Predictors of Increased Arterial Stiffness in Hypertensive Patients

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REZUMAT

Predictorii rigidității arteriale 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 indentificați 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 crescută a TAS). 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 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 unde de puls, index de augmentație aortică, variabilitatea TAS, acid uric, index aterogenic plasmatic

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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 pulse wave 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±2.22 m/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 fibrillation 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: arterial 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 challege (1-5), adopting a treatment approach strategy based on total cardiovascular risk assessment can maximize the cost-effectiveness of hypertensive patient management, ensuring the best use of the limited resources of our health-care system, to prevent cardiovascular diseases 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 accurate CV risk assessment, especially in hypertensive patients, comes from the fact that current risk assessment tools, although performing well at populational level, are not 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 arterial 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 excessive 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 levels 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 recommendations, 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 discussed 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).

Severity 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/m² 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 lifestyle was defined as daily physical activity of less than 30 minutes.

Family 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 recommendations (27): Hypertrigliceridemia: triglyceride (TG) serum level ≥ 150 mg/dl, hypercholes-terolemia: 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 - 5.70 mg/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 m² 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/1,72m² 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 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 living 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 9.8 m/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
Traditional risk factors and their association with increased arterial stiffness

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

Sedentary lifestyle, 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 fulfilled the BMI $\geq 30$ kg/m$^2$ criterion, visceral obesity based on waist circumference measurements was recorded in 482 subjects, representing 60.4% of the total sample.

Traditional risk factors associated with increased PWV$\text{ao}$ 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 AIX$\text{ao}$ 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 $\geq 30$ 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 lifestyle.

| Table 2. Traditional cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of premature CV disease</td>
<td>189 (24.1)</td>
<td></td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>536 (67.3)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>160 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• BMI $\geq 30$ kg/m$^2$</td>
<td>335 (42.5)</td>
<td></td>
</tr>
<tr>
<td>• WC $&gt;0.95$ in males $&gt;0.85$ in females</td>
<td>482 (60.4)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>155 (19.4)</td>
<td></td>
</tr>
<tr>
<td>MS (ATP III)</td>
<td>448 (56.1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Total cholesterol (mg/dl)</td>
<td>215.29±46.83</td>
</tr>
<tr>
<td>• Hypercholesterolemia</td>
<td>488 (61.2)</td>
</tr>
<tr>
<td>• LDL-cholesterol (mg/dl)</td>
<td>139.75±42.02</td>
</tr>
<tr>
<td>• High LDL-cholesterol</td>
<td>460 (57.6)</td>
</tr>
<tr>
<td>• HDL-cholesterol (mg/dl)</td>
<td>54.74±17.82</td>
</tr>
<tr>
<td>• Low HDL-cholesterol</td>
<td>164 (33.1)</td>
</tr>
<tr>
<td>• Triglycerides (mg/dl)</td>
<td>153.87±140.11</td>
</tr>
<tr>
<td>• Hypertriglyceridemia</td>
<td>274 (34.3)</td>
</tr>
</tbody>
</table>

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 syndrome; ATP III: Adult Treatment Panel III.

Visit-to-visit SBP variability

Mean SBP’s.d. value was $7.73\pm8.6$ 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: rs = 0.199; r^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: rs = 0.184; r^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; r^2 = 0.021; p = 0.001) proving 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; r^2 = 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: rs = 0.140; r^2 = 0.019; p = 0.003; AIXao: rs = 0.126; r^2 = 0.016; p = 0.005) proving that increased plasmatic atherogenity is more frequently associated with higher PWVao values (higher rigidity) and AIXao values (more wave reflection).
Target organ damage (TOD) and 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, microalbuminuria 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 corollation analysis showed a significant association between the presence of at least 1 subclinical TOD and increased values of both PWVao and AIXao (PWVao: rs = 0.587; rs² = 0.345; p < 0.000; AIXao: rs = 0.219; rs² = 0.048; p < 0.0001). Only the presence of microalbuminuria was associated only with increased PWVao (rs = 0.106; rs² = 0.011; p = 0.026), while no significant association was proved 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 hypertensives (28.5% of total sample) having 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: rs = 0.137; rs² = 0.019; p = 0.004; AIXao: rs = 0.114; rs² = 0.013; p = 0.027) and the presence of at least one form of clinical manifest CV disease (PWVao: rs = 0.109; rs² = 0.012; p = 0.022; AIXao: rs = 0.176; rs² = 0.031; p = 0.020).

Is worth mentioning that while PWVao were directly associated with the presence of atrial fibrillation (rs = 0.196; rs² = 0.038; p = 0.043), AIXao values were directly associated with the presence of stroke history (rs = 0.385; rs² = 0.1481; p=0.040) and the presence of ischemic heart disease (rs = 0.130; rs² = 0.017; p = 0.004).

Treatment and BP control and their association with increased arterial stiffness

Although 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 control under current antihyper-
tensive treatment was significantly associated both with
increased PWVao values and AIX values (PWVao:
rs = 0.213 rs² = 0.045; p = 0.005; AIXao: rs = 0.255;
rs² = 0.065; p = 0.005).

**DISCUSSIONS**

The results of our study provide data regarding
arterial stiffness parameters obtained by an oscillo-
metric device obtained at a populational level, in a
very large sample of adult hypertensives coming
from a national representative survey- SEPHAR II.

The associations between increased arterial 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 surprising 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 reflection, evidenced by an increased
AIXao, may lead to the increase of central pressure,
which is the major determinant of cerebral perfusion
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 ventricu-
lar 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 investigates 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 surprising 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 disorders. 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 stiffness and other 2 well 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 inflammatory response and
chronic exposure to hyperuricemia leads to systemic
inflammation 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 arterial stiffening
process that will manifest itself as
increased blood pressure variability.

**CONCLUSIONS**

- From all traditional risk factors, age above 60
  years, different types of dislipidemia, visceral
  obesity, diabetes mellitus and metabolic syn-
  drome 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 organ damage could be the lack of
  optimal BP control often encountered 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 further studies.

**Aknowlegments**

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

I express my gratitude to Romanian Society of Hypertension’s board that granted me the permission 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.

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**Conflict of interest**

None declared.

**REFERENCES**

1. Dorobanțu M, Tăutu O. Proiecte românești de cercetare a factorilor de risc cardiovascular. Medicina Internă, 2012; IX, suppl 2012: 7-14
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


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