GENERAL REVIEW

UDC: 616.12
https://doi.org/10.2298/VSP170701161S

Arterial stiffness as predictive factor of cardiovascular diseases

Arterijska krutost kao prediktivni faktor kardiovaskularnih oboljenja

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Key words:
antihypertensive agents; arteries; cardiovascular diseases; elasticity; equipment and supplies; hypertension; pulse wave analysis; risk assessment.

Ključne reči:
antihipertenzivi; arterije; kardiovaskularne bolesti; elastičnost; oprema i pribor; hipertenzija; pulsni talas, analiza; rizik, procena.

Introduction

Understanding the basic hemodynamic principles is necessary for the assessment of arterial stiffness and its possible clinical practice. Hydraulic and elasticity theory was established by Young in 1840, Moens in 1878, and Korteweg in 1878 [1]. The main determinants of pulse wave velocity (PWV) relates to the velocity of pulse wave travel in a vessel to the distenbility of that vessel [2, 3]: (PWV) = $\sqrt{(Eh/2R\rho)}$, (E is the Young's modulus in the circumferential direction, h is the wall thickness, R is the vessel radius and ρ is the density of fluid).

Later, the doctors-physiologists, Marey in 1860, Mahomed in 1872 and Mackenzia in 1902, developed various types of Sphygmocor and, thus, made a significant progress in pressure waveform analysis [4]. Clinical application was discovered by Safar and O'Rourke [5, 6], which turned out to be very useful in the prognosis of the outcome and the correction of therapy.

In healthy persons, the peripheral arteries are stiffer than the central and that leads to an increase of amplitude of pulse wave in blood vessels, from heart to periphery, which is known as pressure amplification [6, 7]. The stiffness of mid-size arteries is assessed by a vasomotor tone which depends on the endothelial function or the sympathetic nervous system [8–10] or on renin-angiotensin system [11].

Elastic properties of arteries vary along the arterial tree, with more elastic proximal and stiffer distal arteries. In humans, PWV increases from 4–5 m/s in the ascending aorta to 5–6 m/s in the abdominal aorta, and 8–9 m/s in the iliac and femoral arteries [11]. This difference in the arterial stiffness has the significant physiological and pathophysiological consequences.

Due to an increase of pulse pressure (PP) between the central and peripheral arteries, brachial PP should not be used as a replacement for aortic or carotid PP, especially in younger persons.

The stiffness of the common carotid artery is approximately six times higher in 70-year old persons than in a 20-year old person [6, 12]. In the older patients with hypertension or diabetes, the carotid arteries may become stiffer than the femoral or radial arteries which become slightly stiffer with age, or due to hypertension.

Noninvasive assessment of arterial stiffness

The regional and local arterial stiffness may be measured directly in a noninvasive manner, in various locations along the arterial tree and it is based on measuring the parameters which are directly connected to the arterial stiffness.

Local assessment of arterial stiffness

The arterial stiffness can be assessed locally through the use of ultrasound device which also provides precise measures of intima-media thickness (IMT) which allows the assessment of elastic properties of arterial vessel according to the Young's elastic modulus [13]. The assessment of carotid stiffness and thickness is important for the development of atherosclerosis. The local arterial stiffness of deep arteries such as aorta may also be measured by the magnetic resonance imaging (MRI), but this is not commonly applied in routine practice. Aortic PWV assessed by transformation of the brachial pressure waveform did not show a significant difference comparing with the cardiac magnetic resonance – derived transit time method [14].

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Although the carotid-femoral PWV and carotid stiffness provide similar data on how age affects the stiffness of big arteries in healthy persons, this is not the case with the persons with hypertension and/or diabetes. With age and other cardiovascular risk factors, the aorta gets stiffer than the carotid arteries and that is why the aortic and carotid stiffness can not be used as the variable predictors of the high-risk patients [15].

Regional assessment of arterial stiffness

Aorta is the main blood vessel of interest in the assessment of regional arterial stiffness, but all of the arterial branches have their own impact. *Arteria brachialis*, where the pressure is most often measured, and the lower extremity arteries get especially altered by atherosclerosis. Measurement of a local carotid stiffness may also provide a significant prognostic information since the carotid artery is often the place where atheroma appears.

Pulse wave velocity measuring

The PWV measurement is the simplest, noninvasive method for the assessment of arterial stiffness. Carotid-femoral PWV is a direct measurement and is considered a golden standard for the assessment of arterial stiffness, but it is important to measure precisely the distance between the carotid and femoral artery, because even small mistakes may affect the absolute value of PWV [16–18]. Measuring along the aorta or aortoiliac path is clinically the most relevant, since the aorta and its first branches are connected to the left ventricle and therefore are the most responsible for the majority of the arterial stiffness effects. Contrary to that, the PWV measured outside of aortic system, that is, in the upper extremities (brachial PWV) or lower extremities (femorotibial PWV) do not have a good predictive value in the patients with terminal kidney disease [19].

It is difficult to register the femoral pressure waveform in persons with metabolic syndrome, excess body mass, diabetes and peripheral arterial disease [20]. In case of aortic, iliac, or stenosis of proximal segment of femoral artery, the pressure waveform may be delayed or reduced. Abdominal obesity, especially in men, and large breasts in women may cause an inaccurate measuring of distance [21].

Arterial stiffness measuring devices

SphygmoCor® is a tonometric device; PWV is calculated on the basis of successive waves produced in short time interval in two arterial locations (most often the carotid and femoral artery) through use of R waves in the electrocardiogram (ECG) for the calculation of the delay [22].

Measurements are most often done at the root of the left subclavian artery (suprasternal space on the skin) or close to abdominal aortic bifurcation (at the level of umbilicus). Transit time is automatically calculated by the recognition of the beginning of pulse. This method is used for the assessment of predictive value of aortic PWV for cardiovascular events in the patients with diabetes and it gives more precise assessment of aortic PWV when compared to the carotid-femoral PWV. The aortic brachial PWV is an important predictor of cardiovascular events in the patients with hypertension [23].

TensioMed Arteriograph® is a device for measuring stiffness of arterial blood vessels that works according to the patented oscillometric principle. Data received via arteriograph [augmentation index (AIx), PWV, central systolic blood pressure (SBP) and PP] match the data received via the brachial artery catheter. Comparison was also made with Applanation Tonometer Sphygmocor® and no significant difference was observed. For the assessment of the arterial stiffness parameters with these devices, it is necessary to prepare the patient adequately: the use of alcohol 10 h before and the use coffee 3 h before the measurement are strictly forbidden; patients must be in a semisupine position 10 min before the measurement. The assessment is performed in supine position at the room temperature of 22 ± 1°C. The arteriograph device measures aortic PWV (PWVao), AIx and central blood pressure (SBPao) values simultaneously with the peripheral blood pressure. By inflating the cuff on the upper-arm to suprasystolic pressure the brachial artery becomes occluded. The brachial flow is stopped, therefore the brachial wall characteristics are excluded (no significant wall movement), consequently the gained information relate to the systematic circulation. For calculating the arterial function parameters the recorded pulse waveform is analyzed and the characteristic points of the first and reflected waves are determined. The true aortic length is estimated with the jugulum symphysis distance (Jug-Sy).

The optimal values are: AIx < -30%, PWV < 7 m/s. The pathological values are: AIx >10%, PWV > 12 m/s.

Besides the classic 24-h blood pressure measurement, the latest device with HMS CS program combined with the Mobil-O-Graph® also has an integrated system for 24-h ambulatory monitoring of arterial stiffness through the use of oscillometric method. The Mobil-O-Graph® measures standard blood pressure parameters, central aortic pressure, central PP, AIx standardized to a heart rate of 75 beats through empirical regression (AIx@75), PWV, cardiac output, cardiac index, and total vascular resistance reflection magnitude. Biolectrical impedance gives us these values at present time [24, 25]. 24-h monitoring both of arterial stiffness and hemodynamic enables the provision of more precise parameters in cardiovascular prediction. There is no specific preparation of patients for wearing this device and one advantage is that all parameters are monitored 24 h during usual the daytime and nighttime values. In addition, the therapeutic effect of medicine can be assessed much better, with a much better prognostic effect on damages of target organs.

The Mobil-O-Graph® parameters are shown in Figure 1.

There is no difference in the value of central aortic pressure measured by using the oscillometric noninvasive method with the Mobil-O-Graph® device and the tonometric method with the SphygmoCor® device. The Mobil-O-Graph® combines the advantages of assessing brachial pressure and central blood pressure in one measurement [20]. As with other populations, the acceptability of Mobil-O-Graph® and SphygmoCor® is evident for central SBP and AIx@75 in the

dialysis patients; PWV is slightly underestimated by the Mobil-O-Graph [22]. Noninvasive 24-hour assessment of blood pressure level and blood vessel stiffness is of prognostic value for a cardiovascular risk [26]. According to the SAFER study, the left ventricular hypertrophy (LVH) is more associated with 24-hour aortic pressure than with 24-hour brachial pressure in the patients with hypertension [27]. Aortic pressure correlates better with all, especially cardiovascular mortality caused by the brachial artery pressure [28].

Noninvasive assessment of arterial stiffness parameters

Central pulse wave analysis

Arterial pressure waveform consists of the pulse wave initiated by the ventricular contraction and reflected wave. The waves are reflected from periphery, mostly from the branching point. In elastic blood vessels, due to the low PWV, reflected wave has a tendency to return to the aortic root during diastole. In case of stiff arteries, PWV increases and reflected wave arrives to the central artery earlier, where it acts as an enhancement to the initiated wave and increases systolic pressure. This phenomenon may be quantified through AIx which is defined as a difference between the second and first systolic peak (P2-P1) expressed as a percentage of PP (Figure 1) [4, 16]. Regardless of high PWV, changes in the location of reflection may affect AIx. In clinical research, the main AIx determinants are not only diastolic blood pressure and height, but also age and aortic PWV.

Central AIx and central PP showed an independent predictive value when it comes to all-cause mortality in the dialysis patients [28] and cardiovascular events in the patients who underwent percentaneous coronary intervention, as well as in the patients with hypertension in the CAFE study [29].

Figure 2 shows AIx which is defined as difference between the second and first systolic peak (P2-P1) expressed as a percentage of PP.

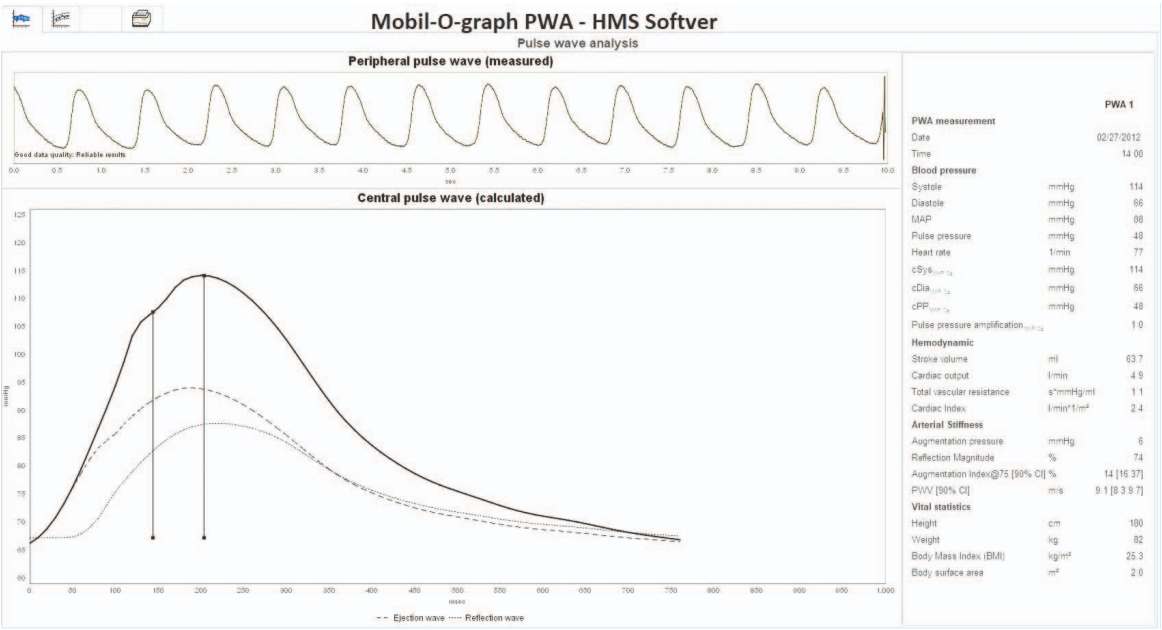

Fig. 1 – Mobil-O-Graph parameters
PWA – pulse wave analysis;MAP – mean arterial pressure; cSys – central systolic pressure; cDia – central diastolic pressure; cPP – central pulse pessure; PWV – pulse wave velocity.

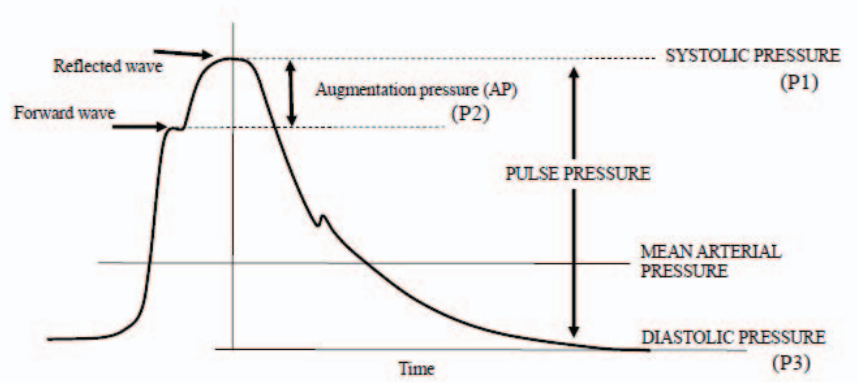

Fig. 2 – Augmentation Index (AIx) – which is defined as difference between the second and first systolic peak (P2-P1) expressed as a percentage of the pulse pressure.

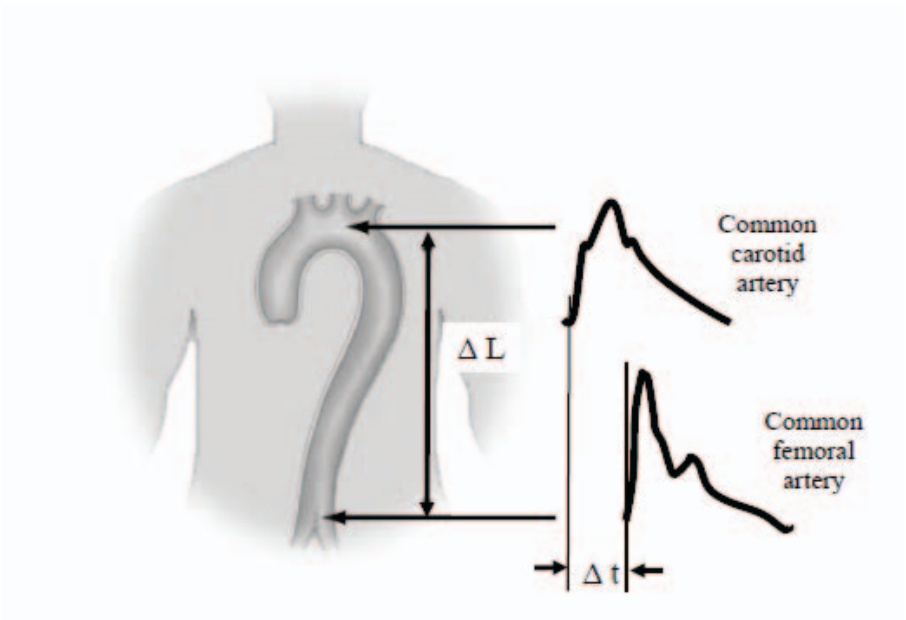

Fig. 3 – The foot to foot method for measurement of carotid-femoral pulse wave velocity.

Central and peripheral systolic and pulse pressure

Peripheral pressure SBP and PP (measured on the brachial artery) should not be equated with central SBP and PP measured on carotids, since peripheral pressure is higher than the central and PP, especially in younger persons, due to the less stiff central artery in younger persons.

Central pulse pressure, augmentation index and arterial stiffness

Central SBP and PP, AIx and PWV increase with age, hypertension, diabetes mellitus and hypercholesterolemia, and they are connected with damage to target organs (LVH, microalbuminuria, carotid plaques, and endothelial dysfunction). Central SBP, PP and AIx depend on the speed at which the wave travels, amplitude of the reflected wave, point of reflection, duration and size of ventricular ejection, especially in relation to heart rate and ventricular contractility [30], while aortic PWV which is the wave propagation speed, presents the internal arterial stiffness according to the Bramwell-Hill equation (Figure 2). Pathophysiological conditions and medicines can change central PP and AIx without changing aortic PWV, which shows the dominant influence of the reflecting wave, heart rate or ventricular ejection, without the change of arterial stiffness [30–31]. AIx is much more sensitive to heart rate than PWV. In the Anglo-Cardiff Collaborative Trial conducted in the general population, it is shown that younger than age of 50 years affects AIx more than it affects PWV in the people below 50 years of age, but it is the opposite after the age of 50 years [34].

Central pressure and AIx have a significant predictive value in the patients with hypertension, coronary disease and kidney diseases [35].

Figure 3 shows the foot to foot method for measurement of carotid-femoral PWV.

Clinical application

Pathophysiology

The stiffness of vascular wall depends on two main fiber proteins which are part of its composition: collagen and elastin. Excessive production of abnormal collagen and reduction of normal elastin plus their inadequate spatial organization lead to arterial stiffness [36].

There are many risk factors for the increased arterial stiffness: age, low birth weight, menstrual cycle, menopause, lack of physical activity, genetic predisposition to hypertension, diabetes, myocardial infarction, genetic polymorphism, obesity, smoking, hypercholesterolemia [37], glucose intolerance, metabolic syndrome, hyperhomocysteinemia, high levels of C-reactive protein (CRP). Also, cardiovascular diseases, such as coronary disease, congestive heart failure [2], stroke, as well as non-cardiovascular diseases, such as moderate chronic kidney disease stage 3 [38], rheumatoid arthritis, systemic vasculitis and systemic lupus erythematosus [30] represent risk factors for the increased arterial stiffness**.**

The arterial stiffness and reflection of waves are important for an increase of systolic pressure in elderly persons, and they play an important role in the occurrence of cerebrovascular stroke and myocardial infarction.

The arterial stiffness causes premature return of reflected wave in early systole, which increases central PP and then systolic blood pressure which increases left ventricular burden and increases the need for oxygen. In addition, the arterial stiffness is combined with LVF [27], which is a significant risk factor for coronary disease in the normotensive and hypertensive patients. The increase of central blood pressure and decrease of diastolic BP can directly cause subendocardial ischemia. The increase of aortic stiffness, together with aging and risk factors for cardiovascular diseases, is caused by various mechanisms including the degradation of elastic

fibers, collagen accumulation, fibrosis, inflammation, medial smooth muscle cell necrosis, calcification and diffusion of macromolecules across the arterial wall [29]. The increased arterial stiffness may increase the risk of stroke through several mechanisms, including the increase of central PP, influence on remodeling of intra- and extracranial arteries, increase of carotid wall thickness, and development of stenosis and plaques [29, 30, 39], with plaque rupture and damage to the white matter of brain. In addition, the coronary disease and heart weakness with high PP and the arterial stiffness are risk factors for the occurrence of stroke.

Routine application of arterial stiffness

The aortic stiffness has an independent and more significant predictive value than classical risk factors for all-cause and cardiovascular mortality in the patients with hypertension, type 2 diabetes, patients on dialysis and elderly persons, since it shows damage to blood vessel through risk factors during the longer time period [22].

Aortic PWV has a better predictive value than the classical cardiovascular risk factors. Central AIx and PP showed an independent predictive value for all-cause mortality in the patients on dialysis, or after kidney transplantation and for cardiovascular events in the persons with hypertension and coronary disease, after percutaneous coronary intervention [40]. It was shown in meta-analysis that the aortic stiffness expressed as aortic PWV is a strong predictor of future CV events and all-cause mortality. The predictive ability of arterial stiffness is higher in the subjects with a higher baseline cardiovascular risk [41, 42]. Also, aortic PWV may enable better identification of the high-risk populations that might benefit from more aggressive cardiovascular disease risk factor management [43].

Predictive value of pulse wave velocity for cardiovascular event reduction

An important question is whether the reduction of PWV is associated with the accompanying reduction of cardiovascular events, regardless of the normalization of classical risk factors?

The reduction of arterial stiffness may indicate an actual reduction of damage to blood vessel wall, while blood pressure, glycaemia and lipids may be normalized in several weeks through medical therapy, resulting in a significant reduction of cardiovascular risk score, but without the improvement of atherosclerotic lesion and the arterial stiffness which require a long-term correction of biochemical parameters. Therefore, a temporary dissociation between the reduction of cardiovascular risk factor and further present arterial stiffness is to be expected.

It is still to be proven whether reduction of central PP is associated with the accompanying reduction of cardiovascular events, regardless of normalization of classical risk factors. There is indirect evidence of this. In the REASON study [38, 44], only the combination of perindopril/indapamide managed to significantly reduce reflection of carotid wave with the resulting relative reduction of central SBP and PP and subsequent reduction of LVH [42] as opposed to no reduction of carotid PP and LVH in the patients who used atenolol in their therapy. The CAFE study [40] and ASCOT study [45] showed that central pressure, AIx and PP were the independent predictors of cardiovascular events in the hypertensive patients and that reduction of central SBP and PP was higher in the amlodipine/perindopril group than in the atenolol/thiazide group, despite of similar reduction of SBP and PP of brachial artery.

How to reduce arterial stiffness (arterial stiffness therapy)

Nonpharmacological and pharmacological therapies have an important place in the arterial stiffness reduction.

Nonpharmacological therapy includes a regular moderate physical activity, weight loss, reduced salt intake, moderate consumption of alcohol, garlic powder, alpha linoleic acid and fish oil, as well as hormone replacement therapy [44–48].

Pharmacological therapy includes the application of antihypertensive medicines and medicines for the cardiac insufficiency treatment: diuretics, beta blockers, angiotensin-converting-enzyme (ACE) inhibitors, type 1 angiotensin-receptor blockers (ARBs) and calcium antagonists, nitrates, hypolipidemic medicines such as statins and fibrates, antidiabetics such as thiazolidinediones as well as sildenafil [17, 49].

The majority of antihypertensive drugs have the main influence on the dynamic component of arterial stiffness and in some part on the structural component in the arterial wall remodeling [18].

In general, the renin-angiotensin system inhibitors are superior to all other antihypertensive drugs in reducing arterial stiffness. One reason is the profibrotic action of the renin-angiotensin system, as the turnover of the extracellular matrix in the arterial wall per se leads to a change in the properties of the vessel [50, 51].

The REASON study showed the positive effects of ACE inhibitors on the arterial stiffness, especially on AIx. The effects lasted even after nine months of treatment [44, 52]. Positive effects were shown for most drugs in this group, including for lisinopril [53].

If reduction of AIx is in focus, losartan in the LIFE [54], OPTIMAAL [55] study and candesartan [56, 57] showed positive effect on reduction. Some others ARBs valsartan (VALUE study) [58, 59] and telmisartan [60] reduce AIx and PWV, but increase PP.

Figure 4 shows the case from our practice (a – before therapy with losartan and b – six months on losartan therapy.

Beta-blockers without the vasodilating effects have a weaker effect on the arterial stiffness and central pulsatile hemodynamics than vasodilating drugs of other antihypertensive groups. The mechanism of action is through the heart rate reduction, as this influences the viscoelastic properties of the arterial wall. Reduced heart rate also leads to increased wave reflections, a lower reduction in aortic than brachial systolic blood pressure and reduced PP amplification. Pe-

ripheral vasoconstriction, achieved by atenolol, is an additional mechanism responsible for the negative effect on wave reflections [61, 62]. New agents such as nebivolol, which have vasodilating effects, seem to be more effective in improving central pulsatility. These effects appear to be related to their ability to donate nitrit oxide (NO), which dilates the small resistance arteries. The effects observed lead to PP amplification, but AIx reduction [61–63].

Calcium channel blockers also lower PWV and reduce wave reflections, but to a lesser degree than renin-angiotensin inhibitors. The largest amount of evidence is for amlodipine. In the CAFE study 64, it was showed to reduce central blood pressure more than peripheral blood pressure; it amplified pulse pressure and reduced AIx.

Diuretics seem to have no beneficial effect on pulsatile hemodynamics. Hydrochlorothiazide showed a neutral effect on reduction of central blood pressure and a neutral effect on PP amplification [65, 66].

Arterial stiffness and damage to target organs

The arterial stiffness also provides data on the damage of target organs, which is of a great importance for the assessment of total cardiovascular risk in the patients with hypertension.

In case of primary coronary event in the hypertensive patients, the value of aortic PWV is much more important for the low-risk patients (first or second tertile of the Framingham risk score) than for the high-risk patients (third or fourth tertile), which shows that the population with low to medium risk benefits the most from the value of PWV [30].

Fig. 4 – The case: a) before therapy with losartan; b) six months on losartan therapy, consecutively.

Sys – systolic; Dia – diastolic; PP – pulse pressure; MAP – mean arterial pressure; SBPao – control systolic blood pressure; HR – heart rate; AIx – augmentation index; PPao – central aortic pulse pressure; ABI – ankle brachial index; ED – ejection duration; SD – standard deviation of the beat to beat measured aortic pulse wave velocity values; PWVao – aortic pulse wave velocity; RT – return time.

The latest results showed that the increased aortic stiffness is an independent predictor of major adverse cardiac and cerebrovascular events (MACCE) after acute ST-elevation myocardial infarction. The assessment of aortic stiffness in addition to classical risk factors significantly improved an early risk stratification [67].

Concerning diastolic dysfunction, the arterial stiffness was correlated with the elevated left ventricular filling pressure and it was shown that the increased level was associated with an elevated left ventricular filling pressure in the patients with the preserved systolic function. It was hypothesized that the increased arterial stiffness is of pathophysiological relevance for the diastolic dysfunction [68].

Conclusion

The existing European and American [70] recommendations for the diagnosis and treatment of hypertension define LVH and albuminuria as evidence of target organ damage, as well as the arterial stiffness and reflection of waves.

The assessment of arterial stiffness and central pressure should be considered as a recommended test for assessment of cardiovascular risk, especially in the patients with the damages on the target organs that went undetected during the routine examinations. According to the recommendations of the American Society of Hypertension (ASH), the assessment of blood vessels stiffness should be performed by a hypertension specialists in the hypertension centers. Introduction of this diagnostic procedure in routine practice is still under the consideration [70].

According to the European Society of Hypertension (ESH) guidelines of 2013, the stiffness of large arteries and wave reflection phenomenon are the important pathophysiological indicators of isolated systolic hypertension, and, together with PP, they increase with age [28, 71]. Carotid-femoral PWV is a golden standard for measuring the aortic stiffness [71]. According to the common guidelines issued by the European Society of Hypertension and European Society of Cardiology (ESC) [72], the PWV value of > 12 m/s indicates a significant deterioration of aortic function in the middle-aged hypertension patients. According to the recent research, due to the use of correct carotid-femoral distance and taking into consideration 20% anatomically shorter pulse wave distance, the PWV value of > 10 m/s indicates the increase of aortic stiffness [73]. Central pressure, especially central SBP and PP are more important predictors of occurrence of cardiovascular events and assessment of cardiovascular risk from brachial pressure [72]. For the valid measuring of central pressure, you can use not only the tonometric devices (SphygmoCorCP®) but also the oscillometric ones (SphygmoCor XCEL®) [74], as well as the 24-hour arterial stiffness monitoring device, the Mobil-O-Graph® [18].

R E F E R E N C E S

1. *Laurent S, Kingwell B, Bank A, Weber M, Struijker-Boudier H.* Clinical applications of arterial stiffness: Therapeutics and pharmacology. Am J Hypertens 2002; 15(5): 453–8.
2. *Franck O.* Die Elasticitat des Blutegefasse. Z Biol 1920; 46: 255–72.
3. *Bramwell JC, Hill AV.* The Velocity of the Pulse Wave in Man. Proc. Roy. Soc. Lond. (Biol.) 1922; 93: 298–306.
4. *Mackenzie IS, Wilkinson IB, Cockcroft JR.* Assessment of arterial stiffness in clinical practice. QJM 2002; 95(2): 67–74.
5. *Safar ME, O'rourke MF.* Arterial Stiffness in Hypertension. In: *Safar ME, O'rourke MF,* editors. Arterial Handbook of Hypertension Series. 1st ed. Amsterdam: Elsevier; 2006. p. 598.
6. *Nichols WW, O'rourke MF.* McDonald's Blood Flow in arterial stiffness, and during treatment of hypertension. Hypertension 2001; 38: 914–21.
7. *Nichols WW, McDonald DA.* Wave-velocity in the proximal aorta. Med Biol Eng 1972; 10(3): 327–35.
8. *Boutouyrie P, Lacolley P, Girerd X, Beck L, Safar M, Laurent* S. Sympathetic activation decreases medium-sized arterial compliance in humans. Am J Physiol 1994; 267(4 Pt 2): 1368–76.
9. *Giannattasio C, Failla M, Lucchina S, Zazzeron C, Scotti V, Capra A,* et al. Arterial stiffening influence of sympathetic nerve activity: Evidence from hand transplantation in humans. Hypertension 2005; 45(4): 608–11.
10. *Paunović K, Stojanov V, Jakovljević B, Belojević G.* Thoracic bioelectrical impedance assessment of the hemodynamic reactions to recorded road-traffic noise in young adults. Environ Res 2014; 129: 52–8.
11. *Giannattasio C, Failla M, Stella ML, Mangoni AA, Turrini D, Carugo S,* et al. Angiotensin-converting enzyme inhibition and radial artery compliance in patients with congestive heart failure. Hypertension 1995; 26(3): 491–6.
12. *Lovic D, Kallistratos MS, Poulimenos L, Skyrlas A, Stojanov V, Jakovljevic B,* et al. Pulse wave velocity: retrospective analysis in a Balkan normotensive and hypertensive population: A study of 9923 patients. Angiology 2018; 69(1): 59–64.
13. *Hoeks AP, Brands PJ, Smeets FA, Reneman RS.* Assessment of the distensibility of superficial arteries. Ultrasound Med Biol 1990; 16(2): 121–8.
14. *Feistritzer HJ, Reinstadler SJ, Klug G, Kremser C, Seidner B, Esterhammer R,* et al. Comparison of an oscillometric method with cardiac magnetic resonance for the analysis of aortic pulse wave velocity. PLoS One 2015; 10(1): e0116862.
15. *Chirinos JA, Segers P, Gillebert TC, de Buyzere MI, van Daele CM, Khan ZA,* et al. Central pulse pressure and its hemodynamic determinants in middle - aged adults with impaired fasting glucose and diabetes: The Asklepios study. Diabetes Care 2013; 36(8): 2359–65.
16. *Struijker Boudier HA, Cohuet GM, Baumann M, Safar ME.* The heart, macrocirculation and microcirculation in hypertension: a unifying hypothesis. J Hypertens Suppl 2003; 21(3): S19–23.
17. *Van Bortel LM, Duprez D, Starmans-Kool MJ, Safar ME, Giannattasio C, Cockcroft J,* et al. Clinical applications of arterial stiffness, Task Force III: Recommendations for user procedures. Am J Hypertens 2002; 15(5): 445–52.
18. *Sarafidis PA, Georgianos PI, Karpetas A, Bikos A, Korelidou L, Tersi M,* et al. Evaluation of a novel brachial cuff-based oscillometric method for estimating central systolic pressure in hemodialysis patients. Am J Nephrol 2014; 40(3): 242–50.
19. *Gosse P, Lasserre R, Minifié C, Lemetayer P, Clementy J.* Arterial stiffness evaluated by measurement of the QKD interval is an independent predictor of cardiovascular events. Am J Hypertens 2005; 18(4 Pt 1): 470–6.
20. *Stojanov V, Saranovic M, Jakovijević B, Paunović K.* Thoracic electrical bioimpedance in the follow-up of patients with cardio-

vascular disorders. Srp Arh Celok Lek 2005; 133(5–6): 297–302. (Serbian)
21. *Stojanov V, Jakovljevic P.* Use of thoracic bioelectric impedance in the assessment of hemodynamic parameters of the cardiovascular system. Vojnosanit Pregl 2005; 62(4): 311–5. (Serbian)
22. *Peco-Antić A, Pejcić I, Stojanov V, Parezanović V, Kostić M.* Ambulatory blood pressure monitoring in chronic haemodialysis children with end-stage renal failure. Nephron 1996; 72(4): 73–40.
23. *Protogerou AD, Argyris AA, Papaioannou TG, Kollias GE, Konstantonis GD, Nasothimiou E,* et al. Left-ventricular hypertrophy is associated better with 24-h aortic pressure than 24-h brachial pressure in hypertensive patients: The SAFAR study. J Hypertens 2014; 32(9): 1805–14.
24. *Wassertheurer S, Baumann M.* Assessment of systolic aortic pressure and its association to all cause mortality critically depends on waveform calibration. J Hypertens 2015; 33(9): 1884–8; discussion 1889.
25. *Chirinos JA, Kips JG, Jacobs DR, Brumback L, Duprez DA, Kronmal R,* et al. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). J Am Coll Cardiol 2012; 60(21): 2170–7.
26. *Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D,* et al.. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27(21): 2588–605.
27. *Albaladejo P, Copie X, Boutouyrie P, Laloux B, Déclère AD, Smulyan H,* et al. Heart rate, arterial stiffness, and wave reflections in paced patients. Hypertension 2001; 38(4): 949–52.
28. *Lantelme P, Mestre C, Lievre M, Gressard A, Milon H.* Heart rate: An important confounder of pulse wave velocity assessment. Hypertension 2002; 39(6): 1083–7.
29. *Wilkinson IB, Mohammad NH, Tyrrell S, Hall IR, Webb DJ, Paul VE*, et al. Heart rate dependency of pulse pressure amplification and arterial stiffness. Am J Hypertens 2002; 15(1 Pt 1): 24–30.
30. *McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR.* ACCT Investigators. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol 2005; 46(9): 1753–60.
31. *Townsend RR, Wimmer NJ, Chirinos JA, Parsa A, Weir M, Perumal K*, et al. Aortic PWV in chronic kidney disease: A CRIC ancillary study. Am J Hypertens 2010; 23(3): 282–9.
32. *Laurent S, Boutouyrie P, Lacolley P.* Structural and genetic bases of arterial stiffness. Hypertension 2005; 45(6): 1050–5.
33. *Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ*, et al. Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. J Am Coll Cardiol 2002; 39(6): 1005–11.
34. *Asmar RG, London GM, O'Rourke ME, Safar ME.* REASON Project Coordinators and Investigators. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. Hypertension 2001; 38(4): 922–6.
35. *Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B*, et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 2003; 34(5): 1203–6.
36. *Williams B, Lacy PS.* Impact of heart rate on control aortic pressures and hemodynamics: Analysis from the CAFE (Conduit Artery Function Evaluation) study. CAFE-Heart Rate. J Am Coll Cardiol 2009; 54(8): 705–13.
37. *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(13): 1318–27.
38. *Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L*, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37(5): 1236–41.
39. *Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ*, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014; 63(7): 636–46.
40. *de Luca N, Asmar RG, London GM, O'Rourke MF, Safar ME.* REASON Project Investigators. Selective reduction of cardiac mass and central blood pressure on low-dose combination perindopril/indapamide in hypertensive subjects. J Hypertens 2004; 22(8): 1623–30.
41. *Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M,* et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicenter randomised controlled trial. Lancet 2005; 366(9489): 895–906.
42. *Balkestein EJ, Aggel-Leijssen DP, Baak MA, Struijker-Boudier HA, Van Bortel LM.* The effect of weight loss with or without exercise training on large artery compliance in healthy obese men. J. Hypertens 1999; 17(12 Pt 2): 1831–5.
43. *Avolio AP, Clyde KM, Beard TC, Cooke HM, Ho KK, O'Rourke MF.* Improved arterial distensibility in normotensive subjects on a low salt diet. Arteriosclerosis 1986; 6(2): 166–9.
44. *Sierksma A, Lebrun CE, van der Schouw YT, Grobbee DE, Lamberts SW, Hendriks HF,* et al. Alcohol consumption in relation to aortic stiffness and aortic wave reflections: a cross-sectional study in healthy postmenopausal women. Arterioscler Thromb Vasc Biol 2004; 24(2): 342–8.
45. *Manisty CH, Hughes AD.* Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. Br J Clin Pharmacol 2013; 75(1): 79–92.
46. *Kampus P, Serg M, Kals J, Zagura M, Muda P, Karu K,* et al. Differential effects of nebivolol and metoprolol on central aortic pressure and left ventricular wall thickness. Hypertension 2011; 57(6): 1122–8.
47. *Pannier B, Guérin AP, Marchais SJ, Safar ME, London GM.* Stiffness of capacitive and conduit arteries: Prognostic significance for end-stage renal disease patients. Hypertension 2005; 45(4): 592–6.
48. *Janić M, Lunder M, Sabovič M.* Arterial stiffness and cardiovascular therapy. Biomed Res Int 2014; 2014: 621437.
49. *Weiss W, Gohlisch C, Harsch-Gladisch C, Tölle M, Zidek W, Giet M.* Oscillometric estimation of central blood pressure: Validation of the Mobil-O-Graph in comparison with the Sphygmo-Cor device. Blood Press Monit 2012; 17(3): 128–31.
50. *Mahmud A, Feely J.* Arterial stiffness and the renin-angiotensin-aldosterone system. J Renin Angiotensin Aldosterone Syst 2004; 5(3): 102–8.
51. *Shahin Y, Khan JA, Chetter I.* Angiotensin converting enzyme inhibitors effect on arterial stiffness and wave reflections: a meta-analysis and meta-regression of randomised controlled trials. Atherosclerosis 2012; 221(1): 18–33.
52. *London GM, Asmar RG, O'Rourke MF, Safar ME.* REASON Project Investigators. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. J Am Coll Cardiol. 2004; 43(1): 92–9.
53. *Deary AJ, Schumann AL, Murfet H, Haydock S, Foo RS, Brown MJ.* Influence of drugs and gender on the arterial pulse wave and natriuretic peptide secretion in untreated patients with essential hypertension. Clin Sci (Lond) 2002; 103(5): 49–9.

54. *Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U,* et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359(9311): 995–1003.
55. *Dickstein K, Kjekshus J.* OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 2002; 360(9335): 752–60.
56. *Ghiadoni L, Virdis A, Magagna A, Taddei S, Salvetti A.* Effect of the angiotensin II type 1 receptor blocker candesartan on endothelial function in patients with essential hypertension. Hypertension 2000; 35(1 Pt 2): 501–6.
57. *Agnoletti D, Zhang Y, Borghi C, Blacher J, Safar ME.* Effects of antihypertensive drugs on central blood pressure in humans: a preliminary observation. Am J Hypertens 2013; 26(8): 1045–52.
58. *Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L,* et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004; 363(9426): 2022–31.
59. *Hayoz D, Zappe DH, Meyer MA, Baek I, Kandra A, Joly MP,* et al. Changes in aortic pulse wave velocity in hypertensive postmenopausal women: comparison between a calcium channel blocker vs angiotensin receptor blocker regimen. J Clin Hypertens (Greenwich) 2012; 14(11): 773–8.
60. *Asmar R.* Effect of telmisartan on arterial distensibility and central blood pressure in patients with mild to moderate hypertension and Type 2 diabetes mellitus. J Renin Angiotensin Aldosterone Syst 2001; 2 Suppl 2: S8–11.
61. *Agabiti-Rosei E, Porteri E, Rizzoni D.* Arterial stiffness, hypertension, and rational use of nebivolol. Vasc Health Risk Manag 2009; 5(1): 353–60.
62. *Polónia J, Barbosa L, Silva JA, Bertoquini S.* Different patterns of peripheral versus central blood pressure in hypertensive patients treated with β-blockers either with or without vasodilator properties or with angiotensin receptor blockers. Blood Press Monit 2010; 15(5): 235–9.
63. *Koumaras C, Tziomalos K, Stavrinou E, Katsiki N, Athyros VG, Mikhailidis DP,* et al. Effects of renin-angiotensin-aldosterone system inhibitors and beta-blockers on markers of arterial stiffness. J Am Soc Hypertens 2014; 8(2): 74–82.
64. *Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D,* 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(9): 1213–25.
65. *Ferguson JM, Minas J, Siapantas S, Komesaroff PA, Sudhir K.* Effects of a fixed-dose ACE inhibitor-diuretic combination on ambulatory blood pressure and arterial properties in isolated systolic hypertension. J Cardiovasc Pharmacol 2008; 51(6): 590–5.
66. *Morgan T, Lauri J, Bertram D, Anderson A.* Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens 2004; 17(2): 118–23.
67. *Feistritzer HJ, Klug G, Reinstadler SJ, Reindl M, Niess L, Nalbach T,* et al. Prognostic Value of Aortic Stiffness in Patients After ST-Elevation Myocardial Infarction. J Am Heart Assoc 2017; 6(9). pii: e005590.
68. *Lüers C, Trippel TD, Seeländer S, Wachter R, Hasenfuss G, Lindhorst R,* et al. Arterial stiffness and elevated left ventricular filling pressure in patients at risk for the development or a previous diagnosis of HF-A subgroup analysis from the DIAST-CHF study. J Am Soc Hypertens 2017; 11(5): 303–13.
69. *Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M,* et al. 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). Eur Heart J 2013; 34(28): 2159–219.
70. *Townsend RR, Rosendorff C, Nichols WW, Edwards DG, Chirinos JA, Fernhall B,* et al. American Society of Hypertension position paper: Central blood pressure waveforms in health and disease. J Am Soc Hypertens 2016;10(1):22–33.
71. *Pini R, Cavallini CM, Palmieri V, Marchionni N, Di Bari M, Devereux RB,* et al. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: The ICARe Dicomano Study. J Am Coll Cardiol 2008; 51(25): 2432–9.
72. *Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G,* et al. 2007 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). J Hypertens 2007; 25(6): 1105–87.
73. *Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T,* et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 2012; 30(3): 445–8.
74. *Shoji T, Nakagomi A, Okada S, Ohno Y, Kobayashi Y.* Invasive validation of a novel brachial cuff-based oscillometric device (SphygmoCor XCEL) for measuring central blood pressure. J Hypertens 2017; 35(1): 69–75.

Received on July 01, 2017.
Revised on October 10, 2017.
Accepted on October 30, 2017.
Online First November, 2017.