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# Arterial stiffness: pathophysiology, clinical implications, assessment methods

## Sztywność naczyń — patofizjologia, implikacje kliniczne, metody oceny

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### Abstract

The concept of vascular age was created to reflect the real condition of one's arterial tree, independent of the calendar age. The term "early vascular ageing" describes an accelerated degenerative process within the arterial wall, while "healthy vascular ageing" relates to slower than expected for a given age progression of arterial degeneration. Vascular age can be estimated by the measurement of arterial stiffness (AS) parameters, carotid intima-media thickness (CIMT) or calcium score. CIMT reflects structural changes within the arterial wall and is regarded as the marker of subclinical atherosclerosis, while AS demonstrates functional alterations of the arterial wall. Some parameters of the AS, including carotid-femoral pulse wave velocity (cf-PWV), were proven to be independent predictors of cardiovascular events, impaired cognitive function, kidney dysfunction and retinal diseases. Increased AS of the aorta has important implications for the development of hypertension and unfavourable arterial-ventricular coupling. Elevated AS leads to increased afterload of the left ventricle, which results in the ventricular negative remodelling with fibrosis and ischemia and ultimately in heart failure. There are various methods of assessment of local, regional or systemic arterial stiffness. The gold standard for the estimation of AS (regional) is the cf-PWV. However, ultrasonographic (including echo tracking) methods offer a bedside tool for the measurement of local AS parameters of the superficial arteries. Increased AS promotes the development of hypertension and other cardiovascular events, therefore its prevention should be a target of the therapy.

Key words: arterial stiffness, atherosclerosis, vascular age

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## Introduction

Age-related pathophysiological processes within the arterial wall and their interactions with cardiovascular risk factors gain a growing interest among researchers recently. This resulted in the introduction of 'vascular age', the term describing the actual severity of pathological lesions within the arterial tree, independent of the calendar age of an individual. Also, the terms 'healthy vascular ageing' and 'early vascular ageing' (EVA) were proposed to describe the condition in which the vascular age is lower and higher than calendar age, respectively [1]. EVA is typically found in patients with multiple cardiovascular risk factors and a family history of early-onset cardiovascular disorders.

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Vascular age can be estimated using several parameters, among them carotid intima-media thickness (CIMT), the measures of arterial stiffness and coronary artery calcium score. Arterial stiffness was shown to be an independent predictor of cardiovascular events in patients with arterial hypertension, diabetes mellitus and chronic kidney disease, as well as in the elderly. Assessment of arterial stiffness is superior to the estimation of conventional risk factors as arterial stiffness reflects long-term cumulative effects of cardiovascular risk factors on the vascular tree, along with the effects of age and genetic predisposition [2, 3].

## Arteriosclerosis versus atherosclerosis

The differences between the processes of arteriosclerosis and atherosclerosis have been highlighted by Pickering as early as 60 years ago [4]. The indices of arterial stiffness and the CIMT (a measure of atherosclerotic processes) are independent markers of subclinical vascular damage in two distinct pathophysiological mechanisms [5]. Atherosclerosis is primarily associated with the formation of plaques composed of an atheromatous core and fibrous cap, within the arterial tunica intima destroyed by inflammatory processes. Meanwhile, an increase in arterial stiffness is associated with the degradation of the normal network of elastic and collagen fibres within the arterial tunica intima and media and with degenerative processes within tunica adventitia [6].

The CIMT reflects structural changes within the arteries. Since the CIMT is an established predictor of myocardial infarction and stroke, independent of other conventional risk factors, it is used as a marker of subclinical atherosclerosis. In turn, arterial stiffness, an independent predictor of cardiovascular events, dementia, and retinal and kidney disorders, is considered a surrogate marker for functional changes within the arteries [2, 7].

*Post mortem* studies demonstrated a moderately strong association between arterial stiffness and the severity of atherosclerosis. Conventional cardiovascular risk factors, other than age and blood pressure, are considered to play a minor role in the progression of arterial stiffness [8].

## Pathophysiology of arterial stiffness

Arterial stiffness increases with age and exposure to risk factors; this association is particularly evident in the case of the central elastic arteries, aorta and carotid arteries. In healthy individuals, peripheral muscular arteries are less distensible and stiffer than the central arteries. This contributes to the so-called pressure amplification, i.e. a progressive increase in blood pressure from the ascending aorta to the peripheral arteries. This phenomenon becomes less evident with age as an increase in the stiffness of the

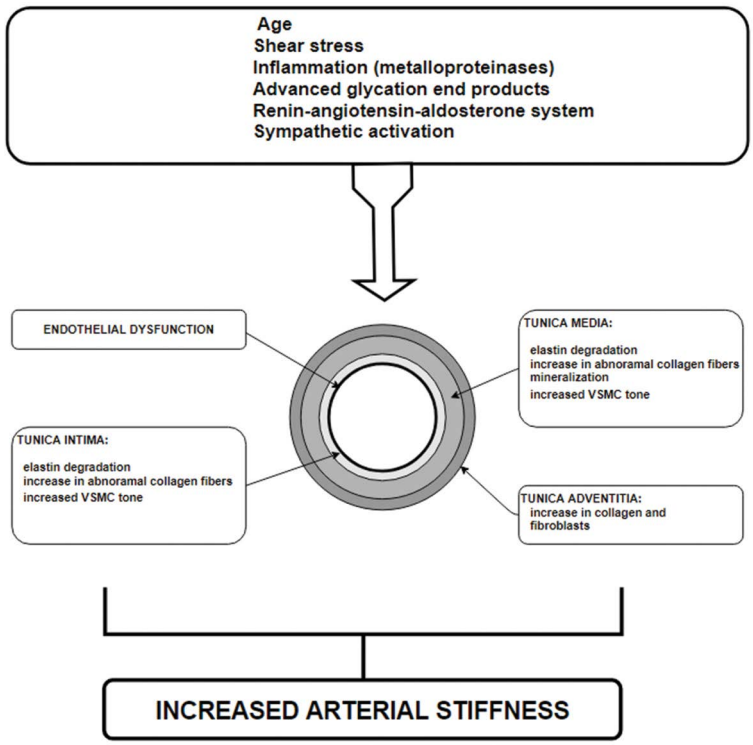


**Figure 1.** Pathophysiology of arterial stiffness

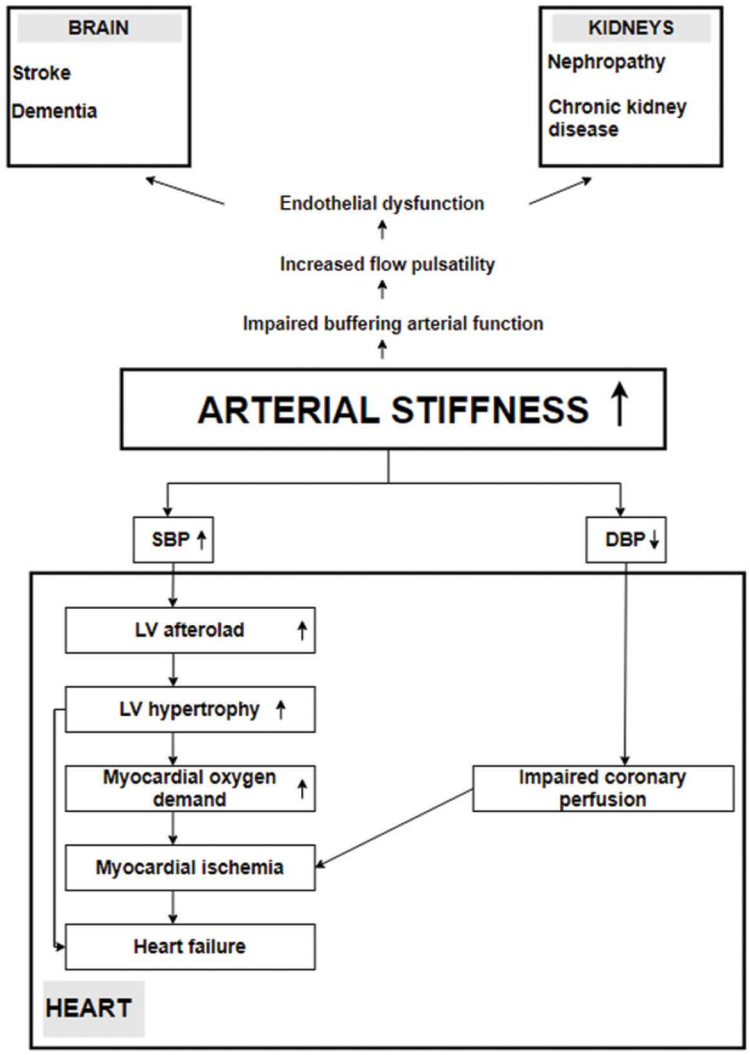


**Figure 2.** Clinical implications of increased vascular stiffness

central arteries is more pronounced than the increase in the peripheral artery stiffness [9].

A principal mechanism involved in arterial stiffening is the disruption of the normal architecture of elastin and collagen fibres within the arterial tunica intima and media. Shear stress and inflammatory mediators activate the processes that lead to the degradation of elastin fibres, which are then replaced by abnormal and synthesized in abundance collagen fibres [10–12]. The pathological changes within elastin and collagen fibres can also be triggered by the end-products of advanced glycation, generated under chronic hyperglycaemia [13]. The deformed elastin fibres are more prone to mineralization with calcium and phosphates, which contributes to a further increase in arterial stiffness [14]. Moreover, arterial stiffness is modulated by a plethora of other factors acting in various layers of the vascular wall, among others by the tension of vascular smooth muscle cells, endothelial function, sympathetic activation and renin-angiotensin-aldosterone system [2, 10].

Arterial hypertension and disorders of carbohydrate metabolism are the risk factors that were shown to correlate strongly with increased arterial stiffness. Arterial hypertension turned out to be associated with an increase in collagen and elastin contents in the extracellular space resulting from both enhanced synthesis of those proteins and their reduced degradation [11]. The processes mentioned above are mediated by metalloproteinases and inflammatory markers [11].

Impaired carbohydrate metabolism contributes to increased arterial stiffness through the activation of the renin-angiotensin-aldosterone system with the promotion of fibrosis within the vascular wall. Furthermore, impaired carbohydrate metabolism is associated with the overproduction of advanced glycation end-products, which contributes to an unfavourable remodelling of the elastin and collagen network within the arterial wall [11, 13]. Another critical process, associated primarily with insulin resistance, is the impairment of endothelial function.

## Clinical implications of increased vascular stiffness

Clinical implications of increased arterial stiffness should be discussed in the context of the interaction with the heart function — the so-called ventricular-arterial coupling. An increase in arterial stiffness contributes to the earlier return of reflected wave during systole, which results in a rise in central systolic pressure, a decrease in diastolic pressure and the resultant increase in pulse pressure (PP). The elevation of central systolic pressure results in increased left ventricular afterload, leading to left ventricular hypertrophy and triggering fibrosis within the ventricular wall. In turn, the premature wave reflection in the ascending aorta during ventricular contraction results in the lack of increase in diastolic pressure, impairment of coronary perfusion and left ventricular ischemia. All these processes lead to unfavourable remodelling of the left ventricular myocardium, its dysfunction and heart failure with preserved or reduced ejection fraction. Moreover, an increase in end-diastolic left ventricular pressure, being a consequence of the unfavourable remodelling of the left ventricle, leads to an overload of the left atrium with its enlargement and fibrosis; this poses a risk of atrial fibrillation and stroke [15]. Another consequence of increased arterial stiffness is impaired buffering function of proximal arteries and resultant shift of pulsatile blood flow to the microcirculation, which causes damage to microvessels, endothelial dysfunction, thrombosis and vasculitis. The changes in renal microcirculation lead to nephropathy, whereas those in the cerebral microvessels may result in stroke, impaired cognitive function and dementia [16].

The relationship between arterial stiffness and arterial hypertension is bidirectional and has a character of a vicious circle as the two processes perpetuate each other. On the one hand, as mentioned above, increased arterial stiffness leads to an increase in systolic arterial pressure. On the other hand, increased systolic pressure is associated with greater shear stress acting onto the arterial wall, which stimulates pathological processes within the latter. Many prospective observational studies demonstrated that increased arterial stiffness was associated with a higher risk of arterial hypertension and constituted a primary factor activating the cascade of unfavourable events which eventually lead to the development of hypertension [17–19].

Some large meta-analyses demonstrated that the indices of arterial stiffness could predict cardiovascular events independently of conventional risk factors. Regional carotid-femoral pulse wave velocity (cfPWV) was shown to be associated with a higher number of cardiovascular events and higher cardiovascular mortality [7, 20]. In Hoorn's study, locally determined stiffness of carotid and femoral artery predicted an increased number of cardiovascular events and all-cause mortality during a 7-year follow-up [21]. In an ARIC study, local indices of carotid stiffness correlated significantly with the risk of ischemic stroke during a 14-year observation [22].

The observation that increased arterial stiffness exerts multiple unfavourable effects within the cardiovascular system constituted the basis for de-stiffening therapy. The de-stiffening treatment aims to obtain a decrease in central SBP and PP through a reduction of arterial stiffness and delay of wave reflection. These therapeutic objectives can be achieved with the blockers of the renin-angiotensin-aldosterone system. Those medications exert a favourable effect on arterial smooth muscle cells, mitigate inflammation and fibrosis within the vascular wall, and hence, prevent the development and progression of arterial stiffness [9].

## Methods to evaluate vascular stiffness

According to the consensus statement of experts from the European Network for Non-Invasive Investigation of Large Arteries from 2006, on methodological issues and clinical application, arterial stiffness can be measured locally, regionally or systemically, either invasively or non-invasively [2]. Arterial stiffness can be determined with various methods, using tonometry, oscillometry, ultrasound or magnetic resonance imaging (Table 1) [2, 23].

Systemic arterial stiffness is assessed based on the model for pulse wave propagation, whereas regional and local stiffness can be measured non-invasively, directly at specific nodes of the arterial tree. The proposed markers of arterial injury include several parameters, such as pulse wave velocity (PWV), augmentation index (AI) and beta stiffness index [2, 23].

## Regional stiffness

Measurement of the cfPWV is considered a gold standard in the assessment of arterial stiffness. This parameter reflects regional stiffness of the aorta between two points, the common carotid and femoral artery. Pulse wave velocity depends on the distensibility of the arterial wall; the more distensible the wall, the slower the wave propagates to the periphery. Pulse wave velocity correlates inversely with vascular distensibility. Since the 1980s, Complior mechanotransducer and beginning in 1990s, also Shygmocor applanation tonometer have been used to measure cfPWV in epidemiological studies [2, 23]. The reference values for cfPWV in the European population were published by Mattace-Raso et al. [24]. However, the applicability of the cfPWV measurement in everyday clinical practice is limited due to technical constraints and the low availability of the equipment [25]. The cfPWV was recommended in the 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension as a marker of hypertension-mediated

**Table 1.** Methods to assess vascular stiffness

| Device | Method | Parameters |
|---|---|---|
| **REGIONAL STIFFNESS** | | |
| Complior System (Colson, Les Lilas, France) | Mechanotransducer | Carotid-femoral PWV<br>Carotid-brachial PWV<br>Femoral-dorsalis PWV |
| SphygmoCor (ArtCor,Sydney, Australia) | Tonometer | Carotid-femoral PWV |
| VP-2000 Omron, Japan | Oscyllometry | Brachial-ankle PWV |
| VaSera VS-Series Vascular Screening System (Fukuda Denshi, Tokyo, Japan) | Pletysmography | Cardio-ankle vascular index |
| Artlab, WallTrack | Doppler ultrasound | Aortic PWV |
| MRI | MRI | Aortic PWV |
| **LOCAL STIFFNESS** | | |
| Aloka Hitachi, Artlab, WallTrack | Echotracking | Beta stiffness index,<br>Peterson's elastic modulus,<br>One-point PWV beta,<br>Arterial compliance |
| MRI | MRI | Aortic distensibility |
| **SYSTEMIC STIFFNESS** | | |
| HDI PW CR-2000 | Modified Windkessel model | |
| | Area method | |

MRI — magnetic resonance imaging; PWV — pulse wave velocity

organ damage that could optimize cardiovascular risk assessment in persons with arterial hypertension [26]. Currently, the cut-off level for the pathological values of cfPWV is set at > 10 m/s [26].

In clinical practice, pulse wave velocity can also be measured as brachial-ankle wave velocity (baPWV); this parameter, determined with an oscillometer, has been primarily used in the Asian population. A significant association was found between the baPWV and the occurrence of cardiovascular events [27]. In the recent decade, the cardio-ankle vascular index (CAVI) has been gaining growing attention too. This parameter combines central and local components of arterial stiffness, determined with a phonocardiogram and curves for the brachial and tibial artery. Importantly, CAVI was shown to be less blood pressure-dependent than cfPWV [28].

## Local stiffness

An alternative to the assessment of regional stiffness is the measurement of local stiffness within a given short segment of the arterial tree. Nowadays, local stiffness is measured primarily with ultrasonographic techniques which are suitable for the determination of this parameter in the superficial arteries, such as the carotid and femoral artery. For research purposes, local stiffness of the deep arteries (e.g. aorta) can be measured using magnetic resonance imaging [23]. The primary advantage of local stiffness assessment stems from the fact that the measurement does not require any model of the circulation, as the stiffness is calculated directly as a ratio of change in arterial pressure in a given segment to the change of arterial diameter in that segment. Furthermore, the ultrasonographic methods are relatively widely available and can be used at a patient's bedside [2, 23].

High-resolution echo tracking is an ultrasonographic method for arterial stiffness assessment which allows monitoring changes in the wall diameter in diastole and during left ventricular ejection. A limitation of this method stems from the fact that calculations include blood pressure in the brachial artery [29]. However, aside from the determination of arterial stiffness, echo tracking can also be used for the simultaneous measurement of CIMT, which is an unquestioned advantage of this method [30]. Furthermore, statistically significant correlations were found between the arterial stiffness parameters determined with echo tracking and those measured using applanation tonometry [31].

Recently, the reference values were published for the local stiffness of the carotid artery determined using echo tracking in the European population. These values were obtained during the ETIC study that involved 1 847 healthy persons aged 3–74 years recruited in 14 European centres, among them, the study clinic [32]. The reproducibility of the echo tracking-based measurements of arterial

stiffness was verified in a group of 20 healthy persons, with the coefficient of variation < 10% [33].

The echo tracking method has been used in several studies, including the research on the effects of cardiovascular risk factors on carotid artery stiffness, interactions between arterial stiffness, left ventricular diastolic function and arterio-ventricular-atrial coupling in patients with arterial hypertension and metabolic syndrome [34–39].

## Systemic stiffness

Noninvasive methods of the assessment of systemic arterial stiffness are built on theoretical assumptions of circulation models and therefore their application is limited. These methods are based on the Windkessel model or "area method" [2].

To summarize, in their 2006 consensus, the experts from the European Network for Non-Invasive Investigation of Large Arteries recommend the determination of cfPWV and pulse wave analysis as the methods to assess arterial stiffness in clinical trials and epidemiological studies and advocated local parameters of arterial stiffness as markers suitable for pathophysiological studies and drug research [2]. The clinical applicability of local stiffness indices still requires empirical verification.

## Conclusions

Arterial stiffness can be used to predict cardiovascular events independently from conventional risk factors. Determination of regional carotid-femoral pulse wave velocity is the gold standard in the assessment of arterial stiffness. Local methods to assess arterial stiffness are gaining a growing interest among clinical practitioners. As increased arterial stiffness predisposes to arterial hypertension, prevention or at least slowing down the progression of arterial stiffening should constitute a therapeutic objective.

## Conflict of interest

The authors declare that there is no conflict of interest.

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### Streszczenie

W ostatnich latach coraz większym zainteresowaniem cieszy się koncepcja wieku naczyniowego, który odzwierciedla faktyczny stan tętnic danej osoby, niezależnie od jej wieku metrykalnego. Wczesne starzenie naczyniowe (*early vascular aging*) określa przyspieszony proces zmian degeneracyjnych tętnic, natomiast zdrowe starzenie naczyniowe (*healthy vascular aging*) odnosi się do sytuacji, gdy stan tętnic jest lepszy niż przewidywany dla danego wieku. Do oceny wieku naczyniowego służą: ocena parametrów sztywności tętniczej (w tym szyjno-udowej prędkości fali tętna — cfPWV), grubości kompleksu błony środkowej i wewnętrznej tętnicy szyjnej (CIMT) oraz ocena wskaźnika uwapnienia. CIMT odzwierciedla zmiany strukturalne tętnic i jest stosowany jako marker subklinicznej miażdżycy, natomiast parametry sztywności tętniczej określają zmiany czynnościowe ściany tętniczej. Wykazano, że cf-PWV jest niezależnym predyktorem zdarzeń sercowo-naczyniowych, demencji, chorób siatkówki i nerek. Podwyższona sztywność aorty powoduje zwiększone obciążenie następcze lewej komory serca, które prowadzi do remodelingu lewej komory, jej włóknienia, przerostu i w konsekwencji do dysfunkcji mięśnia lewej komory i niewydolności serca. Sztywność tętnicza może być oceniana lokalnie, regionalnie lub systemowo. Złotym standardem oceny sztywności tętniczej (regionalnej) jest pomiar cf-PWV. Z kolei metody ultrasonograficzne (w tym *echotracking*) umożliwiają przyłóżkową ocenę lokalnej sztywności tętnic powierzchownych. Zwiększona sztywność tętnicza prowadzi do rozwoju nadciśnienia tętniczego oraz licznych niekorzystnych zdarzeń sercowo-naczyniowych, a zatem opóźnienie jej progresji powinno stanowić cel terapeutyczny.

Słowa kluczowe: sztywność tętnicza, miażdżyca, wiek naczyniowy

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