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Blunted nocturnal fall in blood pressure in isolated clinical hypertension

Nurver Turfaner[a], *Yesarı Karter*[b], *Aslı Curgunlu*[c], *Faruk Ayan*[d], *Ismaıl Mıhmanlı*[e], *Fıkret Sıpahıoglu*[b]

[a] Istanbul University, Cerrahpasa Medical Faculty, Department of Family Medicine, Istanbul, Turkey
[b] Istanbul University, Cerrahpasa Medical Faculty, Department of Internal Medicine, Istanbul, Turkey
[c] Istanbul University, Cerrahpasa Medical Faculty, Department of Internal Medicine, Istanbul, Turkey
[d] Istanbul University, Cerrahpasa Medical Faculty, Department of Cardiology, Istanbul, Turkey
[e] Istanbul University, Cerrahpasa Medical Faculty, Department of Radiology, Istanbul, Turkey

Summary

Objective: The aim of the study is to assess the relation between diurnal blood pressure variations and target organ damage in isolated clinical hypertension (ICH).

Material and methods: Ninety patients with ICH (clinical systolic blood pressure [SBP] superior or equal to [>=] 140 and/or diastolic blood pressure [DBP]> = 90 mm Hg) and ambulatory daytime SBP and DBP <135/85 mm Hg were enrolled in this study.

Patients with ICH were classified into two groups as dippers (13 males, 34 females) and nondippers (7 males, 36 females). Nondippers were defined by a reduction in mean blood pressure of less than 10% from day (06:00–24:00) to night (24:00–6:00); and the rest of the patients were classified as dippers. Left ventricular mass index (LVMI) and early diastolic velocity/late diastolic velocity (e/a) were determined by echocardiography; intima-media thickness (IMT) and compliance of the carotid artery (distensibility coefficient [DC] and compliance coefficient [CC]) were measured by ultrasound. Renal function was measured by glomerular filtrate rate (GFR) and urinary albumin excretion (UAE). Retinal changes were determined by fundoscopy.

Results: There was no difference between the demographic and biochemical characteristics of the two groups. IMT was significantly higher in nondippers (p <0.005). The nondippers had significantly lower levels of DC (p <0.005) and CC (p <0.0005). LVMI was above normal in both groups with no significant difference. The e/a ratio, although normal in both groups, differed significantly between them (p <0.0005). HTRP, microalbuminuria and GFR <90 mL/min/1.73 m^2 were more frequent in nondipper ICH patients.

Conclusion: The results of the study suggest that in ICH nondipping is associated with a decrease in arterial compliance. The global risk load for target organ damage in ICH patients is higher in nondippers.

Key words: dipper; nondipper; ICH; target organ damage

Introduction

Patients with isolated clinical hypertension (ICH) are characterised by elevated arterial pressures in the physician's office, but "normal" pressures at other times. The frequency of ICH is approximately 15% in the general population. Data also show that ICH patients constitute one third of the persons diagnosed as hypertensive. Although it is known that ICH patients have lower cardiovascular risks than sustained hypertensive patients, there is some evidence that ICH is not completely innocent and may cause some target organ damage [1–12].

Time-related changes in cardiovascular parameters – such as blood pressure (BP), heart rate (HR) and coronary vascular tone – which produce distinctive circadian rhythms have been reported [13]. It is known that some normotensives and hypertensives do not present the normal nocturnal fall in blood pressure, and many authors have investigated the causes of this lack of BP fall and its effects on target organs in patients with sustained hypertension.

Those who have nighttime average BP falls exceeding 10% of the average daytime value are classified as "dippers", and those who have BP falls of less than 10% are classified as "nondippers" [14, 15]. Some studies indicate that in nondipper hypertensive patients organ damage

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was much greater than in dipper hypertensive patients [16]. However, in ICH patients the target organ status and the relation between the diurnal variations has not been well investigated.

The aim of our study is to assess target organ damage in dipper and nondipper ICH patients.

Material and methods

Ninety ICH patients (clinical SBP superior or equal to 140 and/or clinical DBP superior or equal to 90 mm Hg and ambulatory daytime SBP and DBP <135/85 mm Hg) were enrolled in the study. They were recruited randomly from the patients admitting to the outpatient clinics of the Family Medicine and Internal Medicine Departments of Cerrahpasa Medical Faculty, Istanbul University, between 2005 and 2007. All the patients had been recently diagnosed as hypertensive and none had been previously treated for hypertension. Isolated clinical hypertensive patients were classified as dippers (13 males, 34 females) and nondippers (7 males, 36 females). Nondippers were defined by a reduction in mean arterial pressure of less than 10% from day (06:00–24:00) to night (24:00–06:00); and the patients excluded by this definition were classified as dippers.

The nocturnal reduction rates of SBP, DBP and mean arterial pressure were calculated according to the following formula:

nocturnal reduction rate (%) = [(daytime mean-nighttime mean)/daytime mean] × 100

The exclusion criteria were hyperlipidaemia (LDL >3.37 mmol/L), any signs or symptoms of atherosclerotic vascular disease, diabetes mellitus and other endocrine diseases, obesity (BMI >27), drugs that may affect blood pressure and lipid metabolism, heavy smoking and alcoholism. All the patients were free of concomitant vascular disease, malignancy and connective tissue diseases. The study was approved by the Ethics Committee of Istanbul University, Cerrahpasa Medical Faculty (date: January 9, 2007/ prt:1589).

Measurements of brachial artery pressures of the patients referred to our clinic for high blood pressure (SBP> = 140 and/or DBP> = 90 mm Hg) were obtained in our outpatient department by a nurse with a mercury sphygmomanometer standardised as approved by the American and British Hypertension Society and the World Health Organization. Measurements were obtained with the patient in the sitting position after resting for 20–30 minutes [17]. Korotkoff phase I was used to determine the systolic pressure and phase V for diastolic pressure. Measurements were performed on three different days within five days. Three blood pressure readings were taken per session and averaged, then subsequently averaged over 3 sessions. An ambulatory 24-hour arterial blood pressure recording was performed in patients whose SBP was >= to 140 and/or DBP was >= to 90 mm Hg in the outpatient department, with an ABPM monitor (A and D Engineering, TM-2421) approved by the European Society of Hypertension [18–19]. Measurements were performed on the left arm. According to the results of the ambulatory measurements, patients were classified into sustained or ICH groups. Isolated clinical hypertension was defined as clinical hypertension with daytime ambulatory blood pressure <135/85 mm Hg.

All patients underwent standard echocardiographic examination, pulsed Doppler echocardiography, carotid ultrasound imaging, fundoscopy, and blood and urine analysis.

Indexes of cardiac structure and function were assessed only at baseline. Left ventricular enddiastolic posterior wall thickness, interventricular septal wall thickness at end diastole (IVSD), left ventricular internal enddiastolic diameter (LVIDD), and left ventricular internal endsystolic diameter (LVIDS) were measured from M-mode images of the left ventricle generated in the short axis view at the level of the mitral chordea (2.5 MHz; Hewlett Packard 2500) according to the American Society of Echocardiography Convention criteria. Using these measurements, left ventricular mass (LVM) was calculated by the formula of Devereux and Reichek and was divided by body surface area to obtain left ventricular mass index (LVMI) [20].

Transmitral pulsed Doppler echocardiography was performed by positioning the sample volume of pulsed wave Doppler between the tips of the mitral leaflets on the apical four-chamber view. Early diastolic velocity (e) and late diastolic velocity (a) were obtained and e/a value was calculated to evaluate diastolic dysfunction [20].

Ultrasonographic imaging was performed in a quiet, temperature-controlled room (22 °C) after an overnight fast. After 20 minutes' rest the examinations were performed between 08:30 and 10:00 with a colour Doppler ultrasound unit (Siemens Elegra, Erlangen, Germany) equipped with a 7.5 L 40 MHz transducer. Patients were examined in the supine position. All ultrasonographic measurements were performed by an experienced radiologist blinded to the grouping of the patients. B-mode ultrasound scans of the left common carotid arteries were performed. The lumen diameter of the common carotid artery, one centimeter proximal to the bulb, was measured as the distance between intima-blood interface anteriorly and intima-blood interface posteriorly. All measurements were done at the time of scanning on frozen images of longitudinal scans using the machine's electronic caliper. Using cinemode of the machine, systolic and diastolic lumen diameters were taken separately and differences between them were calculated.

The difference between the anterior and posterior wall represents arterial distension, i.e. change in diameter during one heart cycle. Data for arterial diastolic diameter (D) and distention (ΔD) were obtained for each heart beat. Brachial blood pressure was measured with a semi-automatic oscillometric device (Dinamap). Pulse pressure was defined as systolic minus diastolic pressure (ΔP). Vessel wall properties were calculated by the following equations:

Distensibility coefficient (DC) = $(2\Delta D/D) / \Delta P$ (in 10^{-3}. kPa^{-1})

Compliance coefficient (CC) = $\pi D \Delta D / (2\Delta P)$ (in mm^2. kPa^{-1}) [21, 22]

Each measurement was repeated three times on each occasion and the mean value for each measurement was calculated. The measurements of 10 different patients were obtained twice at a 2-hour interval and RC (repeatability coefficient) values were 0.35 mm for systolic diameter and 0.18 mm for diastolic diameter, not statistically different from zero [21–22].

Serum total cholesterol, high density lipoprotein (HDL), triglyceride (TG), glucose, urea, creatinine, and 24-h creatinine clearance were measured using standard enzymatic methods with a fully automated analyser (Olympus AU-800). Low density lipoprotein (LDL) was calculated by Friedewald's formula. Blood samples were taken from the antecubital vein after an overnight fast.

Microalbuminuria in 24 h was measured by radioimmunoassay (RIA). Urinary albumin excretion values between 30 and 300 mg/day were regarded as microalbuminuria.

Fundoscopic classification of hypertensive retinopathy was carried out by an experienced ophthalmologist according to the Keith, Wagener and Barker classification [23].

Statistical analysis: The differences between groups in age, gender, BMI, SBP, DBP, and biochemical values were analysed using Student t-test for continuous variables and chi-square test for categorical variables. The differences between LVMI, e/a, IMT, DC and CC were analysed by variance analysis, χ^2 and Mann-Whitney-U test evaluating the effect of gender on these parameters. Data was expressed as mean ± SD. A p value of <0.05 was accepted as significant.

Results

The demographic and biochemical characteristics of the two groups are summarised in table 1.

The results of the clinical and ambulatory blood pressure measurements are shown in table 2.

The LVMI of the nondippers was slightly higher than that of the dippers, but the difference was not significant (95 ± 21.1 versus 94.2 ± 21.5; p = 0.88). In the nondipper group, 34 patients (80%) had high LVMI values while in the dipper group 34 patients (72%) had LVMI values above normal. The nondippers had a significantly lower e/a ratio than the dippers, although both values were in the normal range (1.07 ± 0.05 versus 1.11 ± 0.04; p <0.0005). In the nondipper group the e/a ratio was <1 in 23 patients (53%) whereas in the dipper group, the e/a ratio was <1 in 20 patients (43%) (table 3–4).

Intima media thickness (IMT) was significantly higher in nondippers than dippers (0.69 ± 0.02 mm versus 0.60 ± 0.01 mm; p <0.0005). The nondippers had significantly lower levels of DC (17.7 ± 1.4 versus 19.4 ± 2.6 10^{-3}.kPa^{-1}; p <0.005) and CC (0.60 ± 0.01 versus 0.69 ± 0.02 mm^2. kPa^{-1}; p <0.0005) (table 5).

In the nondipper group, 7 patients (16%) had microalbuminuria while in the dipper group 6 patients (13%) had microalbuminuria. In the nondipper group 35 patients (82%) had GFR <90

Table 1

Demographic and Biochemical Characteristics.

	Dippers (n = 47)	Nondippers (n = 43)	p	t
Age	50.6 + 12.9	49.8 ± 11	0.75	–0.32
Gender (m/f)	13/34	7/36	0.2	×2 = 1.68
BMI kg/m²	29.2 ± 4	29.1 ± 4.6	0.88	0.15
TC (mmol/L)	5.78 ± 1.0	5.66 ± 1.2	0.62	0.50
TG (mmol/L)	1.72 ± 0.74	1.54 ± 0.61	0.25	–1.16
LDL (mmol/L)	3.62 ± 1.13	3.76 ± 1.06	0.59	0.55
HDL (mmol/L)	1.16 ± 0.42	1.36 ± 0.81	0.17	1.40
Glucose (mmol/L)	5.76 ± 1.0	5.98 ± 3.23	0.7	0.39
Urea (mmol/L)	29 ± 8.9	27.6 ± 7.7	0.49	0.7
Creatinine (mmol/L)	72.49 ± 18.56	74.26 ± 13.26	0.33	0.99

BMI: Body mass index, TC: Total cholesterol
TG: Triglyceride

Table 2

Clinical and ambulatory blood pressure measurements.

	Dippers (n = 47)	Nondippers (n = 43)	p	t
Clinical SBP (mm Hg)	158.6 ± 14.7	157.0 ± 18.8	0.66	–0.44
Clinical DBP (mm Hg)	98.5 ± 9,1	96.8 ± 7.8	0.36	–0.93
Daytime SBP (mm Hg)	124.0 ± 5.0	118.0 ± 6.0	<0.0005	–4.26
Daytime DBP (mm Hg)	74.4 ± 5.2	75.4 ± 7.8	0.41	0.82
Nighttime mean SBP (mm Hg)	103.0 ± 7.0	117.0 ± 6.2	<0.01	2.44
Nighttime mean DBP (mm Hg)	61.0 ± 6.0	72.0 ± 5.0	<0.0005	9.8
Daytime MBP (mm Hg)	91.0 ± 5.0	90.0 ± 4.0	0.72	0.50
Nighttime MBP (mm Hg)	76.0 ± 6.0	86.0 ± 4.0	<0.0025	3.3

SBP: Systolic blood pressure, MBP: Mean blood pressure
DBP: Diastolic blood pressure

Table 3

Echocardiographic findings in dippers and nondippers.

	Dippers (n = 47)	Nondippers (n = 43)	p	t
LVMI(g/m²)	94.2 ± 21.5	95 ± 21.1	0.15	0.88
e/a	1.11 ± 0.04	1.07 ± 0.05	<0.0005	4.8

Table 4

Target organ damage frequency in two groups.

	Nondipper (n = 43)	Dipper (n = 47)	p
LVMI above normal	34 (80%)	34 (72%)	n.s
e/a <1	23 (53%)	20 (43%)	n.s
HTRP+ (Stage 1, 2, 3)	13 (30%)	7 (15%)	<0.005
UAE	7 (16%)	6 (13%)	n.s
GFR<90 mL/min/1.73 m^2	35 (82%)	27 (57%)	0.033

GFR: Glomerular filtration rate
UAE: Urinary albumin excretion
LVMI: Normal (male): 76 ± 13 g/m^2
Normal (female): 66 ± 11 g/m^2

Table 5

Carotid doppler ultrasound results.

	Dippers (n = 47)	Nondippers (n = 43)	p	t
IMT (mm)	0.60 ± 0.01	0.69 ± 0.02	<0.0005	17.52
DC ($10^{-3}kPa^{-1}$)	19.4 ± 2.6	17.7 ± 1.4	<0.005	2.90
CC ($mm^2.kPa^{-1}$)	0.69 ± 0.02	0.60 ± 0.01	<0.0005	22.29

IMT: Intima media thickness
DC: Distensibility coefficient
CC: Compliance coefficient

mL/min/1.73 m^2 while 27 (57%) of the dippers had GFR <90 mL/min/1.73 m^2 (p = 0.033) (table 4).

In the dipper group, fundoscopy revealed stage I retinopathy in 5 patients and stage II retinopathy in 2. In the nondipper group, stage I retinopathy was found in 11 patients, stage II retinopathy in 1 patient and stage III HTRP in 1. The HTRP in dippers was rare compared to nondippers (it was present in 7 of the dippers [15%] and 13 of the nondippers [30%]), but the difference was not significant; p = 0.58 (table 4).

Discussion

In our study the global risk load for target organ damage was increased in nondipper ICH patients.

In echocardiographic measurements the mean LVMI was above normal in both dipper and nondipper groups but the difference was not significant. There were more patients with high LVMI in the nondipper group, but the difference was not significant. In the nondipper group patients with e/a<1 were more frequently observed (53%–43%) and the e/a ratio was significantly lower in nondipper patients although both values were >1.

These findings show that in most of the patients cardiac end organ damage exists. The decrease in e/a ratio may be due to early diastolic dysfunction.

There is disagreement between several studies concerning cardiac organ damage in nondippers. Grandi reported that the extent of a decrease in nocturnal BP was not related to left ventricle morpho-functional characteristics and aortic distensibility [5].

Our results are in agreement with some studies which have found a higher interventricular septum thickness and LVMI in nondipper hypertensives [5, 24–26].

There is a significant decrease in arterial compliance and increase in IMT in nondipper ICH patients, although the difference is small (0.09 mm). These findings are early features of carotid atherosclerosis.

Grandi has reported that IMT did not differ between the two groups [5].

Renal function was evaluated by GFR and UAE. There was no difference between the mean values, but the frequency of microalbuminuria was higher in the nondipper group (16%–13%) and there were significantly more patients with a GFR <90 ml/min/1.73 m^2 in the nondipper group (82%–57%, p = 0.033).

HTRP did not differ statistically between the two groups, but it was more frequent in nondippers (30%–15%).

Uzu reported no difference in biochemical characteristics and hypertension-related complications between the dipper and nondipper patients [27].

There are several limitations to our study.

The majority of our patients were female. This may have an important bearing on the significance of the results we found, because nondipping has more serious effects on cardiovascular function in female than male patients.

With regard to gender, in several studies left ventricular mass and cardiovascular morbidity were significantly higher in nondipper than dipper females, whereas a non-significant difference was observed between the two male groups [16, 28].

Another limitation was that since most of our patients were under 65 and the mean age of the dipper and nondipper groups was the same, it was not possible to evaluate the age-related differences in the change of cardiovascular structure and function and the effect of age on nondipping.

Ijiri reported that in sustained HT, the day-night difference in blood pressure significantly decreased with age and the prevalence of nondippers was greater in the elderly. He showed a relationship between nondipping pattern and cardiovascular events only in younger hypertensive nondippers. In elderly people the prevalence of cardiovascular events was similar in dippers and nondippers [24]. This may be due to the fact that in old age some factors other than blunted nocturnal fall may trigger cardiovascular events.

There were only four isolated systolic clinical hypertension patients and as a result it was not possible to evaluate the effect of SBP in determining cardiovascular risk.

Our primary aim was to evaluate target organ damage and LVMI was measured by echocardiography for this purpose. Since only routine echocardiographic techniques were used, other parameters except e/a which can be used to assess diastolic function were not available. e/a is the most widely used parameter for evaluation of diastolic dysfunction in hypertensive patients, but it is not adequate by itself.

In this study target organ damage was present in both dipper and nondipper ICH patients, but was more frequent in nondippers.

These results are in agreement with some former studies [16, 24, 25].

Correspondence:
Nurver Turfaner, M.D
Istanbul Universitesi
Cerrahpasa Tip Fakultesi
Aile Hekimligi Anabilim dali
34303, Istanbul, TURKEY
90-532-4961773
E-Mail: nurver@istanbul.edu.tr;
nurver@doctor.com

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