ORIGINAL ARTICLE

VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY AND TARGET ORGAN DAMAGE IN RURAL DWELLERS WITH UNCOMPLICATED ARTERIAL HYPERTENSION

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ABSTRACT

The aim: To examine the association of hypertensive mediated target organ damage with blood pressure visit-to-visit variability in Ukrainian rural dwellers with uncomplicated hypertension.

Material and methods: The cross-sectional study enrolled 160 adult males with uncomplicated primary hypertension (mean age 50±6 yo). We analyzed office systolic and diastolic blood pressure levels, obtained at four consecutive visits. We used standard deviation (SD) value to assess blood pressure visit-to-visit variability. The patients were referred to the group with high (n=82; 51.3%) vs low (n=78; 48.7%) blood pressure variability (HBPV, LBPV).

Results: HBPV patients were characterized by higher left ventricular myocardial mass indexed to height 2.7: median, interquartile range: 70.9 (61.3-78.2) vs 50.9 (44.9-54.4) g/m2.7, respectively p<0.001. The cases of severe left ventricular hypertrophy prevailed in HBPV group (vs LBPV): 68% vs 5%, respectively, p<0.001. HBPV group was characterized by larger common carotid artery intima-media complex thickness, advanced hypertensive retinopathy, higher urine albumin/creatinine ratio value and worse kidneys' glomerular filtration rate. The obtained results might be helpful in the context of global monitoring of vulnerable high risk population of hypertensive rural males.

Conclusions: The HBPV in rural hypertensive males was associated with more pronounced target organ damage. Further regional research on the various clinical aspects of hypertension, including blood pressure variability, might be useful in extending the existed evidence on prevention of hypertension-related complications.

KEY WORDS: hypertension, blood pressure, variability, target organ

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INTRODUCTION

The negative dynamics of the health indicators of the rural subpopulation, which is almost one third of the total population of Ukraine, merits special attention to the problem of healthcare and health promotion of agricultural workers [1]. Cardiovascular diseases (CVD) are still the leading causes of death in the rural and urban subpopulations of Ukraine. However, CVD mortality in the rural subpopulation exceeds by 42,8% the corresponding parameter in the urban one, and by 25,9% – the average mortality rate in Ukraine [2]. Arterial hypertension (AH) is one of the leading CVD risk factors and a major predictor of cardiovascular adverse events. The global prevalence of AH was estimated to be 1,13 billion in 2015, with a prevalence of over 150 million in Central and Eastern Europe [3]. According to the ESC Cardiovascular Disease Statistics data, higher blood pressure (BP) levels are generally found in Central and Eastern European countries and lower levels in Southern, Western and Northern European countries without a significant positive trend towards decrease [4]. It is worth noting, that virtually all major surveys in the Eastern European region show a significantly higher prevalence of AH in rural areas [5].

Ukraine has one of the highest rates of CVD morbidity and mortality in the Eastern European region. AH is a serious public health problem and is one of the leading causes of preventable mortality in Ukraine [2, 6]. About one third of Ukrainian adults (34%) have AH, with the age-standardized prevalence of AH being reported as 29,3% and 36,3% in urban and rural subpopulations, respectively [2, 7]. Among hypertensives, 80,8% of urban dwellers and 67,8% of rural ones were aware of their condition; 48,4% and 38,3%, respectively, were receiving any antihypertensive treatment; finally, only 18,7% and 8,1%, respectively, had their BP controlled. Thus, the rates of AH awareness, treatment and BP control in Ukraine are still worrisome both in urban and rural areas, especially in the latter one [7].

Existing gaps in the management of patients with AH may be partly due to a lack of consideration of the phenomenon of BP variability, which is defined as BP fluctuations

for a certain period of time [8]. It was found the association of BP variability with adverse cardiovascular events, in addition to BP level [9, 10]. At present, the existing evidence emphasizes the clinical importance of the long-term BP variability – the so-called visit-to-visit variability (VVV) of BP, which is assessed on the basis of data on BP levels at several doctor's visits over a relatively long period of time (weeks, months, years) [10]. For instance, in ASCOT-BPLA study, VVV in systolic BP (SBP) was a strong predictor of stroke and coronary events, independent of mean SBP [10, 11]. It has also been demonstrated the prognostic significance of VVV in diastolic BP (DBP) [9]. Furthermore, a series of studies revealed the association of BP variability, including VVV, with AH -mediated target organ damage [12, 13], although certain aspects of such interactions remain controversial to date [14].

Given the significant burden of CVD in Ukraine, especially in rural areas [1, 2], and also well-established association of AH-mediated target organ damage with AH complications (including cerebrovascular accidents, acute coronary events and heart failure) [3], it would be helpful to assess BP VVV as an additional clinical tool in cardiovascular risk stratification, as well as an additional criterion for evaluating the effectiveness of antihypertensive therapy. Therefore, more work is needed to extend our knowledge as to different clinical and prognostic aspects of AH in rural dwellers of Ukraine, in particular the association of BP VVV with AH-mediated subclinical target organ damage.

THE AIM

The aim of the study was to examine the association of target organ damage with BP VVV in rural dwellers with uncomplicated AH.

MATERIAL AND METHODS

The cross-sectional study retrospectively analyzed clinical, laboratory and instrumental data, derived from consecutive 160 adult males with uncomplicated primary AH (mean age [mean ± standard deviation (SD)] 50±6 years, the min-max range 39-62 years; 150 (93.8%) patients before the age of 60 years), inhabited in rural areas of Khmelnytskyi region of Ukraine, and enrolled in 2016-2019 at the Public Non-Profit Enterprise «Khmelnytskyi Regional Cardiovascular Center» Khmelnytskyi Regional Council (Khmelnytskyi, Ukraine). The mean AH duration was (median (Me), interquartile range [IQR]) 7 (4-11) years. The study was conducted in accordance with the principles of the Council of Europe Convention on Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current regulations of the Ministry of Health of Ukraine. The study protocol was approved by the local ethics committee. All patients signed an informed consent to participate in the study. The study did not include patients with complicated primary AH, secondary AH and diabetes mellitus. Among the enrolled patients, body mass index (BMI) was (Me [IQR]) 27.2 (24.8-30.2) kg/m^2. 73 (45.6%) patients were overweight (BMI 25.0-25.9 kg/m^2), while 41 (25.6%) patients presented with obesity (BMI ≥30.0 kg/m^2). The smoking status was distributed as follows: never-smoker – 28 (17.5%), former smoker – 47 (29.4%), and current smoker – 85 (53.1%). Laboratory tests were performed in all the patients according to standardized procedures. The mean (Me [IQR]) fasting glucose level was 4.7 (4.2-5.0) mmol/l. The mean (Me [IQR]) parameters of lipid profile were as follows: serum cholesterol level – 6.6 (5.5-7.4) mmol/l (156 (97,5%) patients with the level >4.9 mmol/l; 21 (13.1%) patients with the level >8.0 mmol/l); triglycerides – 2.6 (1.9-3.2) mmol/l (149 (97.5%) patients with the level >1.7 mmol/l); low-density lipoproteins (LDL) – 4.7 (3.3-5.2) mmol/l (153 (95.6%) patients with the level >3.0 mmol/l); and high-density lipoproteins – 1.2 (0.9-1.3) mmol/l (70 (43.8%) patients with the level <1.0 mmol/l).

The functional state of the kidneys was assessed by serum creatinine level, estimated glomerular filtration rate (eGFR), and urine albumin/creatinine (A/C) ratio (in morning spot urine). The urine A/C ratio range 3.4-34 mg/mmol was interpreted as microalbuminuria (MAU), and the level >34 mg/mmol was judged as proteinuria. The mean (Me [IQR]) serum creatinine level was 113 (99-119) μmol/l. The *CKD-EPI* (Chronic Kidney Disease Epidemiology Collaboration) *equation* [15] was used to calculate eGFR. The mean (Me [IQR]) eGFR was 65 (59-75) ml/min/1.73 m^2 (min-max range 48-116 ml/min/1.73 m^2). The distribution of eGFR grades in total sample of enrolled patients was as follows: ≥90 ml/min/1.73 m^2 – in 8 (5.0%) patients; 89-60 ml/min/1.73 m^2 – 108 (67.5%); and <60 ml/min/1.73 m^2 – 44 (27.5%). The mean urine A/C ratio (Me [IQR]) was 19.3 (7.3-30.3) mg/mmol. The vast majority of patients (142 of 160 [88.8%]) presented with MAU, and 18 (11.2%) patients had proteinuria – urine A/C ratio was 36.1-51.3 mg/mmol.

Echocardiography was performed in all the patients by the use of «SONOLINE Versa Pro» scanner (Siemens, Switzerland; 35C40 convex probe 2,6-4,0 MHz), in accordance with the current guidelines of the American Society of Echocardiography (ASE) [16]. Among the parameters we assessed the following ones: left atrial anterior-posterior dimension (LAD), LV end-diastolic dimension (EDD), interventricular septum thickness (IVST), LV posterior wall thickness (PWT) and LV ejection fraction (EF). LV myocardial mass (MM) was calculated by the use of the Devereux «cube» formula (ASE modified) [16]. We indexed LV Mass Myocardium (LV MM) by the height$^{2.7}$ according to 2018 ESC/ESH guidelines [3]. The mean LV EF (Me [IQR]) in the total sample of enrolled patients was 57% (55-60%) (min-max range 45-68%). The distribution of LV EF grades was as follows: preserved systolic function (LV EF ≥50%) – 155 (96.9%) patients; mid-range LV EF (40-49%) – 5 (3.1%) patients.

Duplex scanning of extra cranial carotid arteries (common, external and internal) was performed in all the patients by the use the above mentioned device (75L40 linear probe 7,5 MHz), with the measurement of common carotid artery (CCA) intima-media complex thickness (IMT). The mean (Me [IQR]) right CCA IMT was 1.21 (1.13-1.30) mm,

Table I. Baseline clinical characteristics of patients in groups with LBPV and HBPV

Parameter	LBPV N=78	HBPV N=82	p
Age, years	50 (46-56)	51 (45-56)	0.529
HTN duration, years	4 (2-6)	10 (7-13)	<0.001
SBP*, mm Hg	154.5 (150.2-161.3)	165.7 (161.2-170.7)	<0.001
SD (SBP), mm Hg	5.5 (3.6-8.2)	15.8 (15.2-17.3)	<0.001
DBP*, mm Hg	90.2 (84.0-95.7)	93.7 (88.5-99.5)	<0.001
SD (DBP), mm Hg	4.2 (3.4-5.8)	10.6 (7.3-13.0)	<0.001

Note: * – four visits averaged

Table II. Parameters of structural and functional state of the myocardium in groups with LBPV and HBPV

Parameter		LBPV N=78	HBPV N=82	p
LAD, cm		3.8 (3.4-4.0)	4.1 (3.9-4.3)	<0.001
LV EDD, cm		4.9 (4.8-5.2)	5.5 (5.2-5.7)	<0.001
LV PWT, cm		1.20 (1.14-1.24)	1.37 (1.30-1.42)	<0.001
IVST, cm		1.23 (1.17-1.28)	1.40 (1.35-1.49)	<0.001
LV MM, g		233.3 (216.3-249.7)	325.4 (297.9-358.9)	<0.001
LV MM/$h^{2,7}$, g/$m^{2,7}$		50.9 (44.9-54.4)	70.9 (61.3-78.2)	<0.001
LVH, n (%)		47 (60)	82 (100)	<0.001
LVH degree, n (%)	No LVH[z]	31 (40)	0	<0.001
	Mild[z]	31 (40)	3 (4)	
	Moderate	12 (15)	23 (28)	
	Severe[z]	4 (5)	56 (68)	
LV EF, %		57 (56-60)	56 (55-59)	0.043
LV EF grades, n (%)	Preserved (≥50%)	76 (97)	79 (96)	0.691
	Mid-range (40-49%)	2 (3)	3 (4)	

Note: z – statistically significant difference by z-test

left CCA IMT – 1.21 (1.13-1.31) mm. The vast majority of patients (155 of 160 [96.9%]) presented with bilateral CCA IMT >0,9 mm. Totally, the carotid stenosis was detected in 148 (92,5%) patients. Among them, 84 (56,8%) patients presented with significant carotid stenosis (≥50%) [3].

At standard ophthalmic examination (including fundoscopy), the vast majority of patients (155 of 160 [96.9%]) presented with hypertensive retinopathy, assessed by Keith-Wagener-Barker (KWB) scale [17] *(*grade 1 – 78 (50.3%) patients; grade 2 – 77 [49.7%]*)*.

We retrospectively analyzed the office SBP and DBP levels, obtained at four consecutive doctor`s visits (the measurements occurred over the period (Me [IQR]) of 25 (19-34) months). The mean values (Me [IQR]) of SBP and DBP (four visits averaged) were 161.3 (154.1-167.3) mmHg and 92.0 (86.4-98.0) mm Hg, respectively. As a metric of BP VVV, we used the SD value, calculated for abovementioned four SBP and DBP levels (SD (SBP) and SD (DBP), respectively). The patients were referred to the group with high BP variability (HBPV) in case of SD (SBP) ≥15 mm Hg and/or SD (DBP) ≥14 mm Hg [18, 19]. Finally, the total sample of enrolled patients was subdivided into two groups: low BP variability (LBPV) – 78 (48.7%) patients, and HBPV – 82 (51.3%). AH-mediated subclinical target organ damages were analyzed according to ESC/ESH Guidelines criteria (2013, 2018) [3, 20].

Statistical software programs were used for data analysis (Statistica v. 12.6; IBM SPSS Statistics v.26.0). Continuous variables were presented as Me (IQR). Categorical variables were presented as absolute and relative (%) frequency (with 95% confidence interval (CI) in certain cases). To compare characteristics between LBPV and HBPV groups, we used Mann-Whitney U-test (for continuous variables) and χ^2 test or Fisher`s exact test (for categorical variables). In case of statistically significant difference in χ^2 test, we used z-test to compare the frequency of certain categorical variables. P<0,05 was considered statistically significant.

RESULTS

The groups of patients with LBPV and HBPV were comparable by mean age, with the longer duration of AH in the

Table III. Carotid stenotic lesions and common carotid artery intima-media complex thickness in groups with LBPV and HBPV

Parameter	LBPV N=78	HBPV N=82	p
CCA (right), stenosis, n (%)	5 (6)	18 (22)	0.005
CCA (right), stenosis ≥50%, n (%)	2 (3)	9 (11)	0.057*
CCA IMT (right), mm	1.16 (1.11-1.21)	1.30 (1.21-1.36)	<0.001
CCA IMT (right) >0,9 mm, n (%)	74 (95)	81 (99)	0.156
CCA (left), stenosis, n (%)	16 (20)	21 (26)	0.445
CCA (left), stenosis ≥50%, n (%)	0**	11*** (13)	0.001
CCA IMT (left), mm	1.15 (1.09-1.20)	1.30 (1.23-1.38)	<0.001
CCA IMT (left) >0,9 mm, n (%)	74 (95)	81 (99)	0.156
ECA (right), stenosis, n (%)	19 (24)	24 (29)	0.484
ECA (right), stenosis ≥50%, n (%)	1 (1)	19 (23)	<0.001
ECA (left), stenosis, n (%)	18 (23)	35 (43)	0.008
ECA (left), stenosis ≥50%, n (%)	1 (1)	27 (33)	<0.001
ICA (right), stenosis, n (%)	21 (27)	37 (45)	0.017
ICA (right), stenosis ≥50%, n (%)	0#	27## (33)	<0.001
ICA (left), stenosis, n (%)	15 (19)	28 (34)	0.049*
ICA (left), stenosis ≥50%, n (%)	4 (5)	20 (24)	0.001

Notes: ECA – external carotid artery; ICA – internal carotid artery; * – Fisher`s exact test; ** – 95% CI [0-3%]; *** – 95% CI [7-22%]; # – 95% CI [0-3%]; ## – 95% CI [23-44%]

Table IV. The presence and degree of hypertensive retinopathy in groups with LBPV and HBPV

Parameter	LBPV N=78	HBPV N=82	p
No retinopathy^z	5 (6*)	0**	<0.001
Grade 1^z	56 (72)	22 (27)	
Grade 2^z	17 (22)	60 (73)	

Notes: * – 95% CI [2-13%]; ** – 95% CI [0-2%];z – statistically significant difference by z-test

latter group (Table I). The level of SBP (four visits averaged) was significantly higher in HBPV group, as compared to LBPV group. The difference between the studied groups by DPB (four visits averaged) was also statistically significant, but less pronounced.

After analyzing the echo parameters, we found that HBPV group, in comparison with LBPV group, was characterized by more pronounced structural changes of the myocardium, including higher values of LV MM and LV MM/h$^{2.7}$ (Table II). HBPV group was entirely represented by patients with LVH, as opposed to LBPV group (60%; p<0,001). The frequency of mild LVH cases was higher in LBPV group, as opposed to the alternative group. Conversely, patients with severe LVH were more prevalent in HBPV group (vs. LBPV group). The frequency of patients with moderate LVH tended to be higher in HBPV group (28% [95% CI 19-38%]), as compared to LBPV group (15% [95% CI 8-24%]) (p=0,054). The vast majority of patients in both groups had preserved LV systolic function.

The analysis of parameters, representing the arterial wall damage, revealed higher values of CCA IMT (bilaterally) in HBPV group (vs. LBPV group) (Table III). The cases of the stenosis of right CCA, left external carotid artery and both internal carotid arteries were more frequent in HBPV group. Moreover, HBPV group, as compared to LBPV group, was associated with higher frequency of patients with significant stenotic lesion (≥50%) of extracranial carotid arteries (except the frequency of right CCA significant stenosis cases, which tended to be higher in HBPV group) (Table III).

At fundoscopy, the HBPV group, as opposed to LBPV group, was characterized by higher frequency of patients with grade 2 of hypertensive retinopathy, assessed by KWB scale (Table IV).

While assessment the renal damage, it was found that HBPV group, as compared to LBPV group, was characterized by worse functional state of the kidneys, namely higher serum creatinine and urine A/C ratio value, and lower eGFR (Table V).

It should be noted, that the whole set of 18 proteinuria cases was associated with HBPV. Furthermore, the LBPV group was predominantly represented by patients with eGRF range 60-89 ml/min/1,73 m^2. On the contrary, the frequency of patients with more pronounced kidney filtration function impairment (eGFR <60 ml/min/1,73 m^2) was higher in HBPV group vs LBPV group (p<0.05).

Table V. Parameters of functional state of the kidneys in groups with LBPV and HBPV

Parameter		LBPV N=78	HBPV N=82	p
Serum creatinine, μmol/l		102 (93-111)	119 (115-124)	<0.001
Urine A/C ratio, mg/mmol		7.3 (5.5-9.4)	30.2 (26.5-33.2)	<0.001
Degree of urine A/C ratio, n (%)	MAU	78 (100)	64 (78)	<0.001
	Proteinuria	0*	18 (22**)	
eGFR, ml/min/1,73 m^2		73 (66-81)	60 (56-64)	<0.001
eGFR degree, ml/min/1,73 m^2, n (%)	≥90	6 (8)	2 (2)	<0.001
	89-60^z	69 (88)	39 (48)	
	<60^z	3 (4)	41 (50)	

Notes: * – 95% CI [0-3%]; ** – 95% CI [14-32%]; z – statistically significant difference by z-test

DISCUSSION

To date, the problem of AH among rural dwellers is being actively studied worldwide [21, 22]. At the same time, there is lack of such studies in Ukraine [1, 23]. The largest breakpoints were BP monitoring at the frequency recommended by the official guidelines on AH management (67% and 71% gap in compliance in Lviv and Poltava regions) and achieving normal BP while on treatment (76% and 65% gap among patients with BP monitoring data in Lviv and Poltava regions). Thus, only 24% in Lviv region and 35% in Poltava region achieved the BP target [6]. These data are broadly consistent with the global trend in lower middle-income countries [21]. Well known that BP VVV is associated with cardiovascular risk factors [24], AH-mediated target organ damage [12, 13, 25-27] and major adverse CVD events [9, 10, 28], thus seems to be of crucially importance at different stages of CVD continuum. The present study, enrolled predominantly young and middle-age males with uncomplicated AH, demonstrated that HBPV was associated with more pronounced AH-mediated subclinical target organ damage, namely the LV mass index, carotid arteries and kidneys, which was in agreement with other available studies [12, 13, 25-27]. Moreover, HBPV was also associated with more advanced hypertensive retinopathy, that may reflect potential pathophysiological associations of BP variability with retinal microvascular abnormalities in AH [29, 30]. At the same time, the obtained results are worth consideration due to several aspects. Firstly, there are based on the regional real-world data, which might be helpful in the context of global AH monitoring, including the rural areas [21, 22]. Secondly, based on world and local evidence [1, 6, 21, 23, 31, 32], rural males with AH form the vulnerable population in terms of high risk of adverse cardiovascular events. Previous study [1] enrolled the rural dwellers of Ukraine and has revealed significant gender difference in terms of AH control. Among rural males, there was a much lower awareness of the disease, half the rate of antihypertensive treatment, and nearly five times lower its effectiveness, as compared to females [1]. These results are also compatible with the existed world data [21, 22].

In an earlier paper [33] on this problem, we studied the profile of CVD risk factors among the above mentioned patients and revealed the positive correlation of SBP VVV with the SCORE cardiovascular risk value. Bearing in mind the results of the present work, namely the differences between HBPV and LBPV in terms of the certain parameters being studied (LVH, eGFR <60 ml/min/1.73 m^2 and any carotid stenosis cases, along with CCA IMT value), it is reasonable to suppose that HBPV could be a potential marker of more advanced AH-mediated target organ damage.

CONCLUSIONS

The HBPV in rural males with uncomplicated AH was associated with more pronounced subclinical target organ damage (more advanced LVH, carotid arteries wall IMT, worse kidneys' filtration function and higher level of proteinuria). The cases of stenosis and significant stenosis (≥50%) of the certain external carotid arteries were more frequent among HBPV patients, likewise more advanced hypertensive retinopathy.

Further regional research on the various clinical aspects of AH, including BP variability, might be useful in extending the existed world evidence on the prevention of AH -related complications. The data should be collected from patients of different age categories, taking into consideration gender aspects, location (urban vs. rural), standard of leaving and CVD risk factors. These activities should be aimed at making timely decisions at the regional level on the organization of medical care, including preventive measures.

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