MÆdica - a Journal of Clinical Medicine

Arterial Stiffness and Hypertension – Which Comes First?

Monica ECOBICIa , Elena Laura ILIESCUa, b

aClinic of Internal Medicine, Fundeni Clinical Institute, Bucharest, Romania

b"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Arterial hypertension is one of the traditional risk factors involved in the development of cardiovascular events, while arterial stiffness is an independent predictor of cardiovascular disease in patients with hypertension. It seems that the risk factors involved in the pathology of uncontrolled hypertension are similar to those that contribute to the development of arterial stiffness. After evidence showed that arterial stiffness is an independent prognostic factor for the occurrence of cardiovascular events in patients with arterial hypertension, the importance of assessing arterial stiffness was recognized in a document drafted by the European Society of Hypertension in 2007. Many factors, some still insufficiently studied, are involved in the development and worsening of arterial stiffness, especially in patients with certain comorbidities (diabetes, hypertension, chronic kidney disease). The evaluation of pulse wave velocity (PWV) remains the gold standard for non-invasive assessment of arterial stiffness. It seems that changes in terms of lifestyle and drug therapy have some positive effects on improving arterial stiffness, but further studies are needed to prove this concept. Our review aims to highlight the novelty of the mechanisms, the assessment methods, some of the clinical aspects, as well as the therapeutic implications of arterial stiffness, especially in patients with hypertension.

Keywords: arterial stiffness, cardiovascular events, PWV

Abbreviations:

PWV = pulse wave velocity;
MMP-9 = matrix-metalloproteinase 9;
AGE = advanced glycation end-products;
RAGE =AGE receptor;
RAAS = renin angiotensin aldosterone system;
ARNI = angiotensin-receptor neprilysin inhibitor;
ARB = angiotensin receptor blocker;
CCB = Calcium channel blockers;
ACEI = Angiotensin converting enzyme inhibitors;
BB = Beta-blockers; PP-pulse pressure;
LV = left ventricle;
NO = nitric oxide.

BACKGROUND

High blood pressure remains one of the most important health problems worldwide, involving substantial costs both from a human and financial point of view (1). Although antihypertensive medication has evolved considerably in recent years, only 53% of patients with documented arterial hypertension achieve target blood pressure levels under medication (2). Risk factors contributing to the emergence of uncontrolled hypertension include old

Address for correspondence:
Monica Ecobici
Postal address: Fundeni Clinical Institute, Fundeni Road 258, District 2, Bucharest, 022328
Phone: 0040723666051/00213120991
E-mail: ecobicimonica@yahoo.com

age, left ventricular hypertrophy, obesity, diabetes mellitus, and chronic kidney disease (3). It is important to note that, concomitantly, the same risk factors mentioned above contribute to the increase of arterial stiffness values (4).

On the other hand, arterial stiffness has proven to be an important prognostic factor, and possibly a therapeutic target in patients diagnosed with high blood pressure. Studies conducted to date have shown that arterial stiffness and implicitly, pulse wave reflection are key determinants for elevated systolic pressure at the central level, resulting in the occurrence of cardiovascular events independent of peripheral blood pressure (5).

In 2006, data from the CAFÉ study (a substudy of the ASCOT trial) showed that central aortic pulse pressure (which is also determined by arterial stiffness) is a significant determinant of cardiovascular outcomes, and demonstrated that different treatments for arterial hypertension do not have the same impact on central pulse pressure, despite having a similar effect on brachial blood pressure (6). The importance of arterial stiffness in the management of hypertension is underlined by the fact that in 2007, the European Society of Hypertension drafted a consensus document recommending the assessment of central arterial pressure and hemodynamic parameters for the correct and complete management of hypertension, values over 12 m/sec for pulse wave velocity indicating target organ damage (7). Moreover, in 2006, a panel of experts published a consensus paper on the methodology and clinical implications of evaluating arterial stiffness (8).

Our review aims to highlight the novelty of the mechanisms that increase arterial stiffness, the assessment methods and the clinical aspects, as well as the therapeutic implications.

Pathophysiology

Arterial stiffness represents the rigidity of arterial walls. Different arteries present various degrees of arterial stiffness, with central arteries being more affected and peripheral arteries being less involved (5). All the traditional risk factors for cardiovascular disease have a negative influence on arterial stiffness (4). Factors such as hypertension, diabetes and chronic kidney disease amplify changes in the arterial walls, thus augmenting arterial stiffness. Age is an important factor both in terms of hypertension, but also in increasing

arterial stiffness; the rigidity of large arteries was significantly higher in patients over 55 years old (5). In patients with metabolic syndrome or diabetes mellitus, arterial stiffness was higher for all age groups and was positively correlated with insulin-resistance. Cigarette smoking and obesity can worsen arterial stiffness (4). Some of the mechanisms by which the traditional risk factors contribute to the occurrence/worsening of arterial stiffness are listed below.

During contraction of the left ventricle (LV), the volume of blood ejected into the aorta determines a systolic pressure that causes dilation of the aortic walls, with the storage of elastic energy at this level, as a mechanism of accommodation. A relaxation of the LV occurs at the end of the systole, with the subsequent decrease of the systolic pressure, so that the blood begins to return towards the heart until the aortic valves close. During the diastole, under the effect of energy stored in the aortic wall during the systole, the blood is pushed towards the circulatory system. Thus, to maintain a certain volume of blood ejected during the systole, the systolic pressure should be directly proportional to the degree of stiffness of the aorta (9).

The volume of blood ejected into the aorta during the systole generates a wave (pulse wave), circulating through the arterial system with a certain velocity (pulse wave velocity, PWV). Pulse wave velocity can be measured non-invasively and is used to estimate arterial stiffness.

Studies have shown that the intima has a minor role in the elastic properties of the arteries. The major determinants of arterial rigidity and arterial capacity to alter their dimensions during the cardiac cycle are represented by the media and, more recently demonstrated, by the adventitia of arterial vessels (10, 11). The main components of the media (elastin, smooth vascular cells, collagen, mucopolysaccharides) are arranged in a complex way that has not yet been fully described, and this arrangement varies according to the localization of the arteries, so that the elastin/collagen ratio is a fixed one, being inversely proportional to the distance from the heart (12).

A fragmentation of elastin fibers occurs with age, followed by degeneration and the deposition of a larger amount of collagen, changes that are considered to be the basis for the increase in vascular stiffness in the elderly. An important role is attributed to matrix-metalloproteinase 9 (MMP-9), which is involved in collagen degradation, this

compensatory mechanism being affected by age and by hypertension (13). Hypertension causes increased intraluminal pressure, with subsequent stimulation of collagen production (14).

Studies have shown that another mechanism possibly involved in arterial stiffness is represented by the so-called advanced glycation end products (AGEs), especially in patients with diabetes (increased production) or chronic kidney disease (poor clearance). It appears that AGEs form a crosslink connection in the collagen, making it more rigid and less susceptible to hydrolysis. It causes vasoconstriction by inhibiting nitric oxide (NO) activity, secreting a variety of pro-inflammatory cytokines, increasing oxidative stress and oxidation of LDL (15). At the same time, an AGE receptor activation (RAGE) appears as the triggering factor of a pro-inflammatory reaction, stimulating secretion of free radicals, growth factors and vascular adhesion molecules (9). All these mediators contribute to endothelial dysfunction, with the consequent increase in smooth muscle cell tone; they affect angiogenesis and ultimately promote the formation of atherosclerotic plaques (16). Discussions are still ongoing as to whether endothelial dysfunction contributes to increased arterial stiffness or if arterial stiffness causes endothelial alteration, which in turn further increases arterial stiffness (17).

Aortic wall calcifications have also been associated with the occurrence of isolated high blood pressure and aortic stiffness (18).

Besides structural changes, functional changes also occur in the vascular walls, where the endothelium is believed to have an important role, especially NO. Previous studies have shown that endothelial dysfunction is associated with the development of isolated systolic hypertension, as a consequence of increased aortic stiffness (18).

Other substances involved in the occurrence of arterial stiffness are homocysteine, whose levels increase with age, hyperhomocysteinemia being an independent risk factor for cardiovascular events (19), and prolactin (20). Angiotensin II stimulates collagen formation, vascular hypertrophy and matrix remodeling, reduces elastin production and increases oxidative stress by stimulating growth factors and pro-inflammatory cytokines (21).

Aldosterone stimulates smooth muscle cell hypertrophy, stimulates fibronectomy and synthesis of fibronectin, and endothelin 1 produc-

tion, thereby contributing to arterial stiffness and hypertension (22).

A high-salt diet increases arterial stiffness, especially in the elderly, by stimulating smooth muscle cell tone, increased collagen production, and endothelial damage (23).

In patients with diabetes mellitus, an important role in the development of arterial rigidity is played by insulin resistance, studies demonstrating a positive correlation between these entities (the mechanisms involved are renin-angiotensin-aldosterone system activity, stimulation of vascular hypertrophy and fibrosis, as well as excessive production of AGEs) (24).

In patients with chronic kidney disease, the increase in vascular rigidity is quasi-significant, especially in advanced stages, with PWV being an independent predictive factor for cardiovascular mortality and all-cause mortality in this category of patients (25). The mechanisms involved are related to the increase of the intima-media thickness due to hypertension, but also to the activation of the renin-angiotensin-aldosterone system with the subsequent stimulation of collagen production in the extracellular matrix and smooth muscle hypertrophy and chronic inflammation. AGE products are also involved, as well as calcifications of the media. Chronic kidney disease may cause endothelial dysfunction (high oxidative stress, increased endothelin-1 concentrations, decreased synthesis of NO) (26).

Recent studies have shown the existence of a genetic component in the development of arterial stiffness (17).

Evaluation of arterial stiffness

The "gold standard" for the non-invasive assessment of arterial stiffness is quantification of PWV (velocity is expressed as the ratio between change in distance and change in time). For this purpose, tonometry between the two peripheral arterial sites is the most frequently used method, being an inexpensive, reproducible and relatively simple method to perform. PWV is usually determined over the carotid-femoral region by assessing the length of time in which the pressure pulse wave travels from the carotid to the femoral arteries. The most frequently used systems are the SphygmoCor (AtCor) and the Complior (Artech), which differ with regards to their sensor technology and the algorithm for calculating the propagation time. The SphygmoCor uses an arte-

rial tonometer for recording pressure waveforms. The time of propagation is measured from the foot of the carotid waveform to that of the femoral waveform, using ECG sequential recording. In the Complior system, carotid and femoral waveforms are recorded simultaneously. Another method to asses PWV is the Arteriograph (TensioMed), which allows the simultaneous determination of brachial blood pressure, PWV and Aix, using plethysmography to measure pulsatile pressure changes in the brachial artery. These methods have limitations, such as the existence of heart rhythm disorders (atrial fibrillation, frequent extrasystoles), possible errors due to the measurement of the distance between the two sites, the difficulty of measuring in obese patients, as well as a potential intimate factor derived from the need to measure at the site of the femoral artery (27, 28).

Another alternative method is pulse wave analysis (PWA). The assessment of the pulse wave shape at the peripheral level (usually at the radial artery) can estimate the central pressure and the augmentation index (Aix), using a mathematical transfer function (SphygmoCor, AtCor). Although studies have shown that both PWA and Aix can be considered predictive factors for a number of cardiovascular events in certain patient categories, they cannot directly assess vascular stiffness (29).

Local arterial stiffness can be evaluated using ultrasounds devices. The intima-media thickness at the carotid level is easy to perform, but some studies have shown that ultrasound-based measurement of carotid thickness did not improve prediction of cardiovascular events by the Framingham score (30), in contrast to the PWV assessment, whose role in predicting cardiovascular risk has been demonstrated (31).

In addition to this technique, lately, US scanners are equipped with echo-tracking programs which are able to measure the diameter of the arteries during the phases of the cardiac cycle, based on radiofrequency analysis. The accuracy of this equipment is 6–10 times higher compared to those based on video image analysis. At this moment, two software applications for echo-tracking are available: QIMT (Quality IntimaMedia Thickness) and QAS (Quality Arterial Stiffness). Assessment of arterial stiffness using echo-tracking systems is based on the determination of several parameters: artery distensibility, pulse wave velo-

city, rigidity index-index β, stiffness index α, Aix, elastic modulus index, cardio-ankle vascular index (CAVI), one of the PWV measurement modifications and derived from arterial stiffness index β (32).

Methods derived from MRI assessment have also been used, and studies have shown that there are no significant differences between the PWV values obtained by these methods and the applanation tonometry method, the limitations of MRI evaluation being determined by the financial difficulty of software acquisition (33).

In 2006, the first consensus of experts was published, which included a review on the pathophysiology of arterial stiffness, and which made recommendations on assessment methods, clinical implications and therapeutic measures. Moreover, this expert consensus set the cut-off value for PWV to 12 m/sec. This value was changed in 2012, when the Experts Consensus set the cut-off value for PWV to 10 m/sec (8, 34).

Clinical correlations of arterial stiffness

Increased arterial stiffness causes left ventricular hypertrophy, decreases the efficiency of cardiac ejection and causes a decrease in myocardial infusion. Two other important consequences are represented by isolated systolic hypertension and pulse pressure increase (PP, defined as the difference between systolic and diastolic pressure), these being found to be risk factors for cardiovascular events (stroke, myocardial infarction, heart failure) in elderly patients. It has been reported that each 2 mmHg increase in systolic pressure causes a 5% increase in fatal coronary artery disease and a 7% fatal stroke risk (35).

Studies conducted to date have demonstrated the correlation between arterial stiffness and traditional cardiovascular risk factors. These studies have shown that arterial rigidity is negatively influenced by all pathophysiological changes occurring in the metabolic syndrome (36). It has also been shown that in hypertensive smokers, smoking cessation has positive effects on PWV values (37). J.S. Orr published a study that showed the role of rapid weight gain and visceral fat build-up on vascular stiffness development, with other mechanisms being involved besides the consecutive blood pressure increase (38).

A meta-analysis published in 2010, including 15877 patients from 17 studies, followed over a period of 7.7 years, showed that PWV-quantified

arterial stiffness is a strong predictive factor for cardiovascular events and all-cause mortality (39). There is also evidence showing a positive association between increased vascular rigidity and subclinical cerebrovascular impairment (40), as well as the predictive role and correlation between vascular rigidity and cognitive decline in patients with dementia (41).

Can we reduce arterial stiffness?

Several potentially effective methods for decreasing arterial stiffness have been evaluated:

1. Lifestyle changes

Weight loss is especially recommended in obese patients and in subjects with metabolic syndrome. Although weight loss is associated with a decrease in peripheral blood pressure, there is no evidence to support its efficacy on central pressure or vascular rigidity. The same lack of evidence exists in the case of metabolic syndrome. However, there are studies that highlight the potential beneficial effect of dietary supplements on vascular rigidity. Thus, it has been observed that a diet rich in isoflavones (contained in soy) is associated with a decrease of PWV. The same effect was also observed in healthy volunteers who received isoflavones extracted from red clover (42).

If aerobic exercise has been associated with reduced arterial rigidity in elderly patients without other cardiovascular risk factors, resistance exercises have a reverse effect, being associated with an increase in the incidence of left ventricular hypertrophy and increased stiffness in the proximal aorta (43).

Moderate alcohol consumption has been associated with a decrease in PWV (44).

It has also been shown that a high-salt diet accelerates the aging process in the vascular walls, while low-salt diets increase arterial compliance, relatively independent from the blood pressure-lowering effect (45).

2. Drug therapy

The CAFE study showed, for the first time, the importance of aortic central pressure assessment, and also underlined the fact that antihypertensive regimens with the same effect on brachial pressure have different effects on central pressure, demonstrating a superior efficacy of calcium channel blockers (CCB) *versus* beta-blockers (BB) in reducing aortic central pressure (amlodipine-based regimen *versus* atenolol-based therapy) (6).

In 2009, a study which compared the efficacy of four classes of antihypertensive therapies on vascular stiffness (in patients older than 60 years and with isolated systolic arterial hypertension who received treatment for 10 weeks) was published. The results showed that only angiotensin-converting enzyme inhibitors (ACE inhibitors), calcium channel blockers and diuretics decreased the central pressure, while beta-blockers (atenolol) did not. All four classes have peripheral antihypertensive effect, and none of them have any effect on decreasing the PWV (46). These results may have been influenced by the particular category of patients (older patients, with isolated systolic hypertension), by the treatment period (only 10 weeks), and by the beta-blocker used (atenolol, which determines peripheral vasoconstriction).

Another study has shown the efficacy of an ARB-thiazide combination on arterial rigidity in comparison with calcium channel blockers. Patients with type II diabetes and hypertension were followed-up for six months (47). There were no significant differences regarding the effect on Aix.

The results of the PARAMETER study (Prospective Comparison of an Angiotensin-Receptor Neprilysin Inhibitor with an Angiotensin-receptor Blocker measuring arterial stiffness in the elderly), which included 454 elderly patients with systolic blood pressure greater than 160 mmHg and pulse pressure greater than 60 mmHg, were reported at the ESC Congress in 2015. The study showed that those taking angiotensin receptor-neprilysin inhibitor – ARNI (valsartan/sacubitril combination) – had significantly greater decreases in central aortic systolic pressure, central aortic pulse pressure and brachial systolic blood pressure at 12 weeks compared with those taking angiotensin receptor blockers (ARB) – olmesartan. The differences in favor of ARNI were maintained after the follow-up period of 52 weeks, but without being statistically significant (48).

A study published in 2017 showed that most de-stiffening therapies are based on renin angiotensin aldosterone system (RAAS) inhibitors in combination with a CCB or a diuretic. It seems that RAAS inhibitors are superior to other antihypertensive agents in reducing arterial stiffness, most likely due to an anti-fibrotic effect of the extracellular matrix in the vascular walls. In addition, ACE inhibitors determine the release of bradykinin and NO, with consequent modulation of endothelial function. Long-term studies, such as

REASON and ADVANCE, demonstrated the efficacy of ACEI/ARB therapies in reducing arterial stiffness (49).

A meta-analysis published in 2013 showed that BB increased AIx compared with all other antihypertensive therapies, which decreased Aix (50). This is no longer the case with new beta blockers (nebivolol, carvedilol), which have the ability to decrease arterial stiffness. These effects appear to be related to their ability to release NO, which dilates the small resistance arteries (51).

A study which involved endothelin A receptor blockers showed beneficial effects on vascular rigidity in patients with chronic kidney disease (52), while nitrates did not significantly affect rigidity in the proximal aorta (53).

A beneficial effect has also been observed after statin treatment, although their effect on arterial stiffness is more pronounced in the predominantly muscular arteries (54).

Thiazolidinediones increase insulin sensitivity and control glycemic values, but may also favor vascular rigidity in patients with type II diabetes (55).

Other therapies have been studied (atrial natriuretic peptide, 5-phosphodiesterase inhibitors, anti-TGF-β agents), with promising results in the preclinical phase (17). Another studies aim at the potential effect on vascular stiffness of therapies that reduce AGE formation (aminoguanidine, pyridoxamine), block AGE receptors or non-enzymatically alter AGE (alagebrium). These substances have already been studied on a small number of patients, with satisfactory results (17). ❑

CONCLUSIONS

Although considerable progress has been made in understanding the mechanisms and implicitly determining therapeutic targets for arterial stiffness, there are still many unclear aspects.

Ongoing and future studies are likely to further clarify these issues, so that future therapies include agents with a clear effect on vascular rigidity and thus, have a more significant impact on morbidity and mortality for certain categories of patients. ❑

REFERENCES

1. **Heidenreich PA, Trogdon JG, Khavjou OA, et al.** American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 2011;123:933-944.
2. **Egan BM, Zhao Y, Axon RN.** US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA* 2010;303:2043-2050.
3. **Calhoun DA, Jones D, Textor S, et al.** Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* 2008;51:1403-1419.
4. **Mitchell GF, Guo CY, Benjamin EJ, et al.** Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. *Circulation* 2007;115:2628–2636.
5. **Payne R.A., Wilkinson I.B., Webb D.J.** Arterial stiffness and Hypertension-Emerging Concepts. *Hypertension* 2010;55:9-14.
6. **The CAFE investigators, CAFE Steering Committee and writing Committee, Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, O'Rourke M, et al for The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators.** Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes:principal results of The Conduit Artery Functional Evaluation (CAFE) study. *Circulation* 2006;113:1213-1225.
7. **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).** *Eur Heart J* 2007;12:1462-536.
8. **Laurent S, Cockcroft J, Van Bortel L, et al.** Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588-2605.
9. **Greenwald S.E.** Ageing of the conduit arteries. *J Pathol* 2007;211:157-172.
10. **von-Maltzahn WW, Warriyar RG, Keitzer WF.** Experimental measurements of elastic properties of media and adventitia of bovine carotid arteries. *J Biomech* 1984;11:839-847.
11. **Xie J, Zhou J, Fung YC.** Bending of blood vessel wall: stress–strain laws of the intima-media and adventitial layers. *J Biomech Eng* 1995;1:136-145.
12. **Wagenseil JE, Mecham RP.** Elastin in large artery stiffness and hypertension. *Journal of Cardiovascular Translational Research* 2012;3:264-273.
13. **Flamant M, Placier S, Dubroca C, et al.** Role of matrix metalloproteinases in early hypertensive vascular remodeling. *Hypertension* 2007;50:212-218.
14. **Xu C, Zarins CK, Pannaraj PS, et al.** Hypercholesterolemia superimposed by experimental hypertension induces differential distribution of collagen and elastin. *Arterioscler Thromb Vasc Biol* 2000;20:2566-2572.
15. **Kass DA, Shapiro EP, Kawaguchi M, et al.** Improved arterial compliance by a novel

advanced glycation end-product crosslink breaker. *Circulation* 2001;104:1464-1470.

16. **Wendt T, Bucciarelli L, Qu W, et al.** Receptor for Advanced Glycation Endproducts (RAGE) and Vascular Inflammation: Insights into the Pathogenesis of Macrovascular Complications in Diabetes. *Curr Atheroscler Rep* 2002;4:228-237.

17. **Zieman S.J, Melenovsky V, Kass D.A.** Mechanisms, pathophysiology and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005;25:932-943.

18. **Wallace SM, Yasmin, McEniery CM, et al.** Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. *Hypertension* 2007;50:228-233.

19. **Wang X, Ye P, Cao R.** Plasma homocysteine is a predictive factor for arterial stiffness: a community-based 4.8-year prospective study. *J Clin Hypertens* (Greenwich) 2015;17:594-600.

20. **Georgiopoulos GA, Stamatelopoulos KS, Lambrinoudaki I, et al.** Prolactin and preclinical atherosclerosis in menopausal women with cardiovascular risk factors. *Hypertension* 2009;54:98-105.

21. **Shon S.I., Kim C.J.** Modulation of renin-angiotensin system and arterial stiffness: evidence from clinical trials. *Curr Hypertens Rev* 2014;1:37-40.

22. **Leibovitz E, Ebrahimian T, Paradis P, Schiffrin EL.** Aldosterone induces arterial stiffness in absence of oxidative stress and endothelial dysfunction. *J Hypertens* 2009;11:2192-200.

23. **Safar ME, Thuilliez C, Richard V, et al.** Pressure-independent contribution of sodium to large artery structure and function in hypertension. *Cardiovasc Res* 2000;46:269-276.

24. **Salomaa V, Riley W, Kark JD, et al.** Non-insulindependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation* 1995;91:1432-1443.

25. **Briet M, Boutouyrie P, Laurent S, London GM.** Arterial stiffness and pulse pressure in CKD and ESRD. *Kidney Int* 2012;4:388-400.

26. **Goldsmith D, Ritz E, Covic A.** Vascular calcification: a stiff challenge for the nephrologist: does preventing bone disease cause arterial disease? *Kidney Int* 2004;66:1315-1333.

27. **DeLoach S.S., Townsend R.R.** Vascular stiffness:its measurement and significance for epidemiologic and outcome studies. *Clin J Am Soc Nephrol*.2008;3:184-192

28. **Wu C-F, Liu P-Y, Wu T-J, Hung Y, Yang S-P, Lin G-M.** Therapeutical modification of arterial stiffness:An update and comprehensive review. *World J Cardiol* 2015;11:742-753.

29. **Janner JH, Godtfredsen NS, Ladelund S,** et al. The association between aortic augmentation index and cardiovascular risk factors in a large unselected population. *JHH* 2012;26:476-484.

30. **Den Ruijter HM, Peters SA, Anderson TJ, et al.** Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*.2012;308:796-803.

31. **Bérard E, Bongard V, Ruidavets JB, et al.** Pulse wave velocity, pulse pressure and number of carotid or femoral plaques improve prediction of cardiovascular death in a population at low risk. *J Hum Hypertens* 2013;27:529-534.

32. **Melnikova EA, Avdeeva IV, Oleynikov VE.** Echo-Tracking is a Novel Technology to Assess Structural and Functional Properties of Carotid Arteries (Review). *Medical Technologies in Medicine/Sovremennye Tehnologii v Medicine* 2016;2:119-127.

33. **Suever JD, Oshinski J, Rojas-Campos E, et al.** Reproducibility of pulse wave velocity measurements with phase contrast magnetic resonance and applanation tonometry. *Int J Cardiovasc Imaging* 2012;28:1141-1146.

34. **Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank LK , 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;30:445-448.

35. **Lewington S, Clarke R, Qizilbash N, et al.** Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-1913.

36. **Ghiadoni L, Penno G, Giannarelli C, et al.** Metabolic syndrome and vascular alterations in normotensive subjects at risk of diabetes mellitus. *Hypertension* 2008;51:440-445.

37. **Jatoi NA, Jerrard-Dunne P, Feely J, et al.** Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension* 2007;49:981-985.

38. **Orr JS, Gentile CL, Davy BM, et al.** Large artery stiffening with weight gain in humans: role of visceral fat accumulation. *Hypertension* 2008;51:1519-1524.

39. **Vlachopoulos C, Aznaouridis K, Stefanodis C.** Prediction of cardiovascular events and all cause mortality with arterial stifness. *J Am Coll Cardiol* 2010;55:1318-1327.

40. **Henskens LH, Kroon AA, van Oostenbrugge RJ, et al.** Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. *Hypertension* 2008;52:1120-1126.

41. **Elias MF, Robbins MA, Budge MM, et al.** Arterial pulse wave velocity and cognition with advancing age. *Hypertension* 2009;53:668-673.

42. **Teede HJ, McGrath BP, DeSilva L, et al.** Isoflavones reduce arterial stiffness: a placebo-controlled study in men and postmenopausal women. *Arterioscler Thromb Vasc Biol* 2003;23: 1066 -1071.

43. **Miyachi M, Donato AJ, Yamamoto K, et al.** Greater age-related reductions in central arterial compliance in resistance-trained men. *Hypertension* 2003;41:130-135.

44. **Sierksma A, Lebrun CE, van der Schouw YT, 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;24:342-348.

45. **Safar ME, Temmar M, Kakou A, et al.** Sodium Intake and Vascular Stiffness in Hypertension. *Hypertension* 2009;54:203-209.

46. **Mackenzie IS, McEniery CM, Dhakam Z, et al.** Comparison of the effects of antihypertensive agents on central blood pressure and arterial stiffness in isolated systolic hypertension. *Hypertension* 2009;54:409-413.

47. **Karalliedde J, Smith A, DeAngelis L, et al.** Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. *Hypertension* 2008;51:1617-1623.

48. **PARAMETER: LCZ696 Bests Olmesartan in Decreasing Arterial Stiffness in Elderly.** *Medscape* 2015, Sept 01.

49. **Chen Y, Shen F, Liu J, et al.** Arterial stiffness and stroke:de-stiffening strategy , a therapeutic target for stroke. *Stroke and vascular Neurology* 2017;0:e00045.

50. **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;75:79-92.

51. **Koumaras C, Tziomalos K, Stavrinou E.** Effects of renin-angiotensin-aldosterone system inhibitors and beta-blockers on markers of arterial stiffness. *JASH* 2014;2:74-82.

52. **Dhaun N, Macintyre IM, Melville V, et al.** Blood pressure-independent reduction in proteinuria and arterial stiffness after acute endothelin-a receptor antagonism in chronic kidney disease. *Hypertension* 2009;54:11-119.

53. **Starmans-Kool MJ, Kleinjans HA, Lustermans FA, et al.** Treatment of elderly patients with isolated systolic hypertension with isosorbide dinitrate in an asymmetric dosing schedule. *J Hum Hypertens* 1998;12:557-561.

54. **Smilde TJ, van den Berkmortel FW, Wollersheim H, et al.** The effect of cholesterol lowering on carotid and femoral artery wall stiffness and thickness in patients with familial hypercholesterol-aemia. *Eur J Clin Invest* 2000;30:473-480.

55. **Cantini C, Kieffer P, Corman B, et al.** Aminoguanidine and aortic wall mechanics, structure, and composition in aged rats. *Hypertension* 2001;38:943-948.