pressure and its related factors in patients with hypertension

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Abstract

Introduction. Hypertension is a common, almost asymptomatic, detectable and treatable disease. Abnormal circadian rhythm of blood pressure is associated with increased risk of disorders such as sleep problems, metabolic syndrome, cardiovascular disease and cancer. On the other hand, 24-hour blood pressure monitoring, a method for detecting the abnormal pattern of blood pressure decrease over night, gets less clinicians' attention. This study aims to determine the circadian rhythm of blood pressure and its related factors in hypertensive patients.

Material and methods. This analytical cross-sectional study was done in 2015. The study population was patients referred to the offices and clinics in the city of Qom and 183 of them were selected based on convenience sampling. Data were collected by use of demographic checklist and the results of 24-hour monitoring of blood pressure.

Results. The mean age of patients was 52.08 ± 14.16 years, and 57.9% were female. The mean duration of hypertension history was 4.32 ± 4.96 years. 77% of the patients had non-dipper blood pressure pattern. In terms of age ($p = 0.31$) and duration of hypertension ($p = 0.93$), gender ($p = 0.55$) and type of hypertension treatment ($p = 0.96$), there was no significant difference between the two groups of dippers and non-dippers.

Conclusions. In this study, the frequency of non-dipper pattern in patients with hypertension was higher than in similar studies. Since the importance of 24-hour blood pressure monitoring for proper evaluation and management, it is recommended that hypertensive patients undergo 24-hour blood pressure monitoring.

Key words: hypertension, circadian BP rhythm, ambulatory blood pressure monitoring, non-dipper, dipper

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Streszczenie

Wstęp. Nadciśnienie tętnicze jest częstą, niemal bezobjawową, wykrywalną i poddającą się leczeniu chorobą. Nieprawidłowy dobowy rytm ciśnienia tętniczego wiąże się ze zwiększonym ryzykiem zaburzeń, takich jak problemy ze snem, zespół metaboliczny, choroby sercowo-naczyniowe i nowotwory. Jednak całodobowe monitorowanie ciśnienia tętniczego, metoda pozwalająca wykryć nieprawidłowości w zakresie nocnego spadku ciśnienia tętniczego, cieszy się stosunkowo małym zainteresowaniem wśród lekarzy. Badanie przeprowadzono w celu określenia dobowego rytmu ciśnienia tętniczego i powiązanych czynników u chorych z nadciśnieniem tętniczym.

Materiał i metody. To analityczne przekrojowe badanie przeprowadzono w 2015 roku. Badana populacja obejmowała pacjentów gabinetów lekarskich i klinik w mieście Qom, a do analizy włączono próbę 183 chorych. Zgromadzono odpowiednie dane demograficzne chorych oraz wyniki całodobowego monitorowania ciśnienia tętniczego.

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Wyniki. Średni wiek chorych wynosił 52,08 ± 14,16 roku. Kobiety stanowiły 57,9% uczestników. Średnia czas od wykrycia nadciśnienia tętniczego wynosił 4,32 ± 4,96 roku. U 77% uczestników stwierdzono brak nocnego spadku ciśnienia tętniczego (profil *non-dipper*). Nie stwierdzono istotnych różnic pod względem wieku (p = 0,31), czasu od wykrycia nadciśnienia tętniczego (p = 0,93), płci (p = 0,55) i metody leczenia nadciśnienia tętniczego (p = 0,96) między osobami z prawidłowym nocnym spadkiem ciśnienia tętniczego (profil typu *dipper*) a osobami z profilem typu *non-dipper*.

Wnioski. Częstość braku prawidłowego spadku ciśnienia tętniczego w godzinach nocnych była w badaniu autorów większa niż w innych tego typu badaniach. Z uwagi na znaczenie całodobowego monitorowania ciśnienia tętniczego w diagnostyce i leczeniu ciśnienia tętniczego zaleca się wykonywanie tego badania u chorych z nadciśnieniem tętniczym.

Słowa kluczowe: nadciśnienie tętnicze, dobowy rytm ciśnienia tętniczego, całodobowe monitorowanie ciśnienia tętniczego, *non-dipper*, *dipper*

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Introduction

Hypertension is a common, treatable and often asymptomatic disease. However, if untreated, it usually leads to fatal complications [1]. With the rising trend of obesity and average age in populations, the incidence of hypertension is rising. This process can be observed not only in developed but also in developing countries [1, 2]. Environmental and genetic factors might contribute to racial and regional differences in blood pressure and prevalence of hypertension. Various surveys indicate a significant increase in the prevalence of hypertension in the Middle East [3]. In Iran, the prevalence of hypertension in adults is estimated from 25 to 35 percent [4].

Circadian rhythms are known to affect body functions and are controlled by the hypothalamus and higher centres of the brain. Changes in the rhythm of blood pressure throughout the day in humans and different species of mammals has been documented. Some believe that these throughout-the-day changes are in connection with endocrine effects, while others believe that they are of nervous origin [5]. Abnormal distribution of these circadian rhythms of blood pressure is connected with increased risk of developing various disorders including sleep problems, metabolic syndrome, cardiovascular diseases and cancer [6, 7].

Diagnosis of hypertension and making the decision to initiate pharmacotherapy are based on blood pressure measurements in doctor's office [8]. Hassler and Burnier believe the right time to administer medical treatment and new-generation hypertension medications to be affected by the importance of understanding the circadian rhythm of blood pressure [9]. In the conventional method of blood pressure control, technical and human errors of the individual measurements and the changes in blood pressure impair the accuracy of the figures obtained. A better method, which is rapidly becoming more common, is 24-hour blood pressure monitoring (Ambulatory Blood Pressure Monitoring: ABPM) [10].

According to Staessen et al., patients' adherence to ABPM can lead to changes in treatment, reduction in combination therapy (multidrug regimens) and even total withdrawal of antihypertensive drugs and improved blood pressure control [11]. With the increasing clinical use of ABPM, doctors were able to understand the circadian changes in blood pressure [6]. The data from ABPM showed that the blood pressure increases in the morning, stays pretty steady up to the afternoon and declines in the evening. These changes, however, increase in response to stress and activities, and decrease at rest, such as when at home [9].

In some people, the night-time reduction in the blood pressure does not happen, dividing hypertensive patients into two classes: non-dippers and dippers [9]. Non-dipper blood pressure pattern is a reduction of less than 10% in night-time blood pressure and dipper pattern is a reduction of 10% to 20% in night-time blood pressure [6, 12].

ABPM is also a simple and convenient way to describe the patterns of blood pressure in patients with hypertension and identify people with invisible latent hypertension, people having abnormal patterns of blood pressure decline and people who might not be identified using the standard measurement of blood pressure [13, 14]. The importance of 24-hour blood pressure monitoring has been

verified in recent studies. In order to determine the prognosis of cardiovascular diseases, the significance of the blood pressure measured by ABPM out of the doctor's office is greater than that of the blood pressure measured by a doctor in the office [15]. As mentioned, ABPM is a method for the detection of abnormal decline in night-time blood pressure which is an independent risk factor for future cardiovascular events [16]. Kabutoya et al. observed an increase in the risk of cardiovascular diseases with the pattern of no decline in night-time blood pressure (non-dipping) and heart rate [17]. In other words, people having the pattern of blood pressure where the heart rate does not drop at night, have a poorer cardiovascular prognosis.

Currently, 24-hour blood pressure monitoring is not done routinely for diagnosis, follow-up and treatment of patients with hypertension. Regarding to the aforesaid, this study aimed to determine the circadian rhythms of blood pressure and related factors in patients with hypertension.

Material and methods

This cross-sectional analytical study was conducted in 2015. The study population consisted of patients referred to the offices and clinics in Qom, 183 of whom were selected.

The sample size was calculated to be 183 based on the formula of prevalence determination. Inclusion criteria were the age of over 30 years and having hypertension. Data were collected using a checklist form and 24-hour blood pressure monitoring devices. The checklist of this study consists of two parts: the first part consists of demographic characteristics (age, sex, duration of hypertension, family history of hypertension, type of medication (monotherapy/ /combined) and the second part is the result of 24-hour blood pressure recorded. Positive family history in this study was considered having first--degree relatives diagnosed as hypertensive. A history of coronary artery disease was considered cardiovascular disease history in this study.

ENVITE C device (made in Germany) was used for the 24-hour blood pressure monitoring in this study. The 24-hour blood pressure monitoring technique was as follows: the first step was to choose a reliable and appropriate device. In general, devices measure the blood pressure in two ways; using either oscillometric or auscultatory method; however, most large studies are based on oscillometric ABPM. Therefore, because of the lower level of errors in this method, it is referred to as the method of choice. Devices used in the study were also the oscillometric type. All automated blood pressure measuring devices must pass the standardized tests in the US, the UK or Europe successfully [18, 19].

Automatic 24-hour blood pressure monitors using oscillometric method are widely available. These devices do not measure the blood pressure directly, but the mean arterial blood pressure and then the SBP (systolic blood pressure) and DBP (diastolic blood pressure) are inferred based on algorithms (device-specific) according to the oscillometric pressure changes. Hence, device used should be confirmed independently under accepted international protocols for accuracy to be used for different groups of patients (e.g. the elderly and pregnant women).

The devices must be calibrated annually by the companies certified by ISO 9001. Batteries should be checked regularly. The application must have the ability to produce standard reports including the raw data of blood pressure, blood pressure charts, average blood pressure of sleeping and wake time by software, and reduction in blood pressure during sleep (the decline in percentage) [20].

To check the blood pressures, the 24-hour monitoring device was attached to the patients' non--dominant arm. The pattern of blood pressure was based on the timing transferred to the PC software by the program in its memory. The device must be attached to the patient's arm continuously for 24 hours and bathing should be done in the beginning or after the monitoring and the patient should not have a midday nap during ABPM.

The patients were also instructed to maintain their normal routine activities (and rest) as usual during the assessment, and that their night sleep should not be less than six or more than 12 hours. After 24 hours, the patients presented with the recorder, the data recorded were transmitted to the main computer and printed as multiple charts. Day-time intervals in the study were considered from 6–9 am to 9–12 pm and nigh-time intervals were considered from 9–12 pm to 6–9 am and the data from the times in between, i.e. from 6 to 8 am and from 10 to 12 pm were excluded from the study.

Because of moral considerations, confidentiality was fully protected the data being gathered after obtaining verbal consent from the patients and the study method was approved by Qom University of Medical Sciences Ethics Committee (Code IR.MUQ.REC.1394.21). The data collected were analysed by SPSS software version 23 using descriptive indices, t-test and chi-square tests (in order to compare related factors measured in two groups of

patients, dippers and non-dippers). Significance level of tests in this study was considered less than 0.05.

Results

In this study, patients aged from 30 to 85 years with an average age of 52.08 ± 14.16 years, 42.1% (n = 106) were female and 42.1% (n = 77) were male. Mean duration of hypertension was 4.32 ± 4.96 years. 64.5% (118 patients) had positive family history for hypertension; 23% (n = 42) had a history of cardiovascular disease. Of 183 hypertensive patients, 77% (n = 141) were of the non-dipper type and 23% (n = 42) were of the dipper type.

56.8% (104) patients were under monotherapy. In patients receiving monotherapy, 36.06% (n = 66) were on angiotensin receptor blockers (ARB), 8.4% (n = 16) on beta-blockers, 7.1% (n = 13) on calcium channel blocker and 4.9% (n = 9) were on diuretics (thiazides). In patients receiving combination therapy, 22.4% (n = 41) were on ARBs and beta-blockers, 12.02% (n = 22) on diuretics (thiazide) and calcium channel blockers and 3.27% (n = 6) were on ARBs and diuretics (thiazide).

Mean and standard deviation of systolic and diastolic blood pressure of subjects, were respectively 137.53 ± 14.79 and 88 ± 10.49 mm Hg. Dipping systolic and diastolic blood pressures were 138.53 ± 14.78 and 88.95 ± 10.71 mm Hg and systolic and diastolic blood pressures of the non-dipping patients were 134.51 ± 16.75 and 84.67 ± 11.67 mm Hg, respectively.

Table I shows the results of independent t-test for the variables. According to the test results, there was no significant difference between the two groups in terms of age (p = 0.31) and duration of hypertension (p = 0.93).

Also, according to the chi-square test results, no significant difference was observed between the two groups in terms of variables such as gender (p = 0.55) and method of treatment (p = 0.96). More details are provided in table II.

The results of t-test show no significant difference between the groups in terms of general and daytime systolic and diastolic blood pressure, but the night-time systolic and diastolic blood pressures drop in non-dipper group was lower than the dipper group. More details are provided in table III.

Discussion

Findings from this study revealed that most of the patients had a family history of hypertension. Also, a great number of them had a non-dipper blood pressure pattern. Since the risk of cardiovascular diseases is clearly higher in patients with a non-dipper blood pressure pattern [6], these findings show unsatisfactory situation. According to the results of Leao et al. [6], 45.54% of patients have a non-dipper blood pressure pattern, which was much higher in

Table I. Comparison of means and standard deviations of the studied variables in the dipper and non-dipper groups

Variable	Non-dipper		Dipper		Level of significance
	Mean	Standard deviation	Mean	Standard deviation	
Age	51.50	14.4	54.02	13.29	P = 0.31
Duration of Hypertension	4.34	5.07	4.27	4.66	P = 0.93

Table II. Comparison of distribution of the two groups based on the studied variables

Variable		Non-dipper		Dipper		Level of significance
		Frequency	Percentage	Frequency	Percentage	
Gender	Male	61	79.2	16	20.8	p = 0.55
	Female	80	75.5	26	24.5	
Method of treatment	Monotherapy	80	76.9	24	23.1	p = 0.96
	Combination	61	77.2	18	22.8	
History of hypertension	yes	92	78	26	22	p = 0.69
	no	49	75.4	16	24.6	
History of cardiovascular disease	yes	30	71.4	12	28.6	p = 0.32
	no	111	75.7	30	21.3	

Table III. Comparison of the mean and standard deviation of variables between the two groups

Variable		Non-dipper		Dipper		Level of significance
		Mean	Standard deviation	Mean	Standard deviation	
Blood pressure total	systolic	137.94	14.86	136.16	14.67	p = 0.496
	diastolic	88.03	10.65	87.88	10.05	p = 0.934
Blood pressure daytime	systolic	138.21	14.82	138.57	14.8	p = 0.694
	diastolic	88.39	10.83	90.85	10.19	P = 0.191
Blood pressure nighttime	systolic	137.56	16.46	124.28	13.43	p < 0.001
	diastolic	86.79	11.42	77.57	9.58	p < 0.001

this study (77%). Other studies have also reported a smaller percentage than this study [21, 22].

In this study, the majority of patients were on a monotherapy regimen to control their blood pressure. Most used antihypertensive drugs in monotherapy were the ARBs, whereas combination therapy most frequently included ARBs and beta-blockers. Previous studies showed that the majority of patients received combination therapy. For example, according to Ssinabulya et al., the majority of patients were under combination therapy to control their blood pressure (more than 3 drugs) [23]. Also in the study of Leao et al., 62.2% of patients were receiving combination therapy, while only 19.8% of patients were being treated with monotherapy and 18% were not taking any medications. Most frequently antihypertensive drugs (45.54%) were calcium antagonists. Drug classes that were most used in combination therapies were ARBs, diuretics and calcium antagonists. The most prescribed medications in monotherapy were ACEIs (angiotensin converting enzyme inhibitors) [6].

On the other hand, a clinical trial showed that since hypertension is a multifactorial condition, achieving the target blood pressure is usually not possible with a single drug [24]. In addition, Katakam et al. also suggest that the efficacy of combination therapy is probably higher and that monotherapy is the treatment strategy that may have fewer side effects [25].

Hermida et al. reported that taking some hypertension medications at bedtime, can reduce blood pressure during sleep and bring back the normal pattern of blood pressure in some patients [26]. In 2015, a systematic review and meta-analysis of 123 clinical trials on hypertension medications for high-risk patients for stroke and heart failure showed that various antihypertensive drugs have different benefits, the ARBs and CCBs have greater impact on reducing the risk of stroke and diuretic drugs are more effective in preventing heart failure. This difference in drug benefits can be explained by the differences in their profile of 24-hour blood pressure reduction. ARBs and CCBs are the most powerful in lowering blood pressure changes that lead to prevention of stroke, while the diuretics preferably decrease the nighttime blood pressure that is more effective in preventing heart failure [27].

In the present study, there was no significant difference between the two groups in terms of age. However, the age of patients with non-dipper blood pressure pattern was higher than in the dipper group. However, Staessen et al. showed that the risk of developing a non-dipper blood pressure pattern is positively related with age and increases [11]. This finding was not consistent with the results of the study of Kawamura et al. [21].

The findings of this study showed that the duration of hypertension was greater in the non-dippers then in the dipper group, although this difference was not significant. Also in terms of gender, there was no significant difference between the two groups. However, the number of women with a non-dipper blood pressure pattern was higher than in men with a non-dipper blood pressure pattern. While the results of the study by Kawamura and colleagues showed that there were more men than women in non-dipper group [28].

According to the present study, no significant difference was seen in terms of the type of treatment in patients with non-dipper and dipper blood pressure pattern. However, the non-dipper blood pressure pattern was more prevalent among patients receiving combination therapy (multidrug) than in those receiving monotherapy. Also Leao et al. observed no significant difference in the treatment of patients with non-dipper and dipper blood pressure pattern [6].

In this study, no differences were seen between the groups in terms of history of hypertension, history of cardiovascular disease or any type of systolic and/or diastolic blood pressure. No consistent study with the findings of this study was found to be discussed.

Several studies in recent years have shown that the use of ABPM is a cost-effective method for diagnosing and treatment of hypertension and its use can reduce failures to detect unnecessary treatments of hypertension and lead to a better control on blood pressure.

Among the limitations of this study was the use of cross-sectional data that would limit the causal relationships between variables. So to determine the accurate and comprehensive relationship between circadian rhythms of blood pressure and its related factors, further studies in this matter are recommended. It is also recommended for the future studies to evaluate the 48-hour rhythm of blood pressure as well.

Conclusion

Previous studies showed that the distribution of circadian rhythm of blood pressure is associated with increase in the risk of developing various disorders including sleep problems, metabolic syndrome, cardiovascular disease and stroke. Currently rapidly becoming more common method is the 24-hour blood pressure monitoring, a method to detect abnormal patterns of nocturnal blood pressure drop which is independent risk factor for cardiovascular events in the future. The results showed that in the city of Qom patients with hypertension — compared to similar studies — have more frequently non-dipper pattern and therefore are prone to the foresaid problems, especially cardiovascular events in the future, so lowering their nocturnal blood pressure is of special importance. Based on the 24-hour blood pressure monitoring, the timing and the medications can be set in a way to achieve this goal. A drug prescribed in monotherapy is usually a diuretic or calcium channel blocker (CCB) or angiotensin receptor blocker (ARB). ARBs and CCBs are the most powerful in lowering blood pressure changes, which lead to the prevention of stroke, while diuretics preferably lower the night-time blood pressure, which is more effective in preventing heart failure [29]. Therefore, it is recommended to treat patients with a non-dipper pattern on their 24-hour blood pressure monitoring with diuretics**.**

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