

Original Research

Visit-to-Visit Blood Pressure Variability and Arterial Stiffness Independently Predict Cardiovascular Risk Category in a General Population: Results from the SEPHAR II Study

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Introduction: The aim of our study was to evaluate visit-to-visit blood pressure variability (BPV) and the association of this parameter with cardiovascular risk determinants, according to the SEPHAR II survey.

Methods: Following a selection based on the multi-stratified proportional sampling procedure, a total of 1975 subjects who gave informed consent were evaluated by means of a questionnaire, anthropometric, blood pressure (BP) and arterial stiffness measurements (pulse wave velocity and augmentation index), 12-lead ECG recordings, and blood and urine analysis. BPV was quantified in terms of the standard deviation (SD) of the mean systolic blood pressure (SBP) and high BPV was defined as SBP-SD above the 4th quartile. Total cardiovascular risk was assessed by the 2013 ESH/ESC risk stratification chart.

Results: Mean BP was 132.37/82.01 mmHg. Mean systolic BPV was 6.16 mmHg, with 24.62% of values above the 75th percentile (≥ 8.48 mmHg). Factors found to be associated with high systolic BPV were age, SBP, pulse pressure, total and LDL-cholesterol, triglycerides, visceral obesity, diabetes mellitus, metabolic syndrome and increased aortic stiffness. In addition, in the hypertensive group high BPV was associated with the severity of hypertension and a lack of treatment control. Both visit-to-visit systolic BPV and aortic stiffness proved to be positively and independently correlated with the risk category. Based on these parameters it was possible to predict with 72.6% accuracy the probability of finding subjects in a high and very high cardiovascular risk category.

Conclusions: The results of our study indicate a notable prevalence of high BPV, affecting almost a quarter of the Romanian adult population. Visit-to-visit systolic BPV and arterial stiffness are strongly correlated and together might contribute to the improvement of cardiovascular risk prediction models.

Blood pressure variability (BPV) can be assessed either by standard deviation (SD) or by the coefficient of variation (the within-subject SD normalized for mean blood pres-

sure). These parameters can be calculated from repeated measurements in a clinical setting, which characterizes the inter-visit variability, or from successive measurements at short time intervals obtained

during 24-hour ambulatory blood pressure (BP) monitoring.^{1,2}

Visit-to-visit BPV has been considered mostly as a random fluctuation around a baseline, with some dependence on office BP measurement accuracy.^{3,4} Data gathered during the past 30 to 40 years, in both experimental and clinical studies, have brought clarifications regarding the determinants and the significance of BPV.⁵ A strong body of evidence indicates that visit-to-visit BPV is a reproducible, rather than a random phenomenon,⁶ and has an important impact on cardiovascular outcome.^{1,7-11} In 2000, Hata et al reported, in a retrospective case-control study, that office BPV, as expressed by the systolic and diastolic variation coefficient, was an independent predictor of brain infarction in elderly hypertensive patients.⁷ Subsequently, in 2002, the same author and his team revealed that diastolic office BPV is a predictor of myocardial infarction in treated hypertensives.⁸ In another study by Kikuya et al, day-by-day systolic BPV, defined as within-subject SDs of home measurements, was associated with cardiovascular and stroke mortality, but not with cardiac mortality.¹ In 2010, an analysis derived from the ASCOT-BPLA study showed that residual visit-to-visit variability of systolic BP was a strong predictor of stroke and coronary events in treated hypertensives, independent of mean systolic BP in clinic or ambulatory measurements.⁹ Results from the NHANES III survey have emphasized that systolic BPV is associated with a 50% increase in mortality risk for an $SD \geq 8.35$ mmHg in comparison with an $SD < 4.80$ mmHg.¹⁰ Recently, it has been reported that increased visit-to-visit BP fluctuations are significant indicators of cognitive impairment in high-risk elderly subjects.¹¹

More information is needed regarding the distribution of BPV in the general population, since the available data about visit-to-visit BPV are derived specifically from analyses of selected populations (treated or older hypertensives). In addition, finding the link between high BPV and increased cardiovascular risk may be considered as an open field of research. Consistent data indicate that overall 24-hour BPV is associated with target organ damage,^{12,13} but very few studies have addressed the association of visit-to-visit BPV with cardiac and vascular damage. Several hypotheses have been proposed to explain the mechanisms underlying increased BPV. It has been suggested that arterial stiffness may be one factor.¹⁴

The aim of our study was to evaluate visit-to-visit BPV and the association of this parameter with con-

ventional and emerging cardiovascular risk determinants according to the SEPHAR II survey (Study for the Evaluation of Prevalence of Hypertension and Cardiovascular Risk in Romania).

Methods

Study population

SEPHAR II is a cross-sectional national survey, approved by the local Ethics Committee and conducted on a representative sample of the Romanian adult population. The sample selection was based on the multi-stratified proportional sampling procedure and is described in detail elsewhere.¹⁵ Between 15th October 2011 and 15th March 2012, 2044 of the 2223 subjects approached by the investigators gave written consent to participate in the study. At the end of the study, only 1975 subjects provided valid data for analysis (completed questionnaires and both study visits), giving a response rate of 69.06%.

Data collection

The study comprised two study visits, 7-10 days apart. During the first visit, carried out at the subject's home, a trained general practitioner administered a 76-item questionnaire (including information on demographics, lifestyle, medical history, and main cardiovascular risk factors) and measured BP, heart rate and anthropometric parameters: weight – using an approved electronic scale, model Tanita HD 95 (maximum deviation of 0.1 kg); height – using a measuring device (maximum deviation of 0.5 cm); waist circumference, hip circumference, and arm circumference – using a tailor's measuring tool (maximum deviation of 0.5 cm). During the second visit, performed at the general practitioner's office, each subject had BP and heart rate measurements, laboratory tests, a 12-lead ECG – using a General Electric CardioSoft MAC600 1.02 device – and measurement of arterial stiffness parameters using a Medexpert Arteriograph IrDA system: aortic augmentation index (AIXao) and aortic pulse wave velocity (PWVao).

Fasting blood and urine samples were collected by trained nurses representing a central laboratory (Synlab Romania) for laboratory workup (fasting plasma glucose, glycated hemoglobin, total serum cholesterol, serum triglycerides, high-density lipoprotein [HDL]-cholesterol, low-density lipoprotein

[LDL]-cholesterol, serum creatinine, and serum uric acid, microalbuminuria and urinary creatinine).

Blood pressure measurements

At each study visit, three BP measurements were made using an automatic oscillometric BP measuring device – model A&D UA 95 Plus (A&D Company Limited, Tokyo, Japan) certified by the Association for the Advancement of Medical Instrumentation. Measurements were separated by at least 1 minute, in accordance with ESH/ESC recommendations.¹⁶

BP measurements were performed on the first visit at any time of day, depending on the availability of the enrolled subjects. On the second visit, BP measurements were made in the morning. On both occasions, the patient was not allowed to smoke, drink coffee, or do exercise for 30 minutes before the BP measurements.

BP values were defined by the arithmetic mean of the second and third measurements from each of the 2 study visits. The first BP measurement was not taken into account.

Blood pressure variability

Based on previous evidence, visit-to-visit BP variability was assessed as the SD of the mean systolic blood pressure (SBP).^{1,9-11}

Study subgroups

The study participants were divided into 4 subgroups according to the quartiles of SBP-SD. A separate analysis was conducted for hypertensive subjects.

Arterial stiffness measurements

The arterial stiffness parameters PWV_{ao} and AIX_{ao} were measured during the second study visit, using an Arteriograph IrDA (Medexpert, Budapest, Hungary). This device determines PWV and AIX by analysis of the oscillometric pressure curves registered on the upper arm. Measurements were performed according to a specific methodology. The reproducibility of measurements with this device is $1.18 \text{ m}^2/\text{s}^2$.¹⁷

Definitions

Hypertension and target organ damage were defined according to current ESH/ESC guidelines,¹⁶ and di-

abetes mellitus (DM) in conformity with the actual position statement of the American Diabetes Association.¹⁸ Obesity was diagnosed by a body mass index $\geq 30 \text{ kg}/\text{m}^2$ and visceral obesity by a waist-to-hip ratio > 0.95 for males and > 0.85 for females. Metabolic syndrome and the reference values for lipids were defined using NCEP ATP III criteria.¹⁹ Lipid disorders were defined as follows: total serum cholesterol $\geq 200 \text{ mg}/\text{dL}$, LDL-cholesterol $\geq 130 \text{ mg}/\text{dL}$, HDL-cholesterol $\leq 40 \text{ mg}/\text{dL}$ for men and $\leq 50 \text{ mg}/\text{dL}$ for women, triglycerides $\geq 150 \text{ mg}/\text{dL}$. Left ventricular hypertrophy was assessed by Cornell product $\geq 2440 \text{ mm}\cdot\text{ms}$ on 12-lead ECGs. Renal impairment was considered mild if $\text{eGFR}_{\text{MDRD}}$ was between 60-90 mL/min/1.73m² and moderate to severe if $\text{eGFR}_{\text{MDRD}}$ was $< 60 \text{ mL}/\text{min}/1.73\text{m}^2$. Albuminuria was defined by a urinary albumin to creatinine ratio of 30-300 mg/g, while values $> 300 \text{ mg}/\text{g}$ defined macroalbuminuria. Cardiovascular risk categories were defined according to the current ESH/ESC risk stratification chart.¹⁶

Statistical analysis

A descriptive analysis (means, medians, standard deviations, and range for continuous data and frequency analysis for categorical data) was performed for all the target variables. The 25th, 50th and 75th percentiles were calculated in order to determine the 4 quartiles of the SBP-SD distribution.

The Kolmogorov–Smirnov test was used to analyze continuous data distribution, according to which ANOVA or the Kruskal–Wallis test were further used in analysis for differences between means of the 4 independent study subgroups. The chi-square test was used to analyze differences between categorical data.

Bivariate correlation analysis (Spearman correlation coefficient calculation) was used to validate the association between BPV and variables for which statistically significant differences between the 4 study subgroups were highlighted.

Binary logistic regression using a stepwise likelihood ratio method including multicollinearity testing (tolerance less than 0.1 and VIF value greater than 10) was used for validation of predictors of high and very high total cardiovascular risk category (as dependent variable).

Adjustments for major confounders (age, sex, differences in mean SBP between the 2 study visits, heart rate, total cholesterol, LDL-cholesterol, triglycerides, visceral obesity, diabetes mellitus, and smoking) were made whenever considered appropriate.

The performance of the prediction model was assessed by receiver operating characteristics (ROC) curve.

Statistical analysis was performed using IBM SPSS Statistics 20.0 software at a chosen significance threshold of $p < 0.05$.

Results

The characteristics of the study group are summarized in Table 1.

Blood pressure variability

Mean BP was 132.37/ 82.01 mmHg. The standard deviation of SBP across the two study visits ranged be-

tween 0 and 72.12 mmHg, having a mean value of 6.16 mmHg. The 25th, 50th, and 75th percentile values were 1.41 mmHg, 3.88 mmHg, and 8.48 mmHg, respectively. The first quartile included SD values < 1.41 mmHg, the second quartile included values between 1.41-3.88 mmHg, the third quartile included values between 3.89-8.48 mmHg, and the fourth quartile included values ≥ 8.49 mmHg.

Almost one quarter (24.62%) of the study group had an SD of the SBP values in the highest quartile.

Mean heart rate was 74.57 ± 10.10 beats per minute, ranging from 46 to 143 beats per minute, 63.4% of subjects having a heart rate above 70 beats per minute (1253 cases).

Rates of hypertension prevalence, treatment, and control

Hypertension was detected in 798 subjects (40.41%); 472 (59.1%) of the hypertensive subjects were treated and only 111 (25%) of treated patients achieved BP values $< 140/90$ mmHg.

Distribution of cardiovascular risk categories

Cardiovascular risk categories were distributed as follows: low risk, 843 subjects (42.7%); moderate risk, 423 subjects (21.4%); high risk, 294 subjects (14.9%), very high risk, 415 subjects (21%). High to very high cardiovascular risk class was thus identified in 709 cases (35.9%).

Distribution of risk determinants across the four quartiles of blood pressure variability

Age, SBP, and pulse pressure were higher in the 4th quartile than in the other 3 quartile groups ($p < 0.0001$), with no significant differences for heart rate or sex. Similar distributions were observed for total and LDL-cholesterol levels and triglycerides (Table 2).

The proportion of obese subjects defined by waist to hip ratio increased significantly from the first quartile group ($p = 0.001$), while no significant differences were observed among the four groups for obesity defined by body mass index ($p = 0.065$).

Between the first and the fourth SBP-SD quartile there was a slight increase in the percentage of diabetic subjects ($p = 0.029$) and a highly significant rise in the number of hypertensives ($p < 0.0001$). Consequently, the metabolic syndrome was preponderant in the fourth quartile group, with 198 cases (29.3%)

Table 1. Baseline characteristics of the study group.

| | |
|---|--------------------|
| Age (years) | 47.14 \pm 15.41 |
| Female | 1038 (52.6) |
| Medical history | |
| • Myocardial infarction | 44 (2.3) |
| • Interventional myocardial revascularization | 19 (1) |
| • Surgical myocardial revascularization | 3 (0.2) |
| • Stroke | 41 (2.2) |
| Smoking | 532 (27.1) |
| Obesity | |
| • Body mass index ≥ 30 kg/m ² | 536 (27.5) |
| • Waist to hip ratio > 0.95 in males, > 0.85 in females | 844 (45.8) |
| Diabetes mellitus | 201 (10.2) |
| Metabolic syndrome (ATP III) | 1339 (68.2) |
| Lipid profile | |
| • Total cholesterol (mg/dL) | 205.16 \pm 46.22 |
| • Hypercholesterolemia | 1004 (50.84) |
| • LDL-cholesterol (mg/dL) | 133.03 \pm 42.04 |
| • High LDL-cholesterol | 979 (49.57) |
| • HDL-cholesterol (mg/dL) | 54.83 \pm 16.98 |
| • Low HDL-cholesterol | 580 (29.37) |
| • Triglycerides (mg/dL) | 128.67 \pm 117.9 |
| • Hypertriglyceridemia | 506 (5.62) |
| Arterial stiffness | |
| • PWVao (m/s) | 8.98 \pm 2.25 |
| • AIXao (%) | 30.34 \pm 17.2 |
| SBP (mmHg) | 132.37 \pm 21.34 |
| SBP-SD (mmHg) | 6.16 \pm 6.97 |
| • 25th percentile | 1.41 |
| • 50th percentile | 3.89 |
| • 75th percentile | 8.49 |
| Diastolic blood pressure (mmHg) | 82.01 \pm 11.25 |
| Pulse pressure (mmHg) | 50.46 \pm 15.93 |

Values are given as mean \pm SD (standard deviation) for continuous data and absolute number (percent) for categorical data. ATP III – Adult Treatment Panel III; HbA1c – glycosylated hemoglobin; PWVao – aortic pulse wave velocity, AIXao – aortic augmentation index, SBP – systolic blood pressure; SBP-SD – standard deviation of systolic blood pressure.

Table 2. Characteristics across quartiles of standard deviation of systolic blood pressure.

| | Q1 n=410 | Q2 n=556 | Q3 n=503 | Q4 n=506 | p |
|-------------------------------------|----------------|-----------------|-----------------|-----------------|----------------------|
| Age (years) | 44.24 ± 15.35 | 45.57 ± 14.80 | 46.61 ± 14.93 | 51.75 ± 15.61 | <0.0001* |
| Female sex | 213 (52.0) | 298 (53.6) | 261 (51.9) | 266 (52.6) | NS [†] |
| Male sex | 197 (21) | 258 (27.5) | 242 (25.8) | 240 (25.6) | NS [†] |
| Smokers | 108 (26.5) | 156 (28.2) | 138 (27.7) | 130 (25.9) | NS [†] |
| SBP (mmHg) | 127.39 ± 19.56 | 129.44 ± 19.44 | 132.26 ± 21.18 | 139.77 ± 22.93 | <0.0001* |
| Pulse pressure (mmHg) | 47.98 ± 14.89 | 48.53 ± 14.21 | 49.96 ± 15.34 | 55.09 ± 18.03 | 0.0001* |
| Total cholesterol (mg/dL) | 197.47 ± 43.6 | 204.21 ± 45.34 | 204.80 ± 45.7 | 212.81 ± 48.69 | 0.0001 [‡] |
| LDL-cholesterol (mg/dL) | 126.82 ± 40.37 | 131.66 ± 41.43 | 133.18 ± 40.86 | 139.43 ± 44.38 | <0.0001* |
| HDL-cholesterol (mg/dL) | 55.86 ± 16.98 | 55.33 ± 17.05 | 53.69 ± 16.86 | 54.59 ± 17.01 | NS* |
| Triglycerides (mg/dL) | 111.86 ± 74.58 | 126.68 ± 100.69 | 133.02 ± 152.11 | 140.18 ± 123.67 | <0.0001* |
| Obesity by BMI (kg/m ²) | 94 (17.5) | 147 (27.4) | 138 (25.7) | 157 (29.3) | NS [†] |
| Obesity by WHR | 161 (17.9) | 253 (28.1) | 225 (25) | 260 (28.9) | 0.001 [†] |
| DM | 30 (14.9) | 51 (25.4) | 54 (26.9) | 66 (32.8) | 0.003 [†] |
| HT | 128 (16) | 214 (26.8) | 196 (24.6) | 260 (32.6) | <0.0001 [†] |
| MS | 95 (15.2) | 170 (27.3) | 160 (25.7) | 198 (31.9) | <0.0001 [†] |

*Kruskal-Wallis test; [†]chi-square test; [‡]ANOVA; NS – not statistically significant ($p \geq 0.05$). Values are presented as mean ± standard deviation for continuous data and absolute number (percent) for categorical data. Q1-4 quartiles of SBP-SD; SBP – systolic blood pressure; BMI – body mass index; WHR – waist-to-hip ratio; DM – diabetes mellitus; HT – hypertension; MS – metabolic syndrome.

versus 95 cases (23.5%) in the first group ($p < 0.0001$) (Table 2).

PWVao had significantly higher values among subjects from the fourth quartile group compared to the values recorded in the other three groups, rising from a mean value of 8.69 ± 2.22 m/s up to 9.34 ± 2.18 m/s ($p = 0.001$). AIXao had a similar distribution across the four study groups, with highest values among the fourth quartile group and an increase from a mean value of $28.05 \pm 16.43\%$ up to $34.61 \pm 17.18\%$ ($p < 0.0001$). All these differences remained statistically significant after adjustment for age, visceral obesity, lipid disorders, mean SBP, and pulse pressure (Figure 1).

The proportion of subjects in the high and very high cardiovascular risk categories increased significantly from the first quartile to the fourth (from 102 subjects, 24.9%, to 250 subjects, 49.4%; $p < 0.0001$), differences that remained statistically significant after adjusting for age, visceral obesity, medical history, lipid disorders, mean SBP, and pulse pressure.

Distribution of risk determinants across the four quartiles of blood pressure variability in hypertensive subjects

Differences in aortic stiffness parameters were minor, reaching the statistical significance threshold only for PWVao (Table 3).

Although in the highest quartile group the number of hypertensive subjects with subclinical target organ damage was higher than in the other three groups, this difference did not reach statistical significance, most probably because of the low number of subjects in each group (Table 3).

The proportion of hypertensive subjects with uncontrolled BP values increased among the four groups, independently of the grade of hypertension. The highest proportion of uncontrolled hypertensive subjects was recorded in the fourth quartile group: 241 cases (35.4%) ($p < 0.0001$) (Table 3).

Blood pressure variability and cardiovascular risk categories

Factors found to be associated with increased BPV in the whole group were: age ($r_s = 0.173$, $p < 0.0001$); SBP ($r_s = 0.210$, $p < 0.0001$); pulse pressure ($r_s = 0.152$, $p < 0.0001$); lipid profile, i.e. total cholesterol ($r_s = 0.104$, $p < 0.0001$), LDL-cholesterol ($r_s = 0.099$, $p < 0.0001$), and triglycerides ($r_s = 0.111$, $p < 0.0001$); visceral obesity ($r_s = 0.073$, $p = 0.001$); diabetes mellitus ($r_s = 0.067$, $p = 0.003$); metabolic syndrome ($r_s = 0.111$, $p < 0.0001$); parameters of aortic stiffness, PWVao ($r_s = 0.115$, $p < 0.0001$) and AIXao ($r_s = 0.139$, $p < 0.0001$); and cardiovascular risk category ($r_s = 0.158$, $p < 0.0001$).

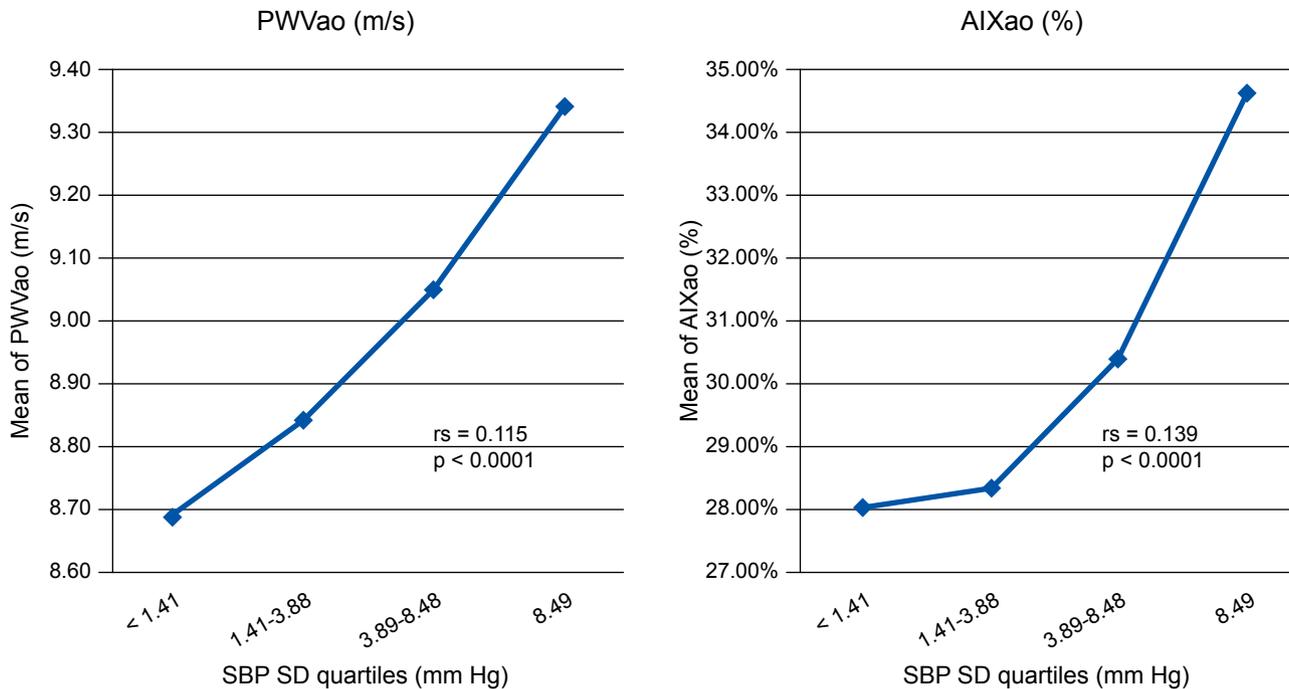


Figure 1. Distribution of arterial stiffness parameters across quartiles of SBP-SD. SBP – systolic blood pressure; PWVao – aortic pulse wave velocity; AIXao – aortic augmentation index; SD – standard deviation.

Table 3. Distribution of target organ damage and severity of hypertension across quartiles of standard deviation of systolic blood pressure in hypertensive subjects.

| | Q1 n=128 | Q2 n=214 | Q3 n=196 | Q4 n=260 | p |
|-----------------------------------|----------------|----------------|----------------|----------------|----------------------|
| Age (years) | 57.55 ± 13.69 | 54.93 ± 14.22 | 57.16 ± 12.54 | 59.59 ± 12.82 | 0.002* |
| Female | 80 (18.3) | 107 (24.4) | 105 (24) | 146 (33.3) | NS [†] |
| Male | 48 (13.3) | 107 (29.7) | 91 (25.3) | 114 (31.7) | NS [†] |
| Target organ damage | | | | | |
| • LVH on ECG | 1 (4) | 7 (28) | 7 (28) | 10 (40) | NS* |
| • Microalbuminuria | 8 (14) | 17 (29.8) | 9 (15.8) | 23 (40.4) | NS* |
| • Macroscopic proteinuria | 0 (0) | 3 (27.3) | 3 (27.3) | 5 (45.5) | NS* |
| • Serum creatinine (mg/dL) | 0.74 ± 0.18 | 0.75 ± 0.17 | 0.81 ± 1.07 | 0.78 ± 0.29 | NS [‡] |
| • eGFR < 60 mL/min/m ² | 6 (13.3) | 10 (22.2) | 10 (22.2) | 19 (42.2) | NS* |
| • PWVao | 10.03 ± 2.26 | 9.83 ± 2.25 | 10.65 ± 10.6 | 10.25 ± 9.9 | 0.046 [†] |
| • AIXao | 38.93 ± 16 | 36.87 ± 16.59 | 40.25 ± 17.68 | 40.39 ± 16.07 | NS [†] |
| Smokers | 23 (14.4) | 48 (30) | 28 (17.5) | 61 (38.1) | NS [†] |
| SBP (mmHg) | 127.39 ± 19.56 | 129.44 ± 19.44 | 132.26 ± 21.18 | 139.77 ± 22.93 | <0.0001 [‡] |
| Pulse pressure (mmHg) | 47.98 ± 14.89 | 48.53 ± 14.21 | 49.96 ± 15.34 | 55.09 ± 18.03 | 0.0001 [‡] |
| Total cholesterol (mg/dL) | 208.86 ± 42.34 | 216.53 ± 48.64 | 214.79 ± 46.43 | 217.83 ± 47.67 | 0.0341 [†] |
| LDL-cholesterol (mg/dL) | 135.73 ± 37.46 | 139.5 ± 43.35 | 138.28 ± 40.94 | 143.05 ± 43.8 | 0.0390 [‡] |
| HDL-cholesterol (mg/dL) | 57.61 ± 17.84 | 55.78 ± 19.43 | 53.10 ± 17.18 | 53.72 ± 16.74 | NS [‡] |
| Triglycerides (mg/dL) | 120.17 ± 66.92 | 156 ± 63.23 | 155.89 ± 61.16 | 170.89 ± 69.78 | 0.015 [‡] |
| Severity | | | | | |
| • Controlled HT | 20 (16.9) | 42 (35.6) | 37 (31.4) | 19 (16.1) | <0.0001 |
| • Uncontrolled HT | 108 (15.9) | 172 (25.3) | 159 (23.4) | 241 (35.4) | < 0.0001 |
| • Grade I HT | 66 (21.6) | 103 (33.8) | 62 (20.3) | 74 (24.3) | < 0.0001 |
| • Grade II HT | 34 (13.2) | 55 (21.3) | 74 (28.7) | 95 (36.8) | < 0.0001 |
| • Grade III HT | 8 (6.8) | 14 (12) | 23 (19.7) | 72 (61.5) | < 0.0001 |

*Chi-square test; [†]ANOVA; [‡]Kruskal-Wallis test; NS – not statistically significant ($p \geq 0.05$). Values are presented as absolute number (percent) for categorical data and mean ± standard deviation for continuous data. Q1-4 quartiles of SBP-SD; SBP – systolic blood pressure; PWVao – aortic pulse wave velocity; AIXao – aortic augmentation index; LVH – left ventricular hypertrophy; eGFR – estimated glomerular filtration rate by Modification of Diet in Renal Disease formula; HT – hypertension

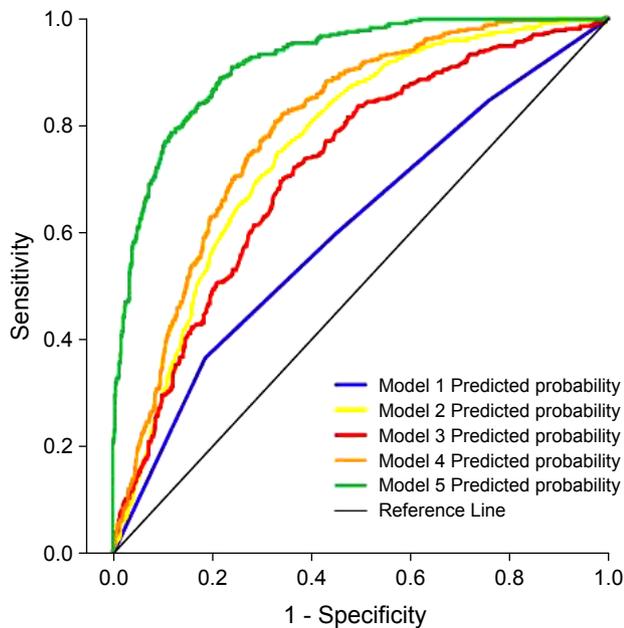


Figure 2. ROC curve for high and very high cardiovascular risk category prediction. ROC – receiver operating characteristic; CV – cardiovascular; SBP – systolic blood pressure; PWVao – aortic pulse wave velocity; AIXao – aortic augmentation index; PP – pulse pressure; SD – standard deviation.

Model 1: -2 log likelihood = 2514.52; $R^2=0.032$ (Cox & Snell); 0.044 (Nagelkerke), model $\chi^2=40.01$. Variables in equation: SBP-SD quartiles, constant; 64.1% power of correctly predicting high and very high total CV risk category.

Model 2: -2 log likelihood = 1242.87; $R^2=0.152$ (Cox & Snell); 0.210 (Nagelkerke), model $\chi^2=45.06$. Variables in equation: PWVao, constant; 69.7.% power of correctly predicting high and very high total CV risk category.

Model 3: -2 log likelihood = 1414.87; $R^2=0.125$ (Cox & Snell); 0.172 (Nagelkerke), model $\chi^2=42.03$. Variables in equation: AIXao; 69.5.% power of correctly predicting high and very high total CV risk category.

Model 4: -2 log likelihood = 1170.83; $R^2=0.206$ (Cox & Snell); 0.284 (Nagelkerke), model $\chi^2=37.26$. Variables in equation: SBP-SD quartiles, PWVao, AIXao, constant; 72.6.% power of correctly predicting high and very high total CV risk category.

Model 5: -2 log likelihood = 765.03; $R^2=0.450$ (Cox & Snell); 0.624 (Nagelkerke), model $\chi^2=59.51$. Variables in equation: SBP-SD quartiles, PWVao, AIXao, mean SBP, PP, age, constant; 84.7.% power of correctly predicting high and very high total CV risk category.

In the hypertensive group, in addition to the abovementioned factors (age, SBP, pulse pressure, lipid profile, visceral obesity, diabetes mellitus, and metabolic syndrome), increased BPV was associated with severity of hypertension ($r_s=0.283$, $p<0.0001$) and lack of treatment control ($r_s=0.111$, $p<0.002$). There was also a significant direct association between PWVao and BPV ($r_s=0.112$, $p<0.014$).

Regression analysis

The probability of an adult subject with $BPV \geq 8.49$ mmHg belonging to a high or very high cardiovascular risk category was 2.95 times higher than that of one with $BPV < 1.41$ mmHg (95%CI: 2.22-3.92, $p<0.0001$) (Figure 2, Model 1).

For every 1 m/s increase in PWVao, the odds of belonging to a high or very high cardiovascular risk category rose by 1.51 (95%CI: 1.41-1.61, $p<0.0001$) (Figure 2, Model 2), and for every 1% increase in AIXao this probability rose by 1.05 (95% CI: 1.04-1.06, $p<0.0001$) (Figure 2, Model 3).

Based only on the aforementioned 3 parameters (Figure 2, Model 4) it was possible to predict with 72.6% accuracy the probability of finding subjects in a high or very high cardiovascular risk category. Furthermore, the addition of BPV and arterial stiffness parameters to mean SBP, pulse pressure, and age increased the accuracy of the prediction model to 84.7% for detecting persons with a high or very high estimated cardiovascular risk (Figure 2 - Model 5).

Discussion

While relatively few data are available for BPV evaluation at a population level, this study reports results based on a representative sample for an East European country. Almost a quarter of our adult population were found to have high systolic BPV. The cutoff value of the highest quartile of SBP-SD found in our study (8.48 mmHg) is similar to the value obtained in the NHANES III survey (8.3 mmHg).¹⁰

Our results show that high systolic BPV is associated with age, SBP, pulse pressure, total and LDL-cholesterol, triglycerides, visceral obesity, diabetes mellitus, metabolic syndrome, and increased aortic stiffness. Moreover, both visit-to-visit systolic BPV and aortic stiffness proved to be positively and independently correlated with the risk category. Based on these parameters it was possible to predict with 72.6% accuracy the probability of finding subjects in a high or very high cardiovascular risk category.

BPV and arterial stiffness are considered emerging indicators of cardiovascular risk. On the one hand, we have already underlined the data that sustain the association of high BPV with cardiovascular morbidity and mortality.^{1,7-11} On the other hand, arterial stiffness is currently considered as a cumulative measure of the damaging effects of cardiovascular risk factors on the arterial wall,²⁰ and there is an

impressive amount of data to suggest that this emerging biomarker can independently predict cardiovascular events and increase the accuracy of risk prediction beyond the classical risk scores.²¹⁻²⁷ The ability of aortic stiffness parameters to predict future events is stronger in high-risk populations compared to low-risk populations, as was shown in a meta-analysis published in 2010.^{28,29}

The association of BPV with arterial stiffness highlights a pathogenetic link that could contribute to the augmentation of cardiovascular risk. Data on the relationship between BPV and arterial stiffness are limited. The first report was published in relation to short term BPV (assessed by ambulatory BP monitoring).¹⁴ Recently, the MESA study identified an association between aortic distensibility and elasticity and long-term visit-to-visit variability.³⁰ Our observations, based on systolic visit-to-visit BPV and aortic stiffness evaluated by PWVao and AIXao, are among the few that address the link between these two emergent markers of risk. It is worth noting that visit-to-visit systolic BPV was associated in our study mostly with conventional risk factors that define the metabolic syndrome, a condition proved to amplify the age-associated increases in vascular thickness and arterial stiffness.³¹ However, most investigators consider that aortic stiffness induces high BPV mainly through sympathetic nerve activation³² and impaired baroreflex sensitivity.³³

Study limitations

One important limitation of this study is related to the methodological restrictions imposed by a population survey. Therefore, BPV was investigated using measurements performed during only two study visits in two different settings: the subject's home and the general practitioner's office. In order to overcome the bias, the same person (a specially trained general practitioner) performed the measurements, using the same arm, and the statistical analysis included adjustment for the difference in mean SBP between the two study visits.

Because of the logistic and financial aspects of the SEPHAR II study, arterial stiffness parameters were measured at only one study visit with an oscillometric device (Arteriograph) and not with Complior or Sphygmocor devices, which have defined reference values.³⁴ However, published data acknowledge the close agreement between arterial stiffness parameters (aortic PWV and AIX) measured by the three different techniques.³⁵⁻³⁸

Although the use of antihypertensive medications is recognized as a potential determinant of BPV, the

limited sample size of participants on antihypertensive monotherapy precluded a direct head-to-head comparison of the drug classes' effect on BPV.

Conclusions

This survey provides information about visit-to-visit BPV at a population level, showing that high BPV (≥ 8.48 mmHg) has a significant prevalence (24.62%) in the adult population of an East European country.

In addition, we found an association between visit-to-visit systolic BPV, arterial stiffness, and high and very high cardiovascular risk categories, independent of mean SBP, pulse pressure, or age. This result reveals a pathogenetic link between visit-to-visit systolic BPV and arterial stiffness, with possible implications for cardiovascular risk prediction beyond the classical scores. The prediction model based on these parameters needs validation in a prospective survey.

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