Medicina modernă. 2014, Vol. 21, No. 2 : 96-105

Original Paper

Predictors of Increased Arterial Stiffness in Hypertensive Patients

Oana Florentina Tăutu[1,2], Roxana Darabont[1,3], S. Onciul[1,2], A. Deaconu[1,2], Ioana Petre[1,2], R.D. Andrei[1,2], B. Drăgoescu[1,2], Maria Dorobanțu[1,2]

[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]Cardiology Department, Clinical Emergency Hospital Bucharest, Romania
[3]Cardiology Department, University Emergency Hospital Bucharest, Romania

REZUMAT

Predictorii rigidității areriale crescute la pacienții hipertensivi

Obiective: analiza parametrilor de rigiditate arterială la pacienții hipertensivi și identificarea predictorilor rigidității arteriale crescute.

Material și metodă: 798 de hipertensivi indetificați în studiul SEPHAR II au fost evaluați prin măsurători de tensiune și rigiditate arterială: velocitatea undei de puls la nivel aortic (PWVao) și indexul aortic de augmentație (AIXao) și un chestionar de studiu. Valorile deviației standard (d.s.) a TAS peste percentila 75 au definit variabilitatea crescută a TAS. Indexul aterogenic plasmatic (AIP) a fost calculat prin formula Log(TG/HDL-colesterol).

Rezultate: Valorile medii ale parametrilor analizați au fost: PWVao-10.19±2.22 m/s, AIXao-39.17±16.59%, TA-149.96±20.94/89.18±11.54, PP-60.99±17.95 mmHg, FC-3.75±10.89 bpm and d.s.TAS-7.73±8.6 mmHg (24.9% din hipertensivi cu variabilitate TAS crescută), acid uric - 5.48±1.47 mg/dl și AIP - 0.38±0.34. Factorii asociați cu valori crescute ale PWVao cât și ale AIXao au fost: vârsta peste 60 de ani, obezitatea viscerală, valorile crescute ale acidului uric și ale AIP, prezența a cel puțin unei afectări de organe țintă și lipsa controlului tensional adecvat. Prezența dislipidemiei, microalbuminuriei, a fibrilației atriale și avariabilității crescute aTAS, s-au corelat numai cu valori crescute ale PWVao, iar boala cardiacă ischemică și istoricul de AVC s-a corelat numai cu valori crescute ale AIXao.

Concluzii: Vârsta peste 60 de ani, obezitatea viscerală, dislipidemia, variabilitatea tensională crescută, nivelurile crescute ale acidului uric și ale AIP, lipsa controlului tensional optim și prezența afectării de organe țintă pot fi considerați indicatori ai unei rigidități arteriale crescute la pacienții hipertensivi.

Cuvinte cheie: rigiditate arterială, velocitatea undei de puls, index de augmentașie aortică, variabilitatea TAS, acid uric, index aterogenic plasmatic

Corresponding author: Oana-Florentina Tăutu, MD
Clinical Emergency Hospital Bucharest, Calea Floreasca no.8, sector 1, 014461, Bucharest, Romania
e-mail: dr.tautu@yahoo.com

ABSTRACT

Objectives: to evaluate arterial stiffness in hypertensive patients and to identify predictors of increased arterial stiffness.

Method: 798 hypertensives identified in SEPHAR II survey were evaluated by BP and arterial stiffness measurements: aortic puls weave velocity (PWVao) and aortic augmentation index (AIXao), and a study questionnaire.Values above the 75th percentile of mean SBP' standard deviation (s.d.) defined increased SBP variability. Log(TG/HDL-cholesterol) defined atherogenic index of plasma (AIP).

Results: Mean values of studied parameters were: PWVao-10.19±2.22m/s, AIXao - 39.17±16.59%, BP-149.96±20.94/89.18±11.54, PP-60.99±17.95 mmHg, HR-73.75±10.89 bpm and SBP's.d -7.73±8.6 mmHg (24.9% of subjects with increased SBP variability), SUA-5.48±1.47 mg/dl and AIP - 0.38±0.34. Factors associated with both increased PWVao and AIXao values were: age group, visceral obesity, increased SUA and AIP levels, presence of at least 1 form of TOD and the lack of BP control. While DM, dislipidemias, increased SBP's variability, microalbuminuria and atrial fibrilation were associated only with increased PWVao, ischemic heart disease and stroke history was associated only with increased AIXao levels.

Conclusions: Age above 60 years, visceral obesity, dislipidemia, increased SBP variability, SUA and AIP levels, the lack of optimal BP control and the presence of TOD may be considered as predictors of an increased arterial stiffness in hypertensive patients.

Key words: arteriall stiffness, pulse wave velocity, augmentation index, blood pressure variability, uric acid, atherogenic index of plasma

INTRODUCTION

In Romania, a high cardiovascular (CV) risk East European country, where prevalence of hypertension is still high and optimal blood pressure control still represents a doubtfull challange (1-5), adopting a treatment approach strategy based on total cardiovascular risk assessment can maximize the cost-effectiveness of hypertensive patinets management, ensuring the best use of the limited resources of our health-care system, to prevent cardiovascular diseses and to decrease CV morbidity and mortality.

Recent research show that increased arterial stiffness represents an independent predictor of fatal and non-fatal CV events in hypertensive patients (6-10).

The need for a new parameter for a more acurate CV risk assessment, especially in hypertensive patients, cames from the fact that current risk assessment tools, allthough performing well at populational level, are nor so sensitive at individual level. In this context, arterial stiffness has proved its additive value over traditional scores - Framingham and SCORE, to identify patients at high risk (6, 11-13).

Thus, evaluation of arterial stiffness can be implemented as an early noninvasive screening test for persons at high risk of developing manifest cardiovascular disease.

Current guidelines recommending measurement of arteriall stiffness as part of total CV risk assessment in hypertensive patients, especially in those considered at moderat risk based on SCORE (14) because a substantial proportion of them could be reclassified into higher CV risk class based on arterial stiffness measurements (12,15).

Few studies address so far factors leading to increased arterial stiffness, especially at a populational level. Among these, increase in age, blood pressure (BP), plasma cholesterol and glucose levels and excesive stimulation of the sympathetic nervous system are considered as pathophysiological factors of arterial stiffening (16-19).

As several studies proved that increased arterial stiffness is an independent predictor of cerebral and cardiovascular events, more interest was dedicated to the relationship between arterial stiffening and atherosclerotic process, recent studies evidencing that the extension of atherosclerotic lesions is proportional with the increases of arterial stiffening (20,21). Going further, other studies revealed the association between arterial stiffness and endothelial dysfunction, raising the hypothesis that an increase in arterial stiffness may represent either a cause or a consequence of endothelial dysfunction (22-24).

Aslo, data from populational level regarding new emerging CV risk factors such as increased visit-to-

visit blood pressure variability, elevated leves of uric acid and increased atherogenic index of plasma, that may be also linked to increased arterial stiffness, are lacking, especially in hypertensive patients.

OBJECTIVES

The main objective of our study was to evaluate arterial stiffness in hypertensive patients and to identify predictors of increased arterial stiffness, using arterial stiffness measurements obtained with an oscillometric device, in the second epidemiologic, national representative survey – SEPHAR II.

METHODS

The data from 798 hypertensive adult subjects identified in the second epidemiologic national representative survey – SEPHAR II (Study for the Evaluation of Prevalence of Hypertension and Cardiovascular Risk in Romania II) that was used in this study were: BP measurements (3 measurements according to ESH/ESC recomandations, at each of the 2 study visits, 7-10 days apart), arterial stiffness measurements, a 76-item questionnaire (demographic, life style, CV risk factors and medical history data), anthropometric measurements, 12 lead ECGs and laboratory work-up.

The methodology of SEPHAR II survey was described in detail in previous reports (2-5) and will not be discused further.

Studied parameters and their assessment

Arterial stiffness parameters were measured during the second study visit - aortic pulse wave velocity (PWVao) and aortic augmentation index (AIXao), using an oscillometric device - Arteriograph IrDA (Medexpert, Budapest, Hungary) according to a specific methodology (25).

Blood pressure values were defined by the arithmetic mean of the second and third measurements from each of the 2 study visits, without taking into consideration the first measurement from each study visit. Blood pressure 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 1 minute at least, according to ESH/ESC recommendations, including cuff adjustment to arm's circumference (14).

Severy of Hypertension (HT) was graded as follows: normal BP (controlled BP): Systolic blood pressure (SBP)< 140 mmHg and diastolic blood pressure (DBP)< 90 mmHg, grade I HT: SBP = 140-159 mmHg and/or DBP = 90-99 mmHg, grade II HT: SBP = 160-179 mmHg and/or DBP = 100-109 mmHg, grade III: SBP ≥180 mmHg and/or DBP ≥ 110 mmHg. When SBP and DBP values fell in different categories, the category with the gratest severity was considered.

Visit-to-visit variability was assessed by standard deviation (s.d.) of the mean systolic blood pressure (SBP). Values above the 4th quartile of mean SBP' s.d. defined increased BP variability.

Obesity was defined as BMI equal or greater than 30 kg/m^2 and visceral obesity by waist circumference more than 102 cm in men and more than 88 cm in women. Weight was measured using an approved electronic scale, model Tanita HD 95 with maximum deviation of 0.1 kg, and height using a measuring device with a maximum deviation of 0.5 cm.

Smoking was defined as current smoking of at least one cigarette per day.

Sedentary lifesytle was defined as daily physical activity of less than 30 minutes.

Familly history of premature CV disease was based on subject self-report.

Diabetes mellitus (DM) was assessed by ADA criteria (fasting plasma glucose (FPG) ≥ 126 mg/dl, a glycated hemoglobin (HbA1c) ≥ 6,5% or a previously diagnose by a medical specialist on antidiabetic medication, regardless of FPG or HbA1c values) (26).

Dislipidemia was assessed by NCEP ATPIII recomendations (27): Hypertrigliceridemia: triglyceride (TG) serum level ≥ 150 mg/dl, hypercholesterolemia: total serum cholesterol (TC) level ≥ 200 mg/dl, high levels of LDL-cholesterol: ≥ 130 mg/dl and low levels of HDL-cholesterol: ≤ 40 mg/dl for men and ≤ 50 mg/dl for women. The presence of elevated levels of both TG and TC and/or LDL-C and/ or HDL-C defined mixed dyslipidemia.

Log(TG/HDL-cholesterol) defined atherogenic index of plasma (AIP).

Metabolic syndrome (MS) was defined by NCEP ATP III criteria as follows: at least 3 out of the following 5 criteria: waist circumference > 88 cm in females or > 102 cm in males, TG > 150 mg/dl or the use of lipid-lowering drugs, HDL-C < 50 mg/dl in females or < 40 mg/dl in males or the use of lipid-lowering drugs, SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or current antihypertensive treatment,

fasting plasma glucose > 100 mg/dl or known DM under current treatment (27).

The normal range considered for serum uric acid (SUA) levels was 2.40 mg/dl -5.70mg/dL for women and 3.4 mg/dl - 7.0 mg/dl for men, according to the reference values of the central laboratory, values above these limits defining hyperuricemia (HUA).

Subclinical target organ damage was defined by the presence of at least one of the following:

- left ventricular hypertrophy (LVH) on ECG assessed by Cornell product ≥ 2440 mm x msec; ECG recording were performed during the second study visit using a General Electric CardioSoft MAC600 1.02 device.
- microalbuminuria defined by urinary albumin to urinary creatinine ratio (UACR) of 30 – 300 mg/g)
- mild renal failure defined by estimated glomerular filtration rate (eGFR) between 60 - 90 ml/min/1,72 m^2 using the Modification of Diet in Renal Disease (MDRD) formula

Clinical manifest target organ damage was defined by the presence of at least one of the following:

- clinical manifest CV disease: ischemic heart disease based on subject self-report history of myocardial infarction, angina pectoris, myocardial revascularization procedure (PCI or CABG) and/or the presence of Q waves and /or ST/T abnormalities on ECG, atrial fibrillation based on subject self-report history and /or the presence of AF on ECG, heart failure history, peripheral artery disease and stroke (based on subject self-report)
- clinical manifest renal disease: moderate to severe renal failure by estimated $eGFR_{MDRD}$ < 60 ml/min/1,72m^2 and/or macroscopic proteinuria (UACR > 300 mg/g).

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 20.0 software at a significance level of $p \leq 0.05$.

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.

Kolmogorov-Smirnov test was used to analyze continuous data distribution, according to which independent sample t test or Mann-Whtiney U test were further used in analysis for differences between means of 2 independent study subgroups. Chi-square test was used to analyze differences between categorical data.

Bivariate correlation analysis (Spearman or Person correlation coefficient calculation) was used to validate the association between arterial stiffness parameters and target variables.

RESULTS

General characteristics of the study sample

Study sample had a mean age of 57.42±13.38 years (range: 23-80 years) with a female preponderence (438 subjects, 54.9%), in their majority linving in urban areas (475 subjects, 59.5%). Mean BP value was 149.96±20.94 / 89.18±11.54 mmHg, mean PP value was 60.99 ± 17.95 mmHg and mean HR value was 73.75±10.89 bpm (**Table 1**).

The majority of hypertensive subjects were previously diagnosed (555 subjects, 69.5%) and had grade I HT (304 subjects, 38.1%).

Arterial stiffness parameters

Mean PWVao value was 10.19±2.22 m/s, ranging from 5.4 m/s (minimum value) to 18.5 m/s (maximum value), the most frequent recorded PWVao value being 9.8m/s (**Fig. 1**).

Mean AIXao value was 39.17±16.59%, ranging from -2.10% (minimum value) to 78.8% (maximum value), the most frequent recorded AIXao value being 52% (**Fig. 2**).

Table 1. General characteristics of the study group

Age (years)	57.42±13.38
Female	438 (54.9)
Urban area	475 (59.5)
SBP (mmHg)	149.96 ± 20.94
DBP (mmHg)	89.18± 11.54
PP (mmHg)	60.99 ± 17.95
HR (bpm)	73.75±10.89
Known HT	555 (69.5)
Normal BP values	119 (14.9)
Grade I HT	304 (38.1)
Grade II HT	243 (30.5)
Grade III HT	132 (16,5)

Values are presented as mean ± s.d. (standard deviation) for continuous data and absolute number (percent) for categorical data; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; HR: heart rate; bpm: beats per minute; BP: blood pressure; HT: hypertension

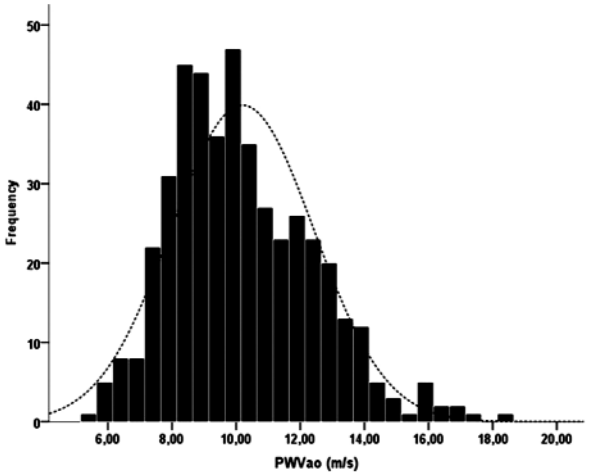

Figure 1. Aortic pulse wave velocity values' distribution across the study group. PWVao – aortic pulse wave velocity; dot line represents normal distribution curve

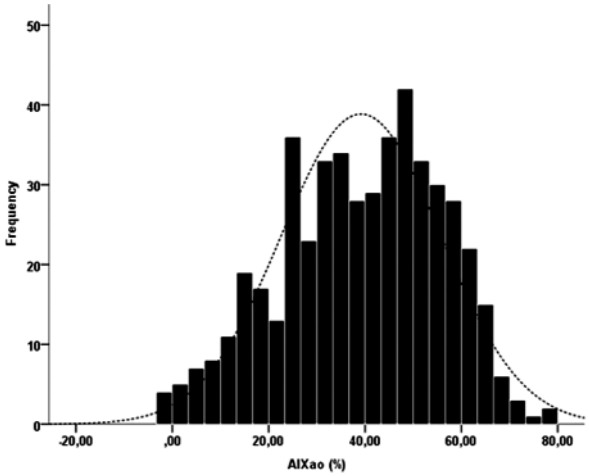

Figure 2. Aortic augmentation index values' distribution across the study group. AIXao – aortic augmentation; dot line represents normal distribution curve

Traditional risc factors and thier association with increased arterial stiffness

The prevalence of traditional risk factors are detailed in Table 2.

Sedentary life style, hypercholesterolemia and visceral obesity are the traditional risk factors with the highest prevalence among studied hypertensive subjects, with values above 60%.

Is worth mentioning that while the majority of studied hypertensives did not fullfiled the BMI ≥ 30 kg/m^2 criterion, visceral obesity based on waist circumference measurements was recorded in 482 subjects, representing 60,4% of the total sample.

Table 2. Traditional cardiovascular risk factors

Familly history of premature CV disease	189 (24.1)
Sedentary lifestyle	536 (67.3)
Smoking	160 (20.2)
Obesity	
• BMI ≥ 30kg/m^2	335 (42.5)
• WC > 0,95 in males > 0,85 in females	482 (60.4)
DM	155 (19.4)
MS (ATP III)	448 (56.1)
Lipid profile	
• Total cholesterol (mg/dl)	215.29±46.83
• Hypercholesterolemia	488 (61.2)
• LDL-cholesterol (mg/dl)	139.75±42.02
• High LDL-cholesterol	460 (57.6)
• HDL-cholesterol (mg/dl)	54.74±17.82
• Low HDL-cholesterol	164 (33.1)
• Triglycerides (mg/dl)	153.87±140.11
• Hypertriglyceridemia	274 (34.3)

Values are presented as mean ± s.d. (standard deviation) for continuous data and absolute number (percent) for categorical data; CV: cardiovascular; BMI: body mass index; WC: waist circumference; DM: diabetes mellitus; MS: metabolic syndrom; ATP III: Adult Treatment Panel III.

Traditional risk factors associated with increased PWVao values were: age groups (r_s = 0,233; r_s^2 = 0,054; p < 0,0001), hypercholesterolemia (r_s = 0.219; r_s^2=0.048; p=0.050), the presence of increased LDL-cholesterol levels (r_s=0.238; r_s^2=0.057; p = 0.048), the presence of low HDL cholesterol levels (r_s = 0.102; r_s^2 = 0.010; p = 0.031), increased triglycerides levels (r_s = 0.142; r_s^2 = 0.020; p = 0.003), the presence of diabetes mellitus (r_s = 0.135; r_s^2 = 0.018; p = 0.004), visceral obesity (r_s = 0.105 r_s^2 = 0.011; p = 0.027) and metabolic syndrome (r_s = 0.137 r_s^2 = 0.019; p = 0.004).

The only traditional risk factors associated with increased AIXao values age >60 years (r_s = 0,354; r_s^2 = 0,013; p < 0,0001) and obesity, regardless of the definition criterion used - BMI ≥ 30 kg/m^2 (r_s= 0.209; r_s^2 = 0.044; p < 0.0001) or visceral obesity (r_s = 0.128; r_s^2 = 0.016; p = 0.005).

There were no significant association between arterial stiffness parameters and family history of premature CV disease, smoking or sedentary life style.

Novel risc factors and their association with increased arterial stiffness

Visit-to-visit SBP variability

Mean SBP's.d. value was 7,73±8,6 mmHg, ranging from 0 mmHg (minimum value) up to 72,12

mmHg (maximum value). The first quartile included SBP' s.d. values less than 2,12 mmHg, the second quartile included values between 2,12 - 4,94 mmHg, the third quartile included values between 4,95 - 10,6 mmHg and the forth quartile included values equal to or greater than 10,7 mmHg (**Fig. 3**).

Almost one quarter (119 subjects, 24.9%) of the study group had SBP' s.d. values in the highest quartile, being considered as having increased visit-to-visit SBP variability.

Bivariate logistic regression analysis showed a positive association between PWVao values and the quartiles of SBP's.d. (PWVao: $r_s = 0.199$; $r_s^2 = 0.039$; $p = 0.036$) proving that high PWVao values are more frequently associated with the SBP's.d. values from the 4th quartile (e.g. increased SBP variability). The association between AIXao values and quartiles of SBP's.d did not reach the statistical significance limit (AIXao: $r_s = 0.184$; $r_s^2 = 0.034$; $p = 0.064$).

Serum uric acid levels (SUA)

Mean SUA level was 5,48±1,47mg/dl, ranging from 1,30 mg/dl (minimum value) to 10,70 mg/dl (maximum value), the most frequently recorded SUA value being 5,50 mg/dl (**Fig. 4**).

The majority of studied hypertensives had normal SUA levels, hyperuricemia being recorded in 127 cases, representing 27% from the study sample.

While bivariate correlation analysis showed an direct association between AIXao values and SUA levels (AIXao: rs= -0.145; rs2 = 0.021; p = 0.001) prooving that higher AIXao values (increased wave reflection) are more frequently associated with higher SUA levels, the direct association between PWVao values and the presence of hyperuricemia did not reached the statistical significance threshold (PWVao: rs= 0.188; rs2 = 0.035; p = 0.064).

Atherogenic index of plasma

Mean AIP value was 0.38±0.34, ranging from -0,60 (minimum value) to 1,78 (maximum value) the most frequently recorded AIP value being - 0,18 (**Fig. 5**).

Both PWVao and AIXao values were significantly associated with AIP levels (PWVao: $r_s = 0.140$; $r_s^2 = 0.019$; $p = 0.003$; AIXao: $r_s = 0.126$; $r_s^2 = 0.016$; $p = 0.005$) prooving that increased plasmatic atherogenity is more frecvently associated with higher PWVao values (higher rigidity) and AIXao values (more wave reflection).

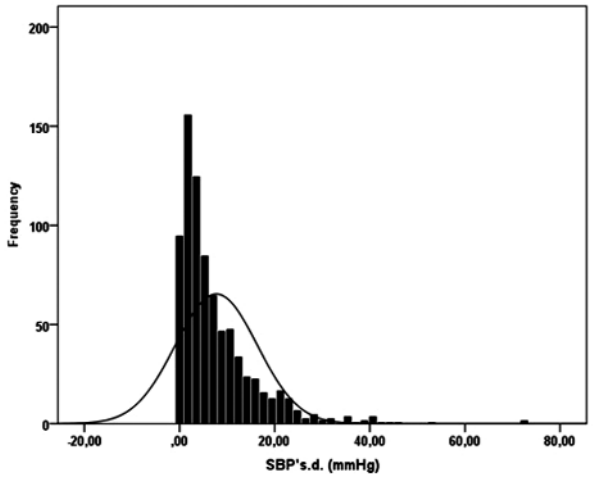

Figure 3. Systolic blood pressure's standard deviation values' distribution across the study group.
SBP's.d.– systolic blood pressure' standard deviation; dot line represents normal distribution curve

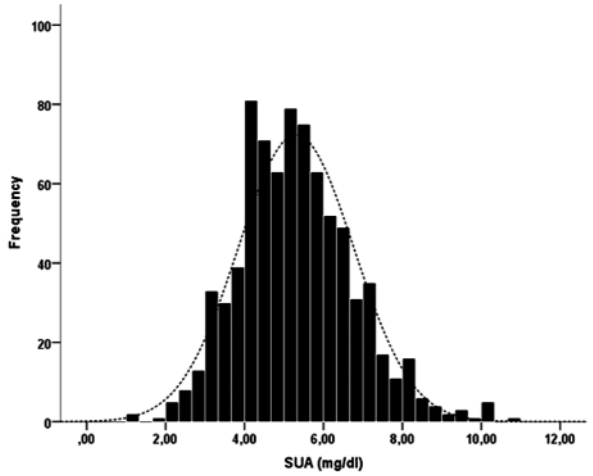

Figure 4. Serum uric acid values'distribution across the study group. SUA – serum uric acid; dot line represents normal distribution curve

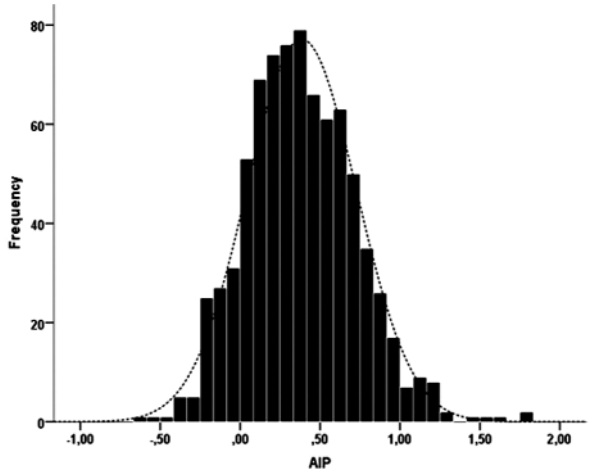

Figure 5. Atherogenic index of plasma values'distribution across the study group. AIP–atherogenic index of plasma; dot line represents normal distribution curve

Table 3. Subclinical target organ damage (TOD)

LVH on ECG (Cornell product ≥ 2440 mmxms)	25 (3.1)
Microalbuminuria (UACR: 30-300 mg/g)	57 (7.1)
Mild renal impairment (eGFR$_{MDRD}$ 60-90 ml/min/ 1.73 m^2)	327 (41)

Values are presented absolute number (percent); LVH: left ventricular hypertrophy, ECG: electrocardiogram; UACR: urinary albumin to urinary creatinine ratio; eGFR$_{MDRD}$: estimated glomerular filtration rate calculated based on MDRD (modifyed diet in renal disease) formula

Table 4. Clinical manifest target organ damage (TOD)

Clinical manifest CV disease	227 (28.5)
IHD	157 (19.7)
AF57 (7.1)	
HF history	70 (8.8)
Stroke history	34 (4.3)
PAD history	23 (2.9)
Clinical manifest renal disease	51 (6.4)
Moderate-severe renal impairment (eGFRMDRD< 60 ml/min/ 1,73 m^2)	45 (5.6)
Proteinuria (UACR ≥ 300 mg/g)	11 (1.4)

Values are presented absolute number (percent); TOD: target organ damage; CV: cardiovascular; IHD: ischemic heart disease; HF: heart faillure; PAD: peripheral artery disease; eGFR$_{MDRD}$: estimated glomerular filtration rate calculated based on MDRD (modifyed diet in renal disease) formula; UACR: urinary albumin to urinary creatinine ratio

Table 5. Treatment and control of hypertension

Antihypertensive treatment	472 (59.1)
1 drug	129 (27.3)
2 drugs	187 (39.6)
3 or more drugs	156 (33.1)
Controlled BP	118 (14.8)

Values are presented absolute number (percent); TOD: target organ damage; BP: blood pressure

Target organ damage (TOD) ant their association with increased arterial stiffness

Subclinical target organ damage (TOD), defined by the presence of at least one of the following: LVS on ECG, microlabuminuria or mild renal impairment) was recorded in 481 hypertensives, representing 60.3% of the total sample. The most frequently recorded subclinical TOD was mild renal impairment – 327 hypertensives representing 41% of the total sample. The prevalence of different types of subclinical TOD are detailed in **Table 4**.

Bivariate correlantion analysis showed a significant association between the presence of at least 1 subclinical TOD and increased values of both PWVao and AIXao (PWVao: $r_s = 0.587$; $r_s^2 = 0.345$; $p < 0.000$; AIXao: $r_s = 0.219$; $r_s^2 = 0.048$; $p < 0.0001$). Only the presence of microalbuminuria was associated only with increased PWVao ($r_s = 0.106$; $r_s^2 = 0.011$; $p = 0.026$), while no significant association was prooved between LVH on ECG or mild renal impairment and both PWVao and AIXao.

Clinical manifest TOD defined by the presence of at least 1 form of clinical manifest CV disease or renal disease was recorded in 248 hypertensives, representing 31.1% of total sample, 227 hyertensives (28.5% of total sample) havig at least 1 form of clinical manifest cardiovascular disease and 51 hypertensives (6.4% of total sample) having at least 1 form of clinical manifest renal disease.

The most frequently recorded clinical manifest TOD was ischemic heart disease – 157 cases, representing 19.7% of the total sample, the other forms of clinical manifest TOD having an frequently less than 10% in the whole sample.

The prevalence of different types of clinical manifest TOD are detailed in **Table 5**.

Both PWVao and AIXao values were directly associated with the presence of at least 1 clinical manifest form of TOD (PWVao: $r_s = 0.137$; $r_s^2 = 0,019$; $p = 0.004$; AIXao: $r_s = 0.114$; $r_s^2 = 0.013$; $p = 0.027$) and the presence of at least one form of clinical manifest CV disease (PWVao: $r_s = 0.109$; $r_s^2 = 0.012$; $p = 0.022$; AIXao: $r_s = 0.176$; $r_s^2 = 0.031$; $p = 0.020$).

Is worth mentioning that while PWVao were directly associated with the presence of atrial fibrillation ($r_s = 0.196$; $r_s^2 = 0.038$; $p = 0.043$), AIXao values were directly associated with the presence of stroke history ($r_s = 0.385$; $r_s^2 = 0.1481$; $p=0.040$) and the presence of ischemic heart disease ($r_s = 0.130$; $r_s^2 = 0.017$; $p = 0.004$).

Tratement and BP control and their association with increased arterial stiffness

Allthough 472 subjects, representing 59,1% of the total sample were currently treated, in their majority with at least 2 drugs (343 subjects, 72.7%), BP control was recorded only in 118 subjects, representing 25%

of total treated hypertensives (Table 1).

Lack of BP controll under current antihypertensive treatment was significatly associated both with increased PWVao values and AIX values (PWVao: $r_s = 0.213$ $r_s^2 = 0.045$; $p = 0.005$; AIXao: $r_s = 0.255$; $r_s^2 = 0.065$; $p = 0.005$).

DISCUSIONS

The results of our study provides data regarding arteriall stiffness parameters obtained by an oscillometric device obatined at a populational level, in a very large sample of adult hypertensives comming from a national representative survey- SEPHAR II.

The associations between increased arteriall stiffness and age, BP values and the lack of optimal BP control, evidenced by our results, is a common knowledge, several studies also supporting these findings (16-19). Knowing that increased PWVao was demonstrated as a predictor of lack of BP treatment control (28), it is not surprinsing that our results show a direct association between increased arterial stiffness parameters and the presence of target organ damage, both subclinical and clinical.

The fact that only increased aortic augmentation index was associated with stroke history and with ischemic heart disease can be explained by the fact that, opposed to aortic pulse wave velocity, which is a direct marker of arterial stiffness, AIXao is a measure of wave reflection phenomenon. An increased wave refletion, evidenced by an increased AIXao, may lead to the increase of central pressure, which is the major determinant of cerebral perfussion pressure, and in this way to cerebral artery remodeling and to increased stroke risk (29). Also this increase of central pressure will augmentate left ventricular pressure loading, triggering left ventricular hypertrophy and decrease of distolic coronarian perfusion pressure, increasing the risk of ischemic cardiac events (29).

Besides traditional CV risk factors and target organ damage, our study investigats new risk factors such as increased BP variability, serum uric acid levels and atherogenic index of plasma and their relation with arterial stiffness parameters.

Arterial stiffness may be interpreted as a cumulative result of the damaging effects of CV risk factors on the arterial wall throughout the lifespan (30), so is not surprinsing that our results show a relation between different forms of dislipidemia on one hand and with conditions such as diabetes mellitus and obesity on the other, conditions that often evolve with such lipidic dissorders. This concept is also supported also by the fact that our results show a direct association between increased arterial stiffness and the presence of metabolic syndrome, a condition proved to amplify the age-associated increase in vascular thickness and arterial stiffness (31).

Until recently, visit-to-visit variability was attributed mostly to deficiencies in hypertension treatment (32), but now data in literature offers support to the link between these two emerging new risk factors. Like in the MESSA study (33), our results suggests that increased arterial stiffness leads to increased long term BP variability.

Our results also point out the association between increased arterial atiffness and other 2 weel known markers of endothelial dysfunction: increased serum uric acid and increased levels of atherogenic index of plasma. Serum uric acid has an important role in mediating the systemic inflamatory response and chronic exposure to hyperuricemia leads to systemic inflamation and raises CRP levels in individuals with primary hypertension (34-36). More, serum uric acid is associated with atherogenic index of plasma levels, a sensitive marker of atherogenity (37,38). Therefore, our results raise the hypothesis that a systemic proinflamatory state represents the „primum movens" triggering endothelial disfunction that will accelerate the normal age-dependent arteriall stiffening proccess that will manifest itsself as increased blood pressure variability.

CONCLUSIONS

- From all traditional risk factors, age above 60 years, different types of dislpidemia, visceral obesity, diabetes mellitus and metabolic syndrome can be used as predictors of an increased arterial stiffness in hypertensive patients.
- Novel risk factors, such as increased visit-to-visit SBP variability, elevated serum uric acid levels and increased atherogenic index of plasma are also predictors of increased arterial stiffness in hypertensive patients.
- The link between increased arterial stiffness and target oragn damage could be the lack of optimal BP control often encounterd in these special goup of hypertensive patients.
- Our results raises the hypothesis that a systemic proinflamatory state can be the trigger that

speeds up the normal age-dependent arterial stiffening process, and this needs to be addressed by fourther studies.

Aknowlegments

This paper is part of PhD thesisentitled "New indicators for total cardiovascular risk assessment in hypertensive patients."

I express my gratitude to Romanian Society of Hypertension's board that grated me the permision to access the data collected in SEPHAR II survey and to use them in order to achieve the related PhD research topic, as a member of the study coordination team, with active participation in study protocol development, methodology implementation and IT support.

This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD) 2007-2013, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/107/1.5/S/82839".

Conflict of interest

None declared.

REFERENCES

1. Dorobanåu M., Tãutu O. Proiecte romβneæti de cercetare a factorilor de risc cardiovascular. Medicina Internã, 2012; IX, suppl 2012: 7-14
2. Dorobanåu M., Darabont R., Ghiorghe S. et al. Hypertension prevalence and control in Romania at a seven-year interval. Comparison of SEPHAR I and II surveys. Journal of Hypertension 2014; 32(1):39-47
3. Dorobanåu M., Bartoæ D., Apetrei E. et.al. Hypertension in Romania: where are we and what we do? Results from SEPHAR II study. Romanian Journal of Cardiology, 2012; 22 (4): 285-292
4. Dorobanåu M., Darabont R., Ghiorghe S. et al. Profile of the Romanian Hypertensive Patient. Data from SEPHAR II study. Rom J Intern Med. 2012; 50 (4): 285 – 296
5. Dorobanåu M., Onciul S., Darabont R. et al. Arterial Hypertension Epidemiology: Romania among the Balkan Countries – Data from SEPHAR Surveys. Medicina Modernã, 2014, Vol. 21, No. 1 : 10-16
6. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001, 37:1236–1241.
7. Boutouyrie P, Tropeano AI, Asmar R, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 2002, 39:10–15.
8. Laurent S, Katsahian S, Fassot C, et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 2003, 34:1203–1206.
9. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006, 113:1213–1225.
10. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55:1318–1327.
11. Sehestedt T, Jeppesen J, Hansen TW. et al. Risk prediction is improved by adding markers ofsubclinical organ damage to SCORE. Eur Heart J 2010; 31:883–891.
12. Sehestedt T, Jeppesen J, Hansen TW. et al. Thresholds for pulse wave velocity, urine albumin creatinine ratio and left ventricular mass index using SCORE, Framingham andESH/ESC risk charts. J Hypertens 2012; 30:1928–1936.
13. Mattace-Raso FU, van der Cammen TJ, Hofman A. et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006; 113:657–663.
14. Mancia G, Fagard R, Narkiewicz K. et al. 2013 ESH-ESC Guidelines for the management of arterial hypertension, Jornal of Hypertension. 2013; 31: 1281–1357
15. Mitchell GF, Hwang SJ., Vasan RS. et al. Arterial stiffness and cardiovascular events: the FraminghamHeart Study. Circulation 2010; 121:505–511.
16. Laurent S., Cockcroft J., Van Bortel, L et.al. on behalf of the European Network for Non Invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical application. Eur. Heart J. 2006; 27: 2588-605
17. Boutouyrie P, Lacolley P., Girerd X., et al. Sympathetic activation decreases medium sized arterial compliance in humans. Am J Physiol 1994; 267: H1 368-76
18. Giannattasio C., Vicenti A., FAilla M. et.al. Effects on heart rate changes on arterial distensibility in humans. Hypertension 2003; 42: 253-6
19. Giannattasio C., Failla M., Lucchina S et.al. Arterial stiffening influence of sympathetic nerve activity: evidence from hand transplantation in humans. Hypertension 2005; 45: 608-11.
20. Giannattasio C., Capra A., Facchetti R. et.al. Relationshiop between arterial distensability and coronary atherosclerosis in angina pectoris patinets. J Hypertens 2007; 25: 593-8
21. Dart A., Bronwyn A. Kingwell, BS. Pulse Pressure—A Review of Mechanisms and Clinical Relevance. JACC 2001; 37: 975-84
22. Gilani M, Kaiser DR, Bratelli CW, et al.: Role of nitric oxide deficiency and its detection as a risk factor forprehypertension. J Am Soc Hypertens 2007, 1: 45-55
23. Nigam A, Mitchell GF, Lambert J, Tardif JC: Relation between conduit vessel stiffness (assessed by tonometry) and endothelial function (assessed by flow-mediated dilatation) in patients with and without coronary heart disease. AmJ Cardiol 2003, 92:395–399
24. Duprez DA., Cohn J.N. Arterial Stiffness As a Risk Factorfor Coronary Atherosclerosis. Current Atherosclerosis Reports 2007, 9:139–144
25. Baulmann J, Schillings U, Rickert S, Uen S, Rainer D, Illyes M et al. – A new oscillometric method for assessment of arterial stiffness: comparison with tonometric and piezo-electronic methods. J. Hypertens., 2008; 26: 523-528
26. American Diabetes Association - Standards of Medical Care in Diabetes—2013, Diabetes Care. 2013; 36 - Supplement 1: S11-S66
27. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143
28. Safar ME, Blacher J, Protogerou A, Achimastos A. Arterial stiffness and central hemodynamics in treated hypertensive subjects according to brachial blood pressure classification. J. Hypertens., 2008, 26: 130-137
29. Laurent S., Cockcroft J. Central aortic blood pressure. Elsevier Amsterdam. 2008. 13-17
30. Nilsson P M, Boutouyrie P, Laurent S. Vascular Aging : A Tale of

EVA and ADAM in Cardiovascular Risk Assessment and Prevention. Hypertension, 2009; 54: 3-10
31. Scuteri A, Najjar SS, Muller DC, Andres R, Hougaku H, Metter EJ, Lakatta EG. Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. J Am Coll Cardiol. 2004;43:1388–1395
32. Parati G, Ochoa JE, Salvi P, Lombardi C, Bilo G. Prognostic value of blood pressure variability and average blood pressure levels in patients with hypertension. Diabetes Care, 2013; Suppl. 2: S312-324
33. Simbo D, Shea S, McClelland RL, et al. - Associations of aortic distensibility and arterial elasticity with long-term visit-to-visit blood pressure variability: the Multi-Ethnic Study of Atherosclerosis (MESA), Am. J. Hypertens., 2013; 26:896-902
34. Sautin Y., Johnson R. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids. 2008; 27 (6): 608-19
35. Zoccali C., Maio R, Mallamaci F., Sesti G., Perticone F.Uric acid and endothelial dysfunction in essential hypertension.J Am Soc Nephrol. 2006 May;17(5):1466-71. Epub 2006 Apr 12.
36. De Oliviera E.P., Burini R.C., High plasma uric acid concentration: causes and consequences. Diabetol Metab Syndr. 2012 Apr 4;4:12. doi: 10.1186/1758-5996-4-12.
37. Baliarsingh S1, Sharma N, Mukherjee R.Serum uric acid: marker for atherosclerosis as it is positively associated with "atherogenic index of plasma"Arch Physiol Biochem. 2013 Feb;119(1):27-31
38. Dobiasova M. Atherogenic index of plasma (log(triglyceride/HDL-C- Colesterol)):Theoretical and practical implications", Cli. Chem., 2004; 50 (7):1113-5