Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 7 (56) No. 2 - 2014

AORTIC STIFFNESS EVALUATED BY M MODE TRANSTHORACIC ECHOCARDIOGRAPHY IN CORRELATION WITH HYPERTENSION DEGREE AND ADDITIONAL CARDIOVASCULAR RISK

C. CIUREA[1] **M. RĂDOI[1]**

Abstract: *Evaluation of arterial stiffness, by non-invasive and costly methods in clinical practice, (aplanation tonometry, Doppler ultrasound, MRI) showed the impact of arterial stiffness on cardiovascular risk in different population groups and suggested the utility of this parameter in the assessment of cardiovascular risk. The aim of the study was to evaluate the noninvasive parameters of aortic stiffness measured by transthoracic M-mode ultrasonography in correlation with the degree of hypertension and additional cardiovascular risk in patients with arterial hypertension (AH).We evaluated 88 hypertensive patients (pts), 34 pts (38,63%) with first degree and 54 pts (61,36%) with second and third degree of AH according with European Society of Cardiology 2013 Guidelines recommendation for the diagnosis of AH. High additional cardiovascular risk was established in 6 pts. (6.81%) with firs degree, 15 pts (17.045%) with second and third degree AH and very high additional cardiovascular risk in 9 pts (10.22%) with firs degree, 9 pts (10.22%) with second and 13 pts (14.77%) with third degree of AH. The results showed increasing of aortic stiffness index and decreasing of aortic strain in parallel with AH degree and with enhancing of additional cardiovascular risk. These data recommend the M-mode transthoracic echocardiography, an available and less expensive method, to asses the aortic stiffness in clinical practice.*

Key words: *aortic stiffness, arterial hypertension, cardiovascular risk assessment.*

1. Introduction

Increased arterial stiffness is one of the earliest detectable structural and functional changes in the vessel wall, parallel to the age, and accelerated by some pathological conditions including hypertension, diabetes mellitus, dyslipidemia, atherosclerosis and chronic renal disease. Optimized imaging techniques for the evaluation of vascular elasticity, quantification of wall and vascular lumen parameters allows

[1] Faculty of Medicine, Transilvania University of Braşov.

evaluation of this phenomenon and its clinical implications.

Several clinical studies have documented the prognostic implication of arterial stiffness in different population groups, and reported its value as independent predictor of cardiovascular morbidity and all-cause mortality [18].

Non-invasive diagnosis of arterial stiffness, and especially of the aortic stiffness, contribute to global cardiovascular risk assessment, and suggests new approaches in the treatment of hypertension [1], [3], [7].

2. Material and method

In this study were included 88 hypertensive patients, 50 women (56.81%) and 38 men (43.18%) with a mean age of 68,022+/-9,023 years. Patients were evaluated anthropometric [age, height, body mass index (BMI)] and by laboratory screening analyses of cardiovascular risk: fasting plasma glucose, hemoglobin A1C, lipid profile, serum creatinine. The history of cardiovascular disease, smoking, daily activity and alcohol consumption over 21 units per week were collected. Obesity was assessed according to the body mass index (BMI) value recommended by World Health Organization (WHO) in 2012 [$\geq$ 30 kg/m^2]. The diagnosis of diabetes was established according to American Diabetes Association criteria from 2014 [22].

Glomerular filtrate rate was estimated (eGFR) by MDRD formula (Modification of Diet in Renal Disease) and used for the evaluation of chronic kidney disease stages according to the criteria of the Kidney Disease Outcome Quality Initiative ((K/DOQI) [10].

Dyslipidemia was considered as controlled according to serum levels of LDL-cholesterol and total cholesterol recommended in 2011 by the European Society of Cardiology guidelines for the prevention of cardiovascular disease [2].

Signed informed consent was obtained from all patients.

We used the M-mode transthoracic echocardiography (M mode-TTE) to asses two aortic stiffness parameters: aortic "strain" and aortic stiffness index [SI].

Aortic elasticity/stiffness parameters were assessed using a 2-D M-mode evaluation of systolic (AoS) and diastolic (AoD) diameters (averages of three measurements), in parasternal long-axis, 3 cm above the aortic valve. The mentioned parameters were calculated using previously validated mathematical formulas:

- Aortic “strain” = 100 (AoS – AoD) / AoD
- Aortic stiffness index (SI) = ln(SBP/DBP)/[(AoS – AoD)/AoD
- SBP - systolic blood pressure
- DBP – diastolic blood pressure
- ln SBP/DBP = natural logarithm of the ratio between SBP and DBP

Depending on hypertension degree (HTA) [1]: 34 patients (38.63%) had hypertension grade I, 40 pts (45.45%) hypertension grade II and 14 patients (15.90%) HTA grade III. 34 patients (38.63%) were smokers, 26 patients (29.54%) declared alcohol consumption over 21 UI/week, and 68 patients (77.27%) were considered sedentary.

Diabetes mellitus (DM) was diagnosed in 28 patients (31.81%), obesity in 30 patients (34.09%) and uncontrolled dyslipidemia in 54 patients (61.36%). Myocardial infarction was found in history of 6 patients (6.81%) with grade I and of 13 patients (14.77%) with grade II and III hypertension; 4 patients (4.54%) with grade I and 8 patients (9.09%) with hypertension grade II and III had history of stroke. The eGFR<60 ml/min/1.73 m^2 was found in 32 patients (36.36%) of which 26 patients (81.25%) with stage III and 6 patients (18.75%) with stage IV chronic kidney disease [10].

Patients were divided according to the hypertension grade in group A: 34 patients (38.63%) with hypertension stage I and group B: 54 patients (61.36%) of which 40 patients (45.45%) with hypertension grade II and 14 patients (15.909%) with hypertension grade III. High additional cardiovascular risk was estimated in 6 patients (6.81%) with grade I and 15 patients (17.045%) with grade II and III of hypertension and very high additional cardiovascular risk in 9 patients (10.22%) with grade I, 9 patients (10.22%) with grade II and 13 patients (14.77%) with grade III of arterial hypertension.

2.1. Statistics

Data were analyzed using MedCalc software (v.9.2.1.0) and Statistics (v. 4.7.0). The results were interpreted as mean values +/- standard deviation (SD). We used analysis of variance (ANOVA) to assess significant differences between group means and nonparametric correlation test Chi-square (PEARSON). The statistical significance threshold was chosen as p value <0.05.

2.2. Results

Clinical characteristics and laboratory data of the patients are shown in Table 1.

Cinical and paraclinical characteristics Table 1

	Group A (n=34)	**Group B (n=54)**	**p***
Gender (female/male)	16F/18M	28F/26M	0.921
Mean age (years)	68.148 ± 9.423	67.823 ± 8.633	0.909
Smokers/non-smokers	18/16	24/26	0.621
Alcohol consumption yes/no	14/20	19/35	0.334
Physical activity yes/no	8/26	14/40	0.01147*
BMI (kg/m^2)	25.38 ± 4.29	28.80 ± 5.89	0.0317*
eGFR	73.166 ± 26.36	70.08 ± 20.86	0.408
Total Cholesterol (mg/dL)	186.03 ± 27.061	207.29 ± 35.41	0.0297*
LDL-Cholesterol (mg/dL)	117.55 ±- 44.61	129.07 ± 40.19	0.3918
Tryglicerides (mg/dL)	125.25 ± 42.79	172.11 ± 83.499	0.018*
HDL-Cholesterol (mg/dL)	52.49 ± 10.52	49.17 ± 11.75	0.973
Glycated hemoglobin A_1C (%)	5.623 ± 1.07	6.618 ± 1.947	0.035*

BMI = body mass index,
eGFR= estimated Glomerular Filtration Rate (MDRD formula)
*p< 0.05, correlation is present and significant;
**p< 0.01, correlation is present and highly significant;
***p< 0,001, correlation is present and very highly significant;

There were no statistically significant differences of age in patients from group A (68.148 ± 9.423) versus those from group B (67.823 ± 0.909). Distribution of patients by gender was consistent across the two groups: 47.05% women and 52.94% men in group A versus 51.85% women and 48.14% men in group B. Physical inactivity was correlated with the degree of hypertension ($\chi 2$ = 6.390705, p = 0.01147, 95% CI). Elevated systolic blood pressure in the group B (SBP≥160 mm Hg) was statistically significant correlated with obesity (BMI ≥ 30 kg/m^2) ($\chi 2$ = 4.47 p = 0.02868, 95% CI), correlation which was confirmed by ANOVA test results (p = 0.0317). Uncontrolled dyslipidemia quantified by serum total cholesterol levels ≥ 200 mg / dL was significantly correlated with BP values in group B ($\chi 2$ = 23.2, p = 0.001, 95% CI). Triglycerides levels were

statistically significant correlated with stage of hypertension in group B ($\chi 2$ = 7.66, p = 0.0372, 95% CI). Glycated hemoglobin > 7% were significantly correlated with blood pressure values in in group B ($\chi 2$ = 9.46, p = 0.0021, 95% CI). LDL-cholesterol was not correlated with the stage of hypertension [(± 117.55 - 129.07 ± 44.61 vs. 40.19) (p = 0.3918)]. Alcohol consumption did not correlate statistically significant with hypertension ($\chi 2$ = 1.118373, p = 0.29027, 95% CI). The eGRF did not shown statistically significant differences between group A and group B [(70.08 ± 20.86 versus 26.36 ± 73.166) (p = 0.408)]. There were no statistically significant correlations between smoking/non-smoking status and hypertension grade ($\chi 2$ = 1.36, p = 0.24229, 95% CI).

Blood pressure and aortic stiffness parameters are shown in Table 2.

Blood pressure and aortic stiffness parameters Table 2

	Group A (n=34)	**Group 2 (n=54)**	**p***
SBP	129.92 ± 14.217	166.411 ± 13.752	0.000001***
DBP	79.444 ± 11.3894	96.647 ± 12.9	0.000035***
MAP (mmHg)	96.76 ± 11.092	119.50 ± 12.302	0.0001***
PP (mmHg)	50.48 ± 12.99	69.88 ± 15.87	0.0006***
Aortic Strain (%)	8.5910 ± 5.424	4.741 ± 3.191	0.0011***
Aortic stiffness index [SI]	8.677 ± 6.007	15.0207 ± 6.34	0.0019***

*p< 0.05, correlation is present and significant;
**p< 0.01, correlation is present and highly significant;
***p< 0,001, correlation is present and very highly significant;

Mean blood pressure values were significantly higher in the group of patients with hypertension grade II and III than in the group of patients with grade I hypertension [(119.50 ± 96.76 vs. 12.302 ± 11.092) (p = 0.0001)]. The pulse pressure mean values were correlated with the grade of hypertension, and statistically significant higher in the group of patients with hypertension grade II and III than in the group of patients with hypertension grade I [(69.88 ± 15.87 vs. 50.48 ± 12.99) (p = 0.0006)] (Table 2).

Aortic "strain" was statistically significant lower in the group patients with hypertension grade II and III than in those with hypertension grade I [(4.741 ± 3.191 vs. 8.591 ± 5.424) (p = 0.0011)] (Table 2).

Aortic stiffness index [SI] was significantly higher in the group of patients with hypertension grade II and III than in the group of patients with hypertension grade I [(15.02 ± 6.34 vs. 8.677 ± 6.007) (p = 0.0019)] (Table 2).

The aortic elasticity parameters evaluation showed that aortic „strain" was statistically significant lower in the group of patients with very high additional risk versus the group with high additional cardiovascular risk, both for patients with hypertension grade I [(5.83 ± 4.91 vs. 9.62 ± 6.21) (p = 0.0001)] and hypertension grade II and III [(3.93 ± 3.65 vs. 7.821 ± 5.79) (p = 0.0002)]. Aortic stiffness index [SI] was statistically significant correlated with very high additional cardiovascular risk both in patients with hypertension grade I [(13.213 ± 9.826 vs. 7.54 ± 5.92) (p = 0.0022)] and in patients with hypertension grade II and III [(16.146 ± 8.513 vs. 7.28 ± 6.52) (p = 0.00001)]. (Tables 3 and 4).

Table 3

Aortic stiffness parameters and cardiovascular risk in patients with AH grade I

BP and Aortic parameters	**High risk (n=6)**	**Very high risk (n=9)**	**p***
MAP (mmHg)	88.46 ± 10.53	116.73 ± 12.28	0.0001***
PP (mmHg)	52.33 ± 11.86	72.61 ± 14.39	0.0007***
Aortic Strain (%)	9.62 ± 6.21	5.83 ± 4.91	0.0001***
Aortic stiffness index [SI]	9.826 ± 5.92	13.213 ± 7.54	0.0022***

Table 4

Aortic stiffness parameters and cardiovascular risk in patients with AH grade II and III

BP and Aortic parameters	**High risk (n=15)**	**Very high risk (n=22)**	**p***
MAP (mmHg)	94.113 ± 12.142	121.03 ± 12.461	0.0002***
PP (mmHg)	54.27 ± 11.72	73.28 ± 16.032	0.0007***
Aortic Strain (%)	7.821 ± 5.79	3.93 ± 3.65	0.0002***
Aortic stiffness index [SI]	8.513 ± 6.52	16.146 ± 7.28	0.00001***

*p< 0.05, correlation is present and significant;
**p< 0.01, correlation is present and highly significant;
***p< 0,001, correlation is present and very highly significant;

We have determinate "cut-off" values for aortic strain and aortic stiffness index in the studied group (Table 5), using ROC curve, and we evaluated the correlations with clinical and paraclinical characteristic of study group patients.

Cut-off values for aortic compliance parameters Table

	AUC	Cut-off values	*p
Aortic strain (%)	0.812	5.81	< 0.0001
Aortic stiffness index [SI	0.825	8.73	< 0.0001

High values of total cholesterol (≥200 mg / dL) were statistically significant correlated with decreased aortic strain and increased aortic stiffness index in the group of patients with hypertension grade II and III and in those with very high risk ($\chi 2 = 9.73$, $p = 0.00226$, 95 % CI). Triglycerides > 150 mg/dL correlated statistically significant with increased aortic stiffness index and decreased aortic strain in patients with very high risk ($\chi 2 = 8.91$, $p = 0.00447$, 95% CI). In hypertensives patients with very high additional risk, there were no significant correlations between LDL-cholesterol > 100 mg / dL and aortic strain ($\chi 2 = 2.32$, $p = 0.167$, 95% CI) or aortic stiffness index ($\chi 2 = 1.82$, $p = 0.0185$, 95% CI) nor between LDL-cholesterol > 70 mg/dL and aortic strain ($\chi 2 = 2.86$, $p = 0.231$, 95% CI) or aortic stiffness index ($\chi 2 = 1.61$, $p = 0.358$, 95% CI). Obesity was statistically significant correlated with decreased aortic strain ($\chi 2 = 20.61$, $p = 0.00192$, 95% CI) and increased aortic stiffness index in patients with hypertension grade II and III and in patients with very high additional cardiovascular risk ($\chi 2 = 10.81$, $p = 0.00312$, 95% CI). In the group of patients with very high additional cardiovascular risk, HbA1c > 7% was statistically significant correlated with aortic strain ($\chi 2 = 9.85$, $p = 0.0118$, 95% CI) and aortic stiffness index ($\chi 2 = 7.48$, $p = 0.0271$, 95% CI). Physical inactivity was statistically significant correlated with

aortic strain ($\chi 2 = 8.83$, $p = 0.00324$, 95% CI) and aortic stiffness index ($\chi 2 = 9.05$, $p = 0.00173$, 95% CI) in patients with very high additional cardiovascular risk.

3. Discussions

In the last decade several clinical studies evaluated arterial stiffness by various invasive and noninvasive methods like Doppler ultrasound and magnetic resonance imaging (MRI). The measurement of pulse wave velocity (PWV) in the femoral artery, brachial or common carotid artery by Doppler ultrasonography was used to estimate arterial stiffness. Recent studies used the cardio-ankle vascular index (CAVI) as a new parameter of arterial stiffness [9]. PWV determined by MRI with the advantage of PWV evaluation in different segments of the arterial system has the disadvantage of high cost [17]. The assessment of arterial stiffness in clinical studies showing a direct relationship between arterial stiffness and increased risk of cardiovascular events, raised the question whether arterial stiffness is a risk factor or a marker of cardiovascular disease [7]. The published data revealed that decreasing in arterial compliance occurs with aging, even in the absence of cardiovascular risk factors. This phenomenon have arteriolosclerosis as morphological substrate [13] and appears to be determined by genetical factors [14]. Arterial stiffness associated with cardiovascular risk factors involved arteriosclerosis or atherosclerosis as morphological substrate. Independent of the morphological substrate, arterial stiffness contributes to enhanced cardiovascular risk due to prematurity of reflected wave in the large vessels which increases the central aortic pressure and cardiac afterload [16].

In this context is important to assess aortic stiffness by a clinical accessible method, such as M-mode transthoracic echocardiography. Elasticity and stiffening parameters of the ascending aorta evaluated by M-mode transthoracic echocardiography in hypertensive patients showed a decreased aortic distensibility and increased aortic stiffness in parallel with increasing values of blood pressure, the patients with second and third degree hypertension, these patients having an "aortic strain" significantly lower and "aortic stiffness index" significantly higher than patients with first degree hypertension.

Since 1997, aortic distensibility reduction was mentioned in association with hypertension [19]. Recent studies involved the arterial stiffness in the pathogenesis [4] and increasing prevalence of isolated systolic hypertension in elderly people [11]. Increased arterial stiffness has been implicated in the pathogenesis of essential hypertension [15] and in enhanced cardiovascular risk of hypertensive patients [5].

In our study, the group of hypertensive patients with very high additional cardiovascular risk versus the group with high additional cardiovascular risk had a significant increase in aortic stiffness and a significant decrease in aortic distensibility. This has been described in the literature by the correlation between arterial stiffness and diabetes, dyslipidemia or obesity. The association of diabetes with increased arterial stiffness was recently reconfirmed using carotid-femoral pulse wave velocity (CAVI) as a parameter for arterial stiffness [8]. Obesity and physical inactivity have also been associated with increased arterial stiffness estimated by increasing of pulse wave velocity in central obesity, both at rest [12] and after exercise [6].

The importance of aortic stiffness evaluation is underline by its independent

predictive value of cardiovascular events and by hypothesis that this parameter may reclassify the cardiovascular risk of various population groups [20].

Because the evaluation of predictive values of arterial stiffness need confirmation in large clinical randomized trials, the American College of Cardiology Foundation/American Heart Association task force guidelines do not recommend the arterial stiffness evaluation in the assessment of cardiovascular risk of asymptomatic patients [8].

Our data, using transthoracic M-mode ultrasonography to estimate the correlation between aortic stiffness and hypertension degree and hypertension additional cardiovascular risk promote this method to assess the aortic stiffness in clinical practice.

3. Conclusions

1. Evaluation by M-mode transthoracic echocardiography of aortic stiffness in hypertensive patients showed decreased elasticity and increased stiffness of the ascending aorta in parallel with increase of hypertension degree.

2. Aortic stiffness is significantly higher in hypertensive patients with very high additional cardiovascular risk than in those with high additional risk.

3. Our data, using transthoracic M-mode ultrasonography to estimate the correlation between aortic stiffness, hypertension degree and hypertension additional cardiovascular risk, recommend this method to assess the aortic stiffness in clinical practice.

References

1. Arnett, D.K., Evans, G.W., et al.: *Arterial stiffness:a new cardiovascular risk factor?* In: Am J Epidemiol. (1994) Oct 15; 140(8):669-82. Review. PubMed PMID: 7942769.
2. Catapano, A.L., Reiner, Z., et al.; European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). In: *ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS).* (2011) Jul; 217(1):3-46. Review. PubMed PMID: 21882396.
3. Cavalcante, J.L., Lima, J.A., et al.: *Aortic stiffness: current understanding and future directions.* In: J Am Coll Cardiol. (2011) Apr 5; 57(14):1511-22.doi: 10.1016/j.jacc.2010.12.017. PubMed PMID: 21453829.
4. Cecelja, M., Chowienczyk, P., et al.: *Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review*. In: Hypertension (2009); 54(6):1328-1336.
5. Cecelja, M., Chowienczyk, P.: *Role of arterial stiffness in cardiovascular disease*. In: JRSM Cardiovasc Dis. (2012) Jul 31; 1(4). pii: cvd.2012.012016. doi: 10.1258/cvd.2012.012016. Review. PubMed PMID: 24175067; PubMed Central PMCID: PMC3738327.
6. Chi, Y.S., et al.: *Overweight and its association with Aortic Pressure Wave Reflection after Exercise*. In: Am J Hypertens. (2011); 24 (10): 1136-1142.
7. Glasser, S.P., Arnett, D.K., et al.: *Vascular compliance and cardiovascular disease: a risk factor or a marker?* In: Am J Hypertens (1997); 10:1175–89.
8. Greenland, P., Alpert, J.S., et al.: American College of Cardiology Foundation/American Heart Association *Task Force on Practice Guidelines.2010 ACCF/AHA guideline*

for assessment of cardiovascular risk in asymptomatic adults: executive summary – a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. In: Circulation (2010); 122:2748–2764.

9. Hongyu, W., Jinbo, L., et al.: *Arterial stiffness evaluation by cardio-ankle vascular index in hypertension and diabetes mellitus subjects*. In: Journal of the American Society of Hypertension (2013); 7(6):426–431.
10. Johnson, C.A., Levey, A.S., et al.: *Clinical practice guidelines for chronic kidney disease in adults:* Part I. *Definition, disease stages, evaluation, treatment, and risk factors*. In: Am Fam Physician. (2004) Sep 1; 70 (5):869-76. Review. PubMed PMID: 15368726.
11. Karen, L.B., et al.: *Large-Artery Stiffness Contributes to the Greater Prevalence of Systolic Hypertension in Elderly Women*. In: J Am Geriatr Soc (2004).52:368–373.
12. Marco, C., Majd, A., et al.: *Impact of Central Obesity on the Estimation of Carotid–Femoral Pulse Wave Velocity*. In: Am J Hypertens (2014) 27 (9): 1209-1217.
13. McEniery, C.M., et al.: *Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT)*. In: J Am Coll Cardiol (2005); 46:1753-1760.
14. Medley, T.L., Kingwell, B.A., et al.: *Matrix metalloproteinase-3 genotype contributes to age-related aortic stiffening through modulation of gene and protein expression*. In: Circ Res (2003); 92:1254-1261.
15. Messerli, F.H., et al.: *Arterial compliance in essential hypertension*. In: J Cardiovasc Pharmacol. (1985); 7(Suppl 2):S33–35.
16. O'Rourke, M.F., Nichols, W.W., et al.: *Changes in wave reflection with advancing age in normal subjects: Response*. In: Hypertension (2004); 44:e10-e11.
17. Oliver, J.J., Webb, DJ.: *Noninvasive assessment of arterial stiffness and risk of atherosclerotic events*. In: Arterioscler Thromb Vasc Biol. (2003) Apr 1; 23(4):554-66. Epub (2003) Feb 6. Review. PubMed PMID: 12615661.
18. Payne, R.A., Wilkinson, I.B., et al.: *Arterial stiffness and hypertension: emerging concepts*. In: Hypertension. (2010) Jan; 55(1):9-14.
19. Resnick, L.M., Militianu, D., et al.: *Direct magnetic resonance determination of aortic distensibility in essential hypertension: relation to age, abdominal visceral fat and in situ intracellular free magnesium*. In: Hypertension (1997); 30:654–9.
20. Vlachopoulos, C., Aznaouridis, K., Stefanadis, C.: *Prediction or cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis*. In: J Am Coll Cardiol. (2010); 55:1318–1327.
21. *2013 ESH/ESC Guidelines for the management of arterial hypertension; The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC); European Heart Journal (2013)* 34, 2159–2219 doi:10.1093/eurheartj/eht151.
22. *American Diabetes Association. Diagnosis and classification of diabetes mellitus*. In: Diabetes Care. (2014) Jan; 37 Suppl 1:S81-90. doi: 10.2337/dc14-S081. PubMed PMID: 24357215.