THE ASSOCIATION BETWEEN OBESITY AND VISIT-TO-VISIT VARIABILITY IN SYSTOLIC BLOOD PRESSURE: A PROSPECTIVE STUDY

Sanja Stojanovic[1], Marina Deljanin Ilic[1], Stevan Ilic[1], Nebojša Tasic[2], Bojan Ilic[1], Dejan Petrovic[1], Dalibor Dragisic[2], Svetlana Djukic[3], Marina Jovanovic[3]
[1]Institute of Cardiology "Niska Banja", Medical Faculty University of Nis, Serbia
[2]University Hospital Center "Dr Dragisa Misovic-Dedinje", Belgrade, Serbia
[3] Faculty of Medical Sciences University of Kragujevac, Kragujevac, Serbia

POVEZANOST GOJAZNOSTI I VARIJABILNOSTI SISTOLNOG KRVNOG PRITISKA PRILIKOM POSETA: PROSPEKTIVNA STUDIJA

Sanja Stojanović[1], Marina Deljanin Ilić[1], Stevan Ilić1, Nebojša Tasić[2], Bojan Ilic[1], Dejan Petrović, Dalibor Dragišić2, Svetlana Đukić3, Marina Jovanović3
[1] Institut za kardiologiju "Niška Banja", Medicinski fakultet Univerziteta u Nišu, Srbija
[2]Univerzitetski bolnički centar "Dr Dragiša Mišović-Dedinje", Beograd, Srbija
[3] Medicinski fakultet Univerziteta u Kragujevcu, Kragujevac, Srbija

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ABSTRACT

With the prevalence of obesity and all accompanying health risks, both prevention and health education, as well as identifying predictors for the development of obesity-related diseases are primary. The pathophysiological relationship between obesity and visit-to-visit variability in systolic blood pressure (SBPV) has not been completely resolved.

To investigate the association between obesity and SBPV in hypertensive patients.

The prospective study comprised three visits was performed at the hypertension outpatient clinic during the follow up period of 22-months between March 2014 and January 2016.

This study included 300 randomly selected hypertensive patients (average 67.76±9.84 years), who were divided in groups of obese/non-obese examinees. SBPV was defined as the standard deviation (SD) from three values of SBP.

The values of SBP and SBP-SD were significantly higher in the group of obese hypertensive patients than in the group of non-obese patients (126.67±8.22 vs 120.45±7.79 mmHg, 11.00±5.64 vs 7.34±3.96; p<0.01). The highest SBPV was recorded in the 4th quartile in obese patients (43.13±7.50 mmHg). There was statistically stronger correlation between SBPV and BMI/Waist cirumferences (WC) (ρo=0.425/ ρo=0.356, p<0.01). During 22-months follow up there was a significant decrease of SBPV for 8.2 mmHg, BP for 31/8 mmHg, BMI for 3.8 kg/m², WC for 10 cm and body weight for 8.24 kg.

During 22-months follow-up, reduction of body weight was associated with reduction of blood pressure variability in hypertensive patients. Persistently decrease both body weight and long term visit-to-visit variability may explain lower cardiovascular risk in obese-related disease.

Key words: *Obesity, hypertension, visit-to-visit systolic blood pressure variability.*

SAŽETAK

Sa prevalencijom gojaznosti i svih pratećih zdravstvenih rizika, primarna je preventivna i zdravstvena edukacija, kao i identifikovanje prediktora za razvoj bolesti povezanih sa gojaznošću. Patofiziološki odnos između gojaznosti i varijabilnosti sistolnog krvnog pritiska prilikom poseta pacijenta (SBPV) nije u potpunosti jasan.

Istražiti povezanost između gojaznosti i SBPV kod hipertenzivnih pacijenata.

Prospektivna studija je obuhvatila tri posete u ambulanti za hipertenziju tokom perioda praćenja od 22 meseca u period od marta 2014 i januara 2016 godine.

U ovoj randomiziranoj studiji uključeno je 300 hipertenzivnih pacijenata (prosečne starosti 67,76 ± 9,84 godina), koji su podeljeni u grupu gojaznih i negojaznih ispitanika. SBPV je definisan kao standardna devijacija (SD) tri vrednosti SBP.

Vrednosti SBP i SBP-SD bile su znatno veće u grupi gojaznih hipertenzivnih pacijenata nego u grupi ne-gojaznih pacijenata (126.67 ± 8.22 vs. 120.45 ± 7.79 mmHg, 11.00 ± 5.64 vs 7.34 ± 3.96, p <0.01). Najveći SBPV zabeležen je u četvrtom kvartilu kod gojaznih pacijenata (43,13 ± 7,50 mmHg). Dokazana je statistički jaka korelacija između SBPV i BMI / obim struka (OS) (ro = 0,425 / ro = 0,356, p <0,01). Tokom 22-mesečnog praćenja došlo je do značajnog smanjenja SBPV za 8,2 mmHg, BP za 31/8 mmHg, BMI za 3,8 kg / m2, OS za 10 cm i telesne težine za 8,24 kg.

Tokom 22-mesečnog praćenja pacijenata, smanjenje telesne težine bilo je povezano sa smanjenjem varijabiliteta krvnog pritiska kod hipertenzivnih pacijenata. Konstatno smanjenje i telesne težine i dugotrajna varijabilnost sistolnog krvnog pritiska prilikom poseta moze se objasniti nižim kardiovaskularnim rizikom kod gojaznih bolesti.

Ključne reči: *gojaznost, hipertenzija, varijabilnost sistolnog krvnog pritiska prilikom poseta*

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Corresponding author: Sanja Stojanovic,
Institute for treatment and rehabilitation "Niska Banja", Nis, Serbia; Bulevar Nemanjića 105/8, 18000 Nis, Serbia
018 221193, 063 1917381, sanjastdr@gmail.com

INTRODUCTION

Obesity and hypertension (HT) are health and economic problems that pandemically spread and increase the risk of cardiovascular events. Worldwide, prevalence of arterial hypertension is about 25-40% in the adult population, which is over 1 billion people (1). As per World Health Organization report, more than 1.9 billion adults aged 18 years and older were overweight in 2015. (2) In Serbia 56.3% of people are overweight in 2014. The more and more concerning fact is that younger population in Serbia is obese (3).

Through human evolution adipose tissue have been a number of protective roles: energetic, metabolic and immunological. In modern society, hypercaloric diets, physical inactivity, make adipocytes show their other side, which means they secrete different bioactive molecules. Researchers have documented that the disorder of immunometabolic regulatory mechanisms, altered levels of proinflammatory adipokines, and "state of low-grade inflammation", oxidative stress in adipose tissue, activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) are the pathogenetic link between central fat accumulation, insulin resistance, hyperlipidemia, and hypertension, which precedes the development of metabolic and vascular disorders (4-6). Obesity, especially visceral adiposity is associated with 65–75% increased risk of the primary (essential) hypertension in overal population It is well know that blood pressure (BP) increases with the body mass index (BMI) on every kilogram of the body mass increase, the BP increases for 2-3 mmHg (7).

On the other hand, recent data indicate that not all obese patients have hypertension and that approximately 10-30% of obese people are not affected by metabolic abnormalities. Recent researchers show that there are 6 different phenotypes of body composition, with different degree of nutrition and metabolic functions, out of which the fifth phenotype is metabolically 'healthy' obesity (MHO). (8,9,10)

Many studies have shown that visit-to-visit variability in systolic blood pressure (SBPV) is independant predictor of clinical events and independant risk factor in hypertensive patients and in overall population (11-13). There are very few studies which examined the correlation between obesity and variability of blood pressure in hypertensive patients (14,15). The questions whether body fat mass, central or peripheral, is harmful for the metabolic status has not been completely resolved, neither has the pathophysiological relationship between blood pressure variability (BPV) and cardiovascular disease.

According to recent reports which indicate that SBPV is independent cardiovascular risk factor and high prevalence of obesity-related diseases, the objective of this study is to investigate the association between obesity and visit-to-visit variability in systolic blood pressure in hypertensive patients.

MATERIALS AND METHODS

Prospective study included 300 randomly selected hypertensive patients (147 men and 153 women, average age 67.76±9.84), who were divided, according to BMI≥30 kg/m^2, to subgroups of obese (n=153) and non-obese examinees (n=147). The study comprised three visits during the follow up period of 22-months. High and unregulated or inadequately regulated blood pressure was included as criteria in the study. The criteria for non-inclusion were: patients with associated diseases of the digestive and renal systems, acute infections in the past three months, neoplastic diseases, diabetes mellitus, surgery in the previous year, weight changes >5 kg within the previous 6 months. BP values were defined by the arithmetic mean of three measurements each of the study visits.

All participants were included in this study at the Institute for Treatment and Rehabilitation "Niska Banja", Niska Banja, Serbia from March 2014 to February 2016. Ethics Committee of Institute for Treatment and Rehabilitation "Niska Banja" approved the study and fully informed written consent was obtained from each patient prior to the investigation.

All participants signed epidemiological questionnaire which were divaded general information, health information, medication situation, family health information and diet and lifestyle.

Hypertension was defined as BP≥140/90 mmHg and/or antihypertensive drug therapy according to the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines (16). In order to estimate detailed evaluation of distribution SBPV quartiles of SBP-SD were formed. SBPV for each participant was defined using the standard deviation from 3 values of SBP. High SBPV was defined as SBP-SD in the 4th quartile.

Obesity was evaluated through body weight (BW), body mass index BMI≥30 kg/m^2 and waist cirumferences WC≥94 cm for males and WC≥80 cm for females. BW measurement (kg) was performed using a digital scale with the accuracy of measuring up to 0.1 kg. Body height measurement (cm) was performed using anthropometer (altimeter), with the accuracy of measurement to the nearest 0.5 cm. We used the most recent weight to calculate BMI, which was calculated as weight in kilograms divided by the square of height in meters. The measurement of WC was performed in a standing position, with heels apart, arms relaxed besides the body, and was measured in the middle distance between the rib cage and the iliac bone on the middle axillary line (at the level of the umbilicus). WC was used as an index of central obesity (17).

STATISTICAL ANALYSIS

All analysis were performed using IBM SPSS Statistics 20.0 software using descriptive and analytical methods. All the data were presented as means ± standard deviations

(SD), as absolute numbers and percentages, dependent on the statistical method used. The chi-square test was used to analyze differences between categorical data. To analyze continuous data distribution and to compare the means of the two examinee groups was applied the Student T-test. The comparison of mean parameters of obesity, BP and visit-to-visit SBPV was achieved using analysis of variance (ANOVA). The 25th, 50th and 75th percentiles were calculated in order to determine the 4 quartiles of the SBP-SD distribution. Bivariate correlation analysis (Spearman's correlation coefficient) was used to estimate the association between parameters of obesity, BP and SBPV. All statistical analysis were two-tailed, performed for the statistical significance level of $p<0.05$.

RESULTS AND DISCUSSION

Table 1. presents baseline and anthropometric characteristics and visit-to-visit variability in sistolic blood pressure of the study group across visits.

The prevalence of obesity evaluated through BMI in hypertensive subjects at the beginning of the follow-up was 153 (51%) and it was evaluated as WC 192 (64%). During 22-months follow up (across three visits) there was a significant decrease in prevalences of obesity defined according to BMI (51% vs. 32% vs. 17%, $p<0.05$, respectively) and WC (64% vs. 39% vs. 23%, $p<0.01$, respectively). There was significant decrease in the apsolute and relative values of SBPV across the three study visits (16.20±13.34 vs. 9.91±6.80 vs. 8.04±4.43 mmHg, $p<0.01$, respectively) and (10.66% vs. 7.34% vs. 6.64%, $p<0.01$, respectively). Moreover, the values of SBP were significantly lower (152.42±14.97 vs. 135.18±10.13 vs. 121.51±8.17 mmHg, $p<0.01$, respectively).

All parameters of both blood pressure and obesity are in significant, positive and moderate correlations (Table 2). It is also, statistically stronger correlation between SBP-SD and BMI as parameter of total obesity compared to large correlation with WC as parameter of central obesity ($\rho o=0.425$ vs. $\rho o=0.356$, $p<0.01$).

The baseline parameters of blood pressure and obesity after the first and the third visits in non-obese and obese hypertensive patients are shown in Table 3.

All parameters of blood pressure and obesity were significantly lower in obese patients after the third visit compared to baseline values ($p<0.01$), except DBP. The values of SBP and SBP-SD after the third visit were significantly higher in the group of obese hypertensive patients than in the group of non-obese patients (127.06±8.30 vs 120.37±7.75 mmHg, 11.29±5.67 vs 7.37±3.94; $p<0.01$). The difference between DBP was not statistically significant ($p>0.05$).

Characteristics across quartiles of the SBP-SD in hipertensive obese and non-obese patients after the third visit are presented in Table 4. There was significantly higher

Table 1. Baseline and anthropometric characteristics of the study group

PARAMETERS	VISITES			P value
	1.	2.	3.	
Age (years)	67.02±9.21	67.73±9.78	68.53±9.97	>0.05
Sex (M/W)	147/153	147/153	147/153	>0.05
BMI≥30 kg/m² (N/%)	153 (51%)	96 (32%)	51 (17%)	**<0.05**
WC≥94(80) cm (N/%)	192 (64%)	117 (39%)	69 (23%)	**<0.01**
Weight (kg)	83.34±10.68	78.14±10.35	75.10±10.77	**<0.01**
Absolute value of SBP (mmHg)	152.42±14.97	135.18±10.13	121.51±8.17	**<0.01**
Relative value of SBP - Cv (%)	9.82%	7.49%	6.76%	**<0.01**
SBPV - SBP-SD (mmHg)	16.20±13.34	9.91±6.80	8.04±4.43	**<0.01**
Relative value of SBP-SD - Cv (%)	10.66 %	7.34%	6.64%	**<0.01**
DBP (mmHg)	85.08±10.68	82.78±10.35	80.14±9.71	**<0.05**

BMI = body mass index, **WC** = Waist cirumferences, **BP** = Blood pressure, **SBP** = systolic BP, **BPV** = blood pressure variability - **SBP-SD** = standard deviation of systolic blood pressure, **DBP** = diastolic BP. **Cv** - coefficient of variation = SD/mean*100 (%).

Table 2. Correlation between parameters of blood pressure and parameters of obesity

Spearman correlation coefficient	SBP-SD	Blood pressure		Obesity		
		SBP	DBP	BW	BMI	WC
SBP-SD	-	0.633**	0.467**	0.428**	0.425**	0.356**
SBP	0.633**	-	0.777**	0.321**	0.359**	0.360**
DBP	0.467**	0.777**	-	0.170	0.262*	0.313**
Body weight	0.428**	0.321**	0.170	-	0.749**	0.743**
BMI	0.425**	0.359**	0.262*	0.749**	-	0.663**
WC	0.356**	0.360**	0.313**	0.743**	0.663**	-

** P<0.01* P<0.05

SBP-SD = standard deviation of systolic blood pressure, **SBP** = systolic blood pressure, **DBP** = diastolic blood pressure, **BW** = Body weight, **BMI** = body mass index, **WC** = Waist cirumferences.

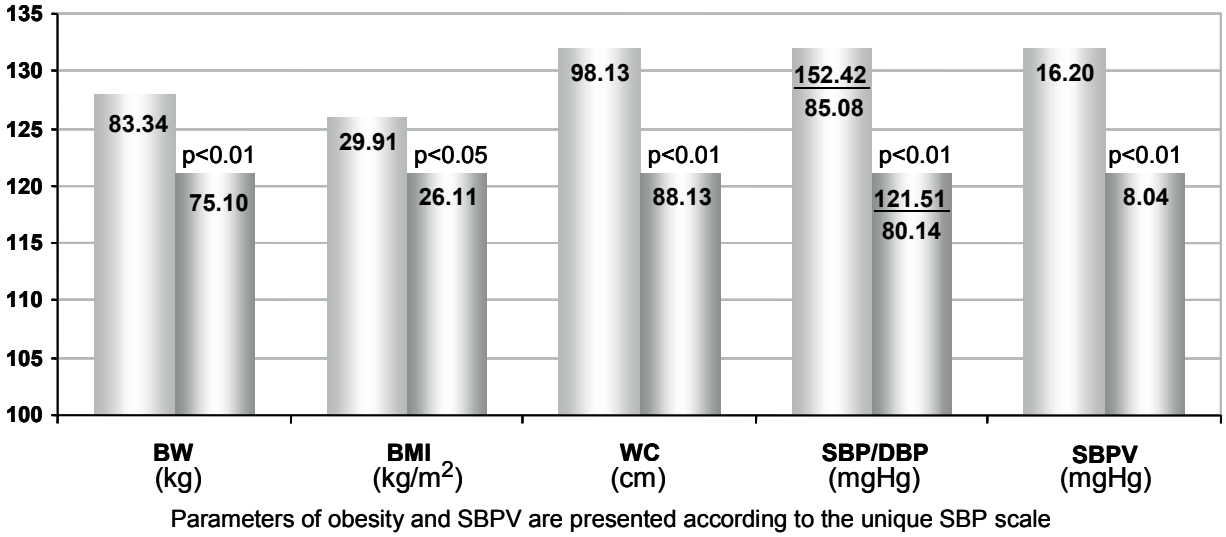
Table 3. Mean values of parameters of blood pressure and obesity after the first and the third visits

PARAMETERS	**Obese patients** (BMI>30)		**Non-obese patients** (BMI≤30)		P value
	N=153	N=51	N=147	N=249	
	1. visit	3. visit	1. visit	3. visit	
SBP-SD (mmHg)	16.52±9.41	11.29±5.67	15.87±17.05	7.37±3.94	0.001
SBP (mmHg)	154.21±15.20	127.06±8.30	150.56±14.59	120.37±7.75	0.007
DBP (mmHg)	87.04±9.18	81.18±7.40	83.03±8.75	79.93±5.22	0.058
Body weight (kg)	91.78±9.45	86.11±8.50	74.56±8.49	72.85±8.24	0.001
BMI (kg/m^2)	33.46±2.21	32.05±1.90	26.21±2.45	24.89±2.85	0.001
WC (cm)	106.12±11.17	101.82±11.07	89.81±10.16	85.33±8.86	0.001

SBP-SD = standard deviation of systolic blood pressure, **SBP** = systolic blood pressure, **DBP** = diastolic blood pressure, **BW** = Body weight, **BMI** = body mass index, **WC** = Waist cirumferences

Table 4. Characteristics across quartiles of the SBP-SD after the third visit

GROUPS	QUARTILES				P value
	1	2	3	4	
OBESE PATIENTS	6.67±2.13	11.67±3.56	25.08±4.35	43.13±7.50	p<0.001
NON-OBESE PATIENS	5.52±1.68	8.12±3.25	20.15±4.21	34.29±5.40	p<0.001



Graph 1. Change of values of obesity and blood pressure parameters at the beginninig and the end of the study

value of SBP-SD in hipertensive obese and non-obese patients in the fourth quartile compared to the values recorded in the other three quartiles. The highest SBPV was recorded in the 4th quartile in obese patients compared to SBPV in the 4th quartile of non-obese patients (43.13±7.50 mmHg vs. 34.29±5.40, p<0.001).

Graph 1. presents the change of values of obesity and blood pressure parameters**.** Comparative analysis of the follow-up data of all hypertensive subjects showed statistically significant average reduction of SBP-SD for 8.2 mmHg, BP for 31/5 mmHg, BW for 8.24 kg, BMI for 3.8 kg/m^2 and WC for 10 cm, at the end of study compared to baseline values.

DISCUSSION:

With the prevalence of obesity in the young, which should already be considered as a pandemic phenomenon (with all accompanying health risks), both prevention and health education, as well as identifying predictors for the development of obesity-related diseases are primary. Etiopathophysiology of development obesity and hypertension is very complicated including a great variety of factors (socio-economic factors, age, sex, menopause) and biological mechanisms (insulin resistance, chronic proinflammatory state, stimulation of the sympathetic nervous system as well as the RAAS, renal and heart dysfunction) which lead to abnormal circardial rhythm of blood pressure. On

the other hand, the role of fat tissue distribution, adipocyte characteristics and products had been involved in the attempt to explain the occurrence of hypertension in the presence of obesity.

Result of famous The Framingham Heart Study during 44-years, showed that obesity as an independent risk factor for cardiovascular disease and prevalence of obesity (evaluated throught body weihgt, including overweight and obesity) in 5209 hypertensive subjects, was approximately 26% in men and 28% in women (18,19). We have found higher prevalence of obesity, particularly abdominal obesity compared to total obesity in hypertensive patients (64% vs. 51%). During 22-months follow up there was a significant decrease in prevalences of obesity (23% vs. 17%). Our results showed significant differences in prevalence of central obesity in women, probably caused by both mutual up-regulation of protective hormones and **fat storage** and redistribution. Large adipocytes of visceral fat are dysfunctional due to the increased secretion of pro-inflammatory factors, reduced secretion of the insulin, estrogen and adiponectin, which increases the presence of chronic subclinical inflammation, the degree of insulin resistance, and metabolic disorders.

Due to frequent spontaneous variation of the blood pressure values during 24 hours, one month or one years, as well as the significance of obesity-related hypertension disease, is important for successful therapy and adequate control BP, without target organ damage. The greatest disadvantages of the classic measurement of BP are the inadequate insight in circardial rhythm and the phenomenon of peripheral resistance. On the other hand, hour 24-hours ambulatory blood pressure monitoring on healthy population has shown technical problems - significant variation on single measurements, compared with the values achived applying classic measurements (20).

The majority of studies (21,22) have analysed sensitivity of many different parameters of visit-to-visit BPV concerning the estimation of prediction of cardiovascular events (CVE): standard deviation, standard deviation independent of the mean (SDIM), coefficient of variation (CV), successive variation (SV), average real variability (ARV), range. We followed the standard deviation of SBP, as it was the simplest and the best indicator of future CVE due to the fact that other parameters of BPV were closely correlated and give similar reflections of BPV.

Just in the past decade, results from research groups (23-25) have documented a relationship between the reduced body weight and abdominal obesity and lower valuae of BP.

Understanding the complex relationship between obesity and hypertension these entities are important in clearing of the increasing prevalence of CVE. According to recent results (14,24,25), we have found, that values of visit-to-visit SBPV were significantly lower in non-obese hypertensive patients compared to obese hypertensive patients (7.37±3.94 vs. 11.29±5.67, $p<0.001$).

This is probably caused by the increase in sympathetic activity, insulin and vascular resistence, and the concentrations of proinflammatory cytokines, which leads to the increased heart pumping activity in hypertension accompanied with obesity. In non-obese patients, the possible mechanisms in the decreased baroreceptor sensitivity, as the results of dysfunction of neurohumoral regulation, as well as the structural and funtional changes on heart and blood vessels.

Our results showed in consistent with the several study there was significant, positive and moderate correlations between SBPV and all parameters of obesity ($p<0.01$) and there was average decrease SBPV across visits (16.20 vs 9.91 vs 8.04 mmHg, $p<0.01$), and also, the highest SBPV was recorded in the 4th quartile in obese patients (43.13 mmHg). The results of the recent study (14) similarly designed as our research, which included more participants (14988) beloning to general population showed the positive correlation between both total and central obesity with BPV. BPV was 6.89 mmHg across study visits.

In addition, the recent The Dallas Heart Study (26) *indicate the significance of the correlation between visceral fat mass distribution measured by dual X-ray absorptiometry (the modern advanced way of measuring abdominal obesity) and s*hort-term and long-term BPV during 5-month-period of observing 2595 overweight subjects with mean BP 127/79 mmHg and BMI 29 kg/m^2. Long-term BPV was 9.8 mmHg across overall visits.

Our study included only hypertensive patients with untreated BP values and the registered values of visit-to-visit SBPV was 8.2 mmHg, which was higher compared to general population in the previously mentioned study. Our results indicate the importance of distribution of fat mass, as well as the more significant impact of BMI as indicator total obesity than of WC, as parameter of central obesity on SBPV in hypertensive patients.

The recent study Tadic and all. (15) showed the relationship between parameters of obesity, BPV and remodeling of right ventricle in hypertensive patients with different nutrition degree. The increased body mass leads to the increased metabolic needs of an organism, extracellular fluid volume expansion, faster blood flow through both adipose and non-adipose tissue and organs, especially through heart, kidneys, skeletal muscles, which parallelly leads to the cardial output increase. However, it can later lead to reduction of "reserve" blood flow and damage of flow endothelium-dependent vasodilation. The rapid endothelial dysfunction along with the arterial stiffening and blood-flow variability lead to vascular endothelial dysfunction and the cascade of CVE, which was also proved in the studies (27-29).

Additionally, central fat accumulation contributes to the changes in the serum levels of adipokines, and also contributes to the decrease of insulin sensitivity, as well as the increase of the activity of the sympathetic nervous system. Large adipocytes are dysfunctional due to the in-

creased secretion of pro-inflammatory factors, reduced secretion of the protective hormones (insulin, estrogen and adiponectin), which increases the presence of chronic subclinical inflammation, and dysregulation of metabolic homeostasis. On the other hand, in hypertensive state, the formed "*circulus vitiosus*" is easily maintained by the up-regulated levels of proinflammatory cytokines and adipokines (30).

Finally, during 22-months follow up, the appropriate diet, the increase in physical activity and antihypertensive therapy, resulted in reduced obesity parameters, particularly body weight, and adequate control of BP, which significantly decreased the values of SBPV.

Similarly to the results presented in a recent study (31) our results showed the long-term effect weight loss on BP, statistically significant average decrease of SBPV for 8.2 mmHg, BP for 31/8 mmHg, BMI for 3.8 kg/m^2 and WC for 10 cm.

Reduction of all parameters of obesity is the most important step in reducing hypertension, and adequate control of BP and metabolically 'healthy' obesity. The results of a recent study showed that during a four- year-follou-up of 181 obese hypertensive patients, a 10 percent weight-loss produced an average of a 4.3/3.8 mmHg decrease in BP. The results of this study showed that the of weight loss for 1 kg produced an average of a 2.1 mmHg reduction in SBP, which could be the results of multiple antihypertensive effects and mechanisms: decrease visceral fat of accumulation, lower simpthatectic nerve activity and improved elasticity of blood vessels. Our results showed that reduction weight for 1 kg produced an average of a 3.76/0.61 mmHg reduction in BP and 1 mmHg in SBPV. Also, reduction weight increased the effectiveness of BP treatment.

Significant factor that contribute to the impact of obesity on BPV in hypertensive patients are distribution of body fat, duration of obesity as well as the degree of target organ injury. The additional important factor is how obesity parameters variability during the long period (several years) influences the BPV, because prolonged obesity leads to development of uncontrolled blood pressures and cardiovascular complications (8,32,33).

CONCLUSION

Results of this study, showed that obesity is strongly correlated with higher variability of systolic blood pressure across study visits. During 22-months, reduction of body weight was associated with reduction of blood pressure values, and lower value of blood pressure variability. Persistent decrease of both BP and long term visit-to-visit variability may explain lower cardiovascular risk in obese-related diseases.

Conflict of interest:
All authors declare no conflict of interest.

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