FOLIA MEDICA CRACOVIENSIA
Vol. LXII, 2, 2022: 109–120
PL ISSN 0015-5616
DOI: 10.24425/fmc.2022.141704

Arterial stiffness — a cardiovascular risk factor to assess among primary care patients

Anna Kamieńska, Sławomir Chlabicz

Department of Family Medicine, Medical University of Białystok, Poland

Corresponding author: Anna Kamieńska, M.D.
Department of Family Medicine, Medical University of Białystok
ul. Mieszka I 4b, 15-054 Białystok
Phone: +48 857 326 820; E-mail: anna.kamienska@onet.eu

Abstract: Arterial stiffness is a characteristic of the arterial wall strongly associated with ageing and hypertension. It has been confirmed as a significant cardio-vascular risk factor. Despite available non-invasive measurement methods of central artery stiffening, it has not become a prevalent diagnostic marker in primary care so far. This article provides an overview of pathophysiology of arterial stiffness, possible diagnostic techniques, association with cardiovascular conditions and potential perspective of primary care to implement an additional distinctive parameter to evaluate cardiac risk.

Keywords: arterial stiffness, cardiovascular risk, atherosclerosis, primary care.

Submitted: 13-Nov-2021; **Accepted in the final form:** 15-Jun-2022; **Published:** 30-Jul-2022.

Introduction

Assessment of cardiovascular risk in primary care is limited by available diagnostic methods and established classical cardiovascular risk factors. There are several cardiovascular risk calculators such as Framingham Risk Score, American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease (ACC/AHA ASCVD) Risk Calculator, and The Systematic Coronary Risk Estimation (SCORE) and QRISK which are valuable tools to improve detection, evaluation and management of cardiovascular risk among primary care patients [1–3]. Unfortunately those scales may not estimate the risk adequately. Moreover SCORE indicates risk of cardiovascular death, not general cardiovascular risk [4]. Therefore a search for additional parameters to establish cardiovascular risk more precisely is needed.

Copyright: © 2022 by the authors. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Arterial elasticity is a characteristic of arterial vessel which describes the potential to contract and expand in response to change of the pressure [5, 6]. The opposite of elasticity is arterial stiffness. Stiffened vessels are less susceptible to volume changes and therefore an increased propagation velocity of the pressure wave is observed along the stiffened arteries [6]. Progressively with age and comorbidities the function of arterial wall worsens.

Arterial stiffness can be measured with the use of invasive and non-invasive methods [7]. Aortic stiffness is determined by pulse wave velocity (PWV), an indicative parameter of arterial stiffness [8]. An increase by 1 m/s in PWV implicates increase of the cardiovascular event risk by 14% [9]. A 10–15% elevation in PWV is observed every 10 years. Women present 5–10% lower arterial stiffness parameters comparing to male contemporaries [10]. Aortic PWV over 10 m/s is a marker of hypertension mediated organ damage [4]. Arterial stiffness is an established cardiovascular risk factor possible to implement in clinical practice.

It was observed that aortic and arterial stiffness illustrate cardiovascular risk comprehensively, over longer period of time, while biochemical factors tend to vary in time [11].

The objective of this review is to demonstrate the applicability and utility of assessing measures of arterial stiffness in primary care to improve risk stratification among patients with subclinical cardiovascular disease.

Pathophysiology

Arterial distensibility presents as capability of arterial volume change (expanding and contracting) during a heartbeat when the blood pressure affects the arterial wall. Based on arterial wall structure, arteries can be categorized as muscular and elastic ones. In elastic arteries, as aorta and carotid arteries, the contain of elastic fibers in the wall structure is higher in proximal parts [7]. Because of the difference in the arterial wall structure between elastic central arteries and distal muscular arteries, a physiological stiffness gradient is observed in healthy individuals. This protects microcirculation from high amplitude pressure waves [12]. With the increase of stiffness in elastic arteries, the gradient is reduced, and as a consequence, the more pulsation pressure is transmitted peripherally [11]. Subsequently the velocity of propagation of the pressure pulse is increased in stiffened arteries. The pulse wave reflection in stiff arteries occurs more proximally than in normal arteries which causes amplification phenomenon. The reflection of the pulse wave during systole increases systolic and reduces diastolic pressure which leads to increased pulse pressure (PP). Augmentation pressure is the difference between the second (P2) and first (P1) pressure peaks in the pulse wave where P1 corresponds to peak systolic ejection and P2 corresponds to the peak caused by arrival of the reflected pulse wave. Augmentation index (Aix) is derived from

the difference between the second (P2) and first (P1) systolic peaks, expressed as a percentage of PP. It reflects the intensity of pulse wave reflection [6, 7]. Pulse wave velocity is a direct determinant of arterial stiffness and central pressure while Aix remains an indirect additional measure for describing pulse wave reflection [13].

There are several conceptions based on pathophysiology which explain why arterial stiffness increases in elderly. The most common one is concerning elastin- collagen ratio in the arterial wall structure which decreases progressively [5, 11]. With the process of ageing the deterioration of elastin fibers and consequently increase of the collagen results in increase of the stiffness [14]. whereas the muscular vessels do not stiffen in the course of time [11].

Other possible causes of the arterial structure ageing include: smooth muscle necrosis, calcification of the arterial wall, change in the extracellular matrix and vascular smooth muscles cells interactions [11, 15]. Calcification is related to atherosclerotic plaques collection and to calcium infiltration into smooth muscle cells in the course of dysregulation of bone metabolism in chronic kidney disease(CKD) [16]. Authors emphasize that the production of vasodilating agents such as nitric oxide decreases with age, while the effect of the vasoconstrictors is increased among elderly [15]. In patients with CKD also uremic toxins such as *p*-cresyl sulfate and indoxyl sulfate affect the arterial wall stiffness [15]. Also atherosclerosis itself increases the stiffness by affecting the structure and function of the arterial walls by the presence of plaques [4].

The second strong factor impacting arterial stiffening except ageing is high blood pressure [12].

Age and classical cardiovascular risk factors are not the only parameters related to arterial stiffness. Some physiological features such as low birth weight, menopausal status, lack of physical activity, genetic background, and primarily non-cardiovascular comorbidities such as end stage renal disease, moderate CKD, rheumatoid arthritis, systemic vasculitis and systemic lupus erythematosus are associated with vascular stiffness [13].

It has been shown that physical activity, weight loss, reduction in salt intake, hormone replacement therapy is correlated with lower arterial stiffness among elderly [17].

Methods of measurement

In clinical practice to access arterial stiffness both invasive and non-invasive utilities and procedures can be used. To determine central aortic pressure invasively a pressure sensing wire is inserted into the vessel. For practical reasons invasive methods are limited to scheduled arteriography procedures [5].

Arterial stiffness measurement, similarly to blood pressure measurement procedure, should be performed under certain conditions. Depending on the method the patient should be seated or supine, the procedure is performed after or at least 10 min of resting

in a dry cool place. Most relevantly last meal should be consumed 3–4 hours before the measurement, alcoholic beverages should not be consumed for 10 hours before measure. A patient should neither speak nor sleep during the procedure [7, 13, 18]. Every measurement should be repeated, second test performed after at least 5 minutes [5, 11].

Assessment of aortic stiffness can be performed with the use methods of oscillometry or applanation tonometry or with mechanotransducer [5, 13, 19]. In tonometric devices the pulse wave latency and the distance between carotid and femoral artery are measured. Those two points, with easily detected pulse, are where the pulse wave is simultaneously recorded to calculate the pulse wave velocity of the aorta [5, 7, 18]. The measure of carotid-femoral pulse wave velocity is a 'gold standard' method of the non-invasive arterial stiffness measurement [5, 11].

With the use of applanation tonometry we can analyze central aortic pressure by analyzing central artery pressure curves, sequentially from different sites, with correlation to electrocardiography (ECG). The distance between two peeks of the curve presents the augmentation pressure [7]. Radial artery tonometry with the use of transduction and calculating aorta waveform from the measured peripheral waveform is also performed [11]. Main disadvantage of tonometry method is being time consuming and demanding of trained medical stuff [20].

Methods such as ultrasonography and magnetic resonance imaging (MRI) enable to assess local arterial stiffness [7]. With the use of bi-dimensional ultrasounds the vessel distention can be assessed. The most favorable sites for the measure are femoral and carotid arteries [5, 13]. Moreover ultrasonography is the only technique measuring intima-media thickness(IMT) and elastic properties of the arterial wall [13]. While MRI enables to determine distention and PWV with more accuracy the procedure is limited by financial and spatial issues [5].

Oscillometric methods performed with the use of cuffs detect waveforms (Fig. 1, Fig. 2) and blood pressure under the inflated cuffs which are usually placed on both

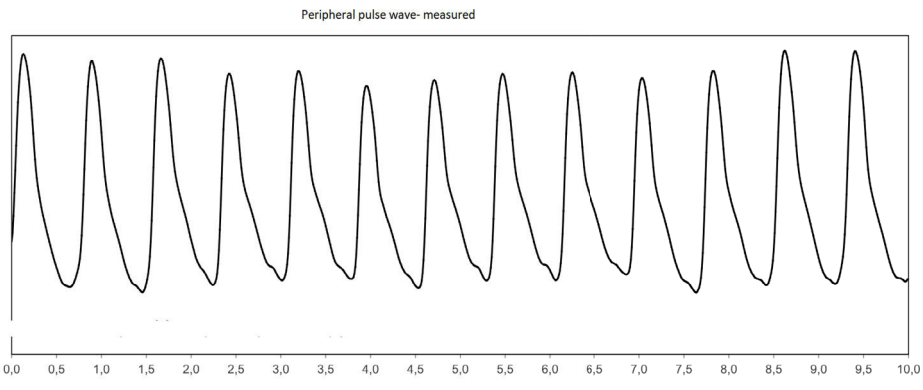

Fig. 1. Peripheral pulse wave; female, 62 years old; Mobil-O-Graph PWA.

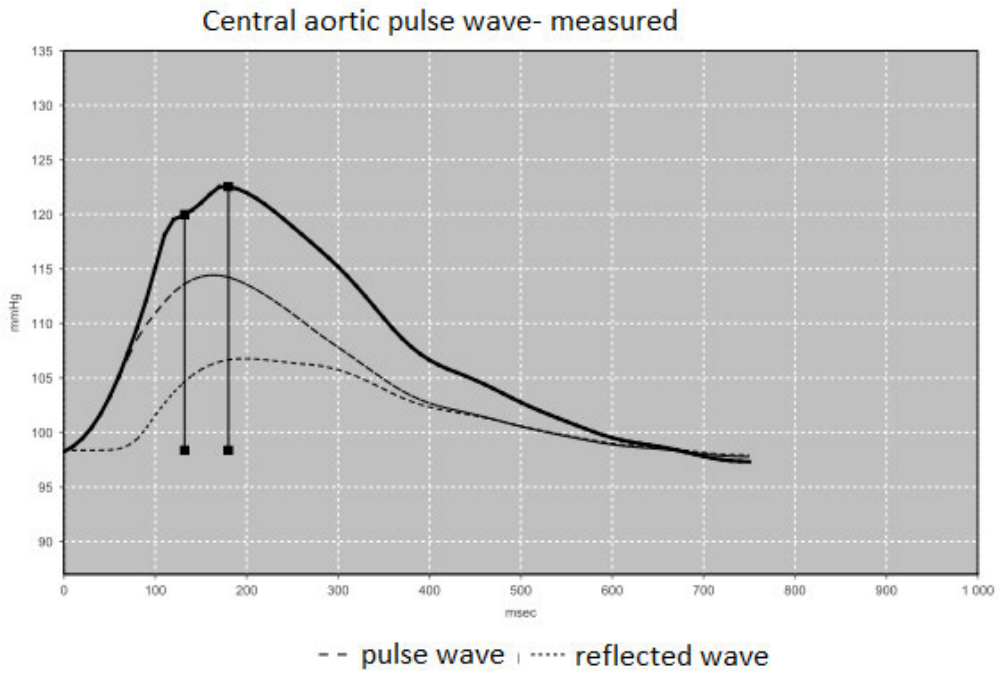

Fig. 2. Aortal pulse wave, calculated; female, 62 years old; Mobil-O-Graph PWA.

arms and ankles (measurement of brachial-ankle PWV) or one arm. Cuffs simultaneously detecting waveforms are connected to plethysmography sensor and oscillometric pressure sensor. The distance between the sites, based on the patient's heigh, is automatically calculated [11]. The PVW measurement is performed when the cuff pressure exceeds the systolic pressure by 35–40 mmHg [21]. During this occlusion early and late systolic wave peaks are detected [20]. The data collected by the oscillometric device with the use of transduction function enable to estimate central aortic pressure and draw a central pressure curve [5, 19]. For oscillometric PWV measurement additional data such as age, heigh and gender need to be combined and analyzed in mathematical model. The oscillometric devices also enable a 24-hour PWV analysis [19] which could be strong advantage of this type of arterial stiffness measure. An example of one-cuff device is Mobil-O-Graph Pulse Wave Analyzer (PWA; Fig. 3, Fig. 4).

Among patients with ambulatory blood pressure monitoring, an ambulatory arterial stiffness index(AASI) can be accessed. It is calculated as 1 minus to the regression slope of the diastolic to systolic pressure in 24-h monitoring. AASI is described to have correlation with PWV and PP [22].

Fig. 3. Mobil-O-Graph PWA measurement of arterial stiffness with one-cuff device, wireless data transmission.

Fig. 4. Mobil-O-Graph Pulse Wave Analyzer (PWA).

Arterial stiffness and arteriosclerosis

Atherosclerosis is an endothelium pathology which is characterized by accumulation of lipids, inflammatory cells, connective tissue fibers and calcium, simultaneously with migration of muscle smooth cells [6]. This abnormality of arterial wall cause increasing of the IMT. Atherosclerosis is the main cause of death worldwide [2]. Atherosclerosis, depending on location and progression, can be subclinical or symptomatic in the form of peripheral artery disease (PAD), carotid artery disease and coronary artery disease (CAD).

Arterial stiffness is associated with atherosclerosis as well as correlates with presence of other cardiovascular risk factors [5]. Other publications reveal that atherosclerotic abnormalities are not always associated with increased arterial stiffness [6].

In the medical literature positive correlation between increased arterial stiffness measured by PWV and occurrence of other cardiovascular risk factors, a cardiovascular event and death because of a cardiovascular incident was described [1, 14]. An association between high PWV and high cardiovascular risk in SCORE ≥5%, and Framingham Score has been proved for both male and female individuals [2]. Moreover it was claimed that arterial stiffness can predict the risk of fatal and non-fatal cardiovascular events as well as all-cause mortality [9]. Central PP correlates with mortality and risk of cardiovascular event while Aix correlates with mortality of cardiovascular and other causes, incidence of cardiovascular and severe cardiovascular events [13].

Peripheral artery disease is a condition where atherosclerotic plaques are found in lower limbs arteries causing stenosis or occlusion in arteries of lower limbs. The evidence of which is defined by a decreased ankle-brachial pressure index [23, 24]. Classical cardiovascular risk factors as smoking, increased blood pressure, elevated low density lipoprotein cholesterol (LDL-C) level and older age are associated with higher risk of PAD. Patients with the diagnosis of PAD are of higher risk of cardiovascular disease and mortality and the risk correlates with impaired small arteries elasticity. It has been confirmed that high aortic stiffness parameters correlate with subclinical PAD, predict progression and improve cardiovascular risk discrimination among those patients.

Coronary artery disease is defined as reduced blood flow to the heart muscle due to the presence of atherosclerotic plaques in coronary arteries. The symptomatic CAD is defined as chronic ischemic heart disease, an acute myocardial infarction or a need of revascularization by percutaneous coronary intervention or coronary artery bypass grafting [27]. Premature CAD occurs before 55 years in men and before 60 years in woman [21]. A study has shown that PWV is increased in patients with premature CAD and in their first-degree relatives without evidence of CAD. Moreover increase of PWV above 15 m/s in previously healthy person could play essential role in premature CAD occurrence [21]. It was shown that increased PWV is predictive of

coronary artery disease, but not of early atherosclerosis [25]. Moreover increased aortic PWV was associated with 48% higher risk of first major cardiovascular risk event (myocardial infarction, unstable angina, heart failure, ischemic or hemorrhagic stroke) [26]. Additionally, an increased diastolic pressure, being a result of arterial stiffness, impaired coronary blood flow and, combined with atherosclerotic narrowing, escalates the ischemic heart disease incidence [11, 27].

Also PWV measured with oscillometric method has been shown to be an early and independent factor to assess the risk of asymptomatic carotid atherosclerosis especially among middle-aged population which are classified to low or moderate risk of cardiovascular disease because of the age [20].

Dyslipidemia is defined as high total cholesterol (TC) level, LDL-C, triglyceride (TG) with low high density lipoprotein cholesterol (HDL-C) level. The research shows that increased arterial stiffness is associated with dyslipidemic measures of cholesterol fractions [28]. It was previously shown that statins reduce arterial stiffness measured as PWV by nearly 7% as well as reduce Aix [13, 15]. Statins have been known for their pleiotropic effect on arterial wall affected by atherosclerotic process and have a settled position in primary and secondary prevention therapy.

Arterial stiffness and other related conditions

Aortic stiffening may influence microcirculation by impairing blood flow and increased pulsation pressure [5, 9].The explanation of this phenomenon is in the fact that when the left ventricle contracts a part of the stroke volume moves to the peripheral tissues (brain, kidneys circulation and coronary arteries) while the rest remains stored in the stretched central arteries. In central arteries of higher stiffness, in hypertensive individuals, a larger part of stroke volume flows to the peripheral circulation causing damage [11]. This effect has consequences in cardiovascular function and explains why stiffness is a predictive factor for cardiovascular risk [5]. An observation has been made that arterial stiffness is a significant cardiovascular risk factor, exceeding the classical risk factors and 24-hours blood pressure measurement [29].

Arterial stiffness has an established association with hypertension, it is suggested that aortic stiffness may rather be a cause not a consequence of this condition. In hypertensive adults the arterial stiffness parameters were two times higher comparing to the normotensive group [30]. Other authors claim that hypertension and arterial stiffness coexist together as a vicious cycle, not directly a cause and effect [31]. In stiffened vessels the regulation of the blood flow is impaired [5, 17]. Central artery stiffness in hypertensive patients causes elevated PP which damages small arterioles [11]. Persistent elevation of carotid-femoral PWV (cfPWV) in hypertensive patients being treated leads to poorer treatment response [5]. It was confirmed in studies that from all hypotensive medications, angiotensin convertase enzyme (ACE) inhibitors,

angiotensin receptor blockers (ARBs), calcium channel antagonists, beta-blockers and diuretics improve arterial stiffness by reducing PWV and arterial wave reflection [5, 11]. On the other hand, calcium blockers play a role in dilatation of the vessels [5]. Authors claim that reduction of the arterial stiffness parameters and blood pressure lowering are closely related [32]. Another study revealed that even in patients with well-controlled hypertension, the PWV remains elevated which means no reduction of cardiovascular risk in adequately treated patients [31]. In one study an interesting claim was presented, that adult normotensive children of hypertensive parents have statistically higher value of PWV comparing to normotensive adult children of normotensive parents [30]. This conclusion may indicate a need for early screening for individuals with genetic background of cardiovascular diseases.

It has been shown that high PWV is associated with higher incidence of stroke [27]. Pathophysiological explanation is an increased PP, remodeling of intracranial circulation and therefore defects of brain tissues and atherosclerosis impairing upward flow [11]. Pulse pressure elevated by 10% was proved to correlate with 11% higher risk of stroke [33].

Increased aortic stiffness is associated with high diastolic pressure, impaired left-ventricle diastolic function and, as a consequence, a diastolic heart failure. Increased wave reflexion amplitude, determined as Aix, correlates with myocardial fibrosis and predicts heart failure development [5]. Moreover, medications used in congestive heart failure treatment, such as ACE inhibitors and aldosterone antagonists, reduce arterial stiffness [13].

As a result of increased pressure and flow in microvascular areas of eye and brain, those microcirculation regions are vulnerable to the hemodynamic consequences of arterial stiffness [5].

Concerning laboratory findings elevated serum glucose level (in diabetic and prediabetic conditions) and insulin level are risk factors for increased arterial stiffness [10, 17]. Impaired glucose tolerance is associated with central arterial stiffness, decreased arterial compliance and increased Aix [15]. In type 2 diabetes increased arterial stiffness parameters were observed in many studies. Also increased PWV was related to duration of the illness and presence of macrovascular complications [15]. Among type 1 diabetic patients distensibility of arteries was decreased, with correlation to diabetes duration [10]. Also metabolic syndrome and central obesity are correlated with arterial stiffness development [15].

Chronic kidney disease is a condition of high incidence (≥10%) among European and Northern-American population. Patients with CKD are group of high risk of cardiovascular events, but the accuracy of grading the cardiovascular risk among those is limited [34].There is pathophysiological correlation between increased blood flow in microvascular structures of kidneys and glomerular damage, demonstrable as proteinuria and reduced glomerular filtration rate(GFR) [5, 32, 34]. Another factor deterior-

ating renal function is an increased peripheral blood pressure in elderly diagnosed with hypertension, which disrupt the renal circulation affecting autoregulation [11]. The increased arterial stiffness in this disorder results from calcification and lower elastin content in arterial wall structure. It was proved that cfPWV is a valuable predictive factor for survival and occurrence of fatal and non-fatal cardiovascular events among 2–5 stage CKD patients while risk-prediction in Framingham score were not accurate [34]. Moreover, elevated PWV correlate with renal function decline [16].

Conclusions

Primary care is instrumental in preventive medicine and for this reason assessment of cardiovascular risk among patients is important.

There is a noticeable demand of easy, approachable and reliable techniques to improve cardiovascular risk stratification among primary care patients.

According to recent studies arterial stiffness is an important cardiovascular risk factor which correlates with incidence of cardiovascular diseases and increases the risk of cardiovascular events in patients.

Non-invasive arterial stiffness measurement could be a promising method in primary care for detection of subclinical cardiovascular disease.

Authors' contribution

Anna Kamieńska — conception of the work, drafting the article, photographs Fig. 3 and Fig. 4.

Sławomir Chlabicz — revision of the article, final acceptance of the version.

Funding

None declared.

Conflict of interest

None declared.

References

1. *Tandon R., Bansal M., Bansal M., et al.*: Comparison of Traditional and Novel Marker of Subclinical Atherosclerosis for Evaluating Cardiovascular Risk in Asymptomatic Patients. J Indian Acad Echocardiogr Cardiovasc Imaging. 2020; 4 (1): 1–6.
2. *Mitu O., Crisan A., Redwood S., et al.*: The Relationship between Cardiovascular Risc Score and Several Markers of Clinical Atherosclerosis in a Asymptomatic Population. J Clin Med. 2021; 10: 955. doi.org/10.3390/jcm10050955.

3. *Conroy R.M., Pyörälä K., Fitzegarld A.P., et al.*: Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003; 24: 987–1003.
4. *Woźniacka-Leśkiewicz L., Posadzy-Małaczyńska A., Ruszkat R.*: The impact of ankle brachial index and pulse wave velocity on cardiovascular risk according to SCORE and Framingham scales and sex differences. J Hum Hypertens. 2015; 29: 502–510.
5. *Townsend R.R., Wilkinson I.B., Schiffrin E.R., et al.*: Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement from the American Heart Association. Hypertension. 2015; 66 (3): 698–722.
6. *Cecelja M., Chowienczyk P.*: Role of arterial stiffness in cardiovascular disease. JRSM Cardiovasc Dis. 2012; 1 (4): cvd.2012.012016.
7. *Cieślik-Guerra U.*: Metody pomiaru sztywności tętnic. Nadciśnienie Tętnicze. 2011; 15: 42–48.
8. *García-Hermoso A., Martínez-Vizcaíno V., Gomez-Marcos M.Á.*: Ideal Cardiovascular Health and Arterial Stiffness in Spanish Adults—The EVIDENT Study J Stroke Cerebrovasc Dis. 2018; 27 (5): 1386–1394.
9. *Vlachopoulos Ch., Aznaouridis K., Stefanadis Ch.*: Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness A Systematic Review and Meta-Analysis. J Am Coll Cardiol. 2010; 55 (13): 1318–1327.
10. *Benetos A., Waeber B., Izzo J., Mitchell G., Resnick L., Asmar R., Safar M.*: Influence of Age, Risk Factors, and Cardiovascular and Renal Disease on Arterial Stiffness: Clinical Applications. Am J Hypertens. 2002; 15: 1101–1108.
11. *Laurent S., Boutouyrie P.*: Arterial Stiffness and Hypertension in the Elderly. Front Cardiovasc Med. 2020; 7: 544302. doi: 10.3389/fcvm.2020.544302.
12. *Boutouyrie P., Bruno R.-M.*: The Clinical Significance and Application of Vascular Stiffness Measurement. Am J Hypertens. 2019; 32 (1): 4–11.
13. *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.
14. *Oliver J.J., Webb D.J.*: Noninvasive Assessment of Arterial Stiffness and Risk of Atherosclerotic Events. Arterioscler Thromb Vasc Biol. 2013; 23 (4): 554–566.
15. *Tsai J.P., Hsu B.G.*: Arterial stiffness: A brief review. Tzu Chi Med J. 2021; 33 (2): 115–121.
16. *Voicehovska J.G., Bormane E., Grigane A., et al.*: Association of Arterial Stiffness With Chronic Kidney Disease Progression and Mortality. Heart Lung Circ. 2021; 30 (11): 1694–1701.
17. *Tyrrell-Sutton K., Najjar S.S., Boudreau R.M., et al.*: Elevated Aortic Pulse Wave Velocity, a Marker of Arterial Stiffness, Predicts Cardiovascular Events in Well-Functioning Older Adults. Circulation. 2005; 111 (25): 3384–3390.
18. *Logan J.G., Suk-Sun Kim S.S.*: Resting Heart Rate and Aortic Stiffness in Normotensive Adults. Korean Circ J. 2016; 46 (6): 834–840.
19. *Grillo A., Parati G., Rovina M., et al.*: Short-Term Repeatability of Noninvasive Aortic Pulse Wave Velocity Assessment: Comparison Between Methods and Devices. Am J Hypertens. 2018; 31 (1): 80–88.
20. *Böcskei R.M., Benczúr B., Müller V., et al.*: Oscillometrically Measured Aortic Pulse Wave Velocity Reveals Asymptomatic Carotid Atherosclerosis in a Middle-Aged, Apparently Healthy Population. Biomed Res Int. 2020. https://doi.org/10.1155/2020/8571062.
21. *Mulders T.A., van den Bogaard B., Bakker A., et al.*: Arterial stiffness is increased in families with premature coronary artery disease. Heart. 2012; 98: 490–494.
22. *Boosa J.C., Thiri-Toona L., Steadmana C.D., Khambekara S., Jordana A., Carpenter J.P.*: The Relationship Between Ambulatory Arterial Stiffness Index and Cardiovascular Outcomes in Women. Cardiol Res. 2021; 12 (3): 161–168.
23. *Takemoto R., Uchida H.A., Toda H., et al.*: Total vascular resistance, augmentation index, and augmentation pressure increase in patients with peripheral artery disease. Medicine. 2021; 100 (32). doi: 10.1097/MD.0000000000026931.
24. *Tomiyama H., Ohkuma T., Ninomiya T., et al.*: Steno-Stiffness Approach for Cardiovascular Disease Risk Assessment in Primary Prevention. Hypertension. 2019; 73 (3): 508–513.

25. *Zhang Y., Yin P., Xu Z., et al.*: Non-Invasive Assessment of Early Atherosclerosis Based on New Arterial Stiffness Indices Measured with an Upper-Arm Oscillometric Device. Tohoku J Exp Med. 2017; 241 (4): 263–270.
26. *Mitchel G.F., Hwang S.H., Vasan R.S., et al.*: Arterial stiffness and cardiovascular events: The Framingham Heart Study. Circulation. 2010; 121 (4): 505–511.
27. *Mattace-Raso F., van der Cammen T.J.M., Hofman A., et al.*: Arterial Stiffness and Risk of Coronary Heart Disease and Stroke The Rotterdam Study. Circulation. 2006; 113: 657–663.
28. *Kilic A., Baydar O., Elcik D., Apaydin Z., Can M.M.*: Role of dyslipidemia in early vascular aging syndrome. Turk J Med Sci. 2021; 51 (2): 727–734.
29. *Hansen T.W., Staessen J.A., Torp-Pedersen Ch., et al.*: Prognostic Value of Aortic Pulse Wave Velocity as Index of Arterial Stiffness in the General Population. 2006; 113: 664–670.
30. *Youssef G., El Tebi I., Osama D., et al.*: Familial history of hypertension as a predictor of increased arterial stiffness in normotensive offspring. Egipt Heart J. 2017; 69 (1): 37–44.
31. *Niiranen T.J., Kalesan B., Hamburg N.M., Benjamin E.J., Mitchell G.F., Vasan R.S.*: Relative Contributions of Arterial Stiffness and Hypertension to Cardiovascular Disease: The Framingham Heart Study. J Am Heart Assoc. 2016; 5 (11). doi: 10.1161/JAHA.116.004271.
32. *Ben-Shlomo J., Spears M., Boustred C., 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): 636–646.
33. *Domanski M., Davis B.R., Pfeffer M.A., Kastantin M., Mitchell G.F.*: Isolated Systolic Hypertension Prognostic Information Provided by Pulse Pressure. 1999; 34: 375–380.
34. *Karras A., Hayman J.P., Bozec E., et al.*: Large Artery Stiffening and Remodeling Are Independently Associated With All-Cause Mortality and Cardiovascular Events in Chronic Kidney Disease. 2012; 60: 1451–1457.