



Prevention and treatment of excessive arterial stiffness

Review

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Abstract

Arterial stiffness affecting mainly the aorta and its large branches is currently the subject of numerous studies. Over the years, such arterial stiffness inevitably deepens. Another factor affecting the arterial stiffness is hypertension. Increased arterial stiffness, however, may precede the development of hypertension. The severity of arterial stiffness is more accurate in assessing the risk of complications and death than in knowing the value of blood pressure alone. A number of studies have identified other factors (except age and hypertension) that have a significant impact on the progression of stiffness. These include inflammation, oxidative stress, increased concentrations of glucose, cholesterol, uric acid, and homocysteine in the blood serum. Arterial stiffness occurs especially quickly in patients with renal failure, as well as in those with diabetes and obesity. Recently, a number of authors have drawn attention to the rapid progression of stiffness in some young people, which Nilsson called early vascular aging (EVA). This paper discusses non-pharmacological and pharmacological treatments that can reduce or at least slow down the progression of vascular stiffness measured by pulse wave velocity (PWV). Diets, especially those that reduce the level of overweight in obese people, as well as smoking cessation have a beneficial effect on inhibiting the development of arterial stiffness. Increased exercise plays a major role in inhibiting arterial stiffness progression. Among the pharmacological treatments, antihypertensive drugs play a leading role. All antihypertensive drugs, although to a different extent, inhibit the progression of stiffness. The paper also discusses why patients with atrial fibrillation should use new anticoagulants instead of warfarin.

Keywords

arterial stiffness • hypertension • prevention and treatment of arterial stiffness

1. Introduction

Blood vessels have two primary functions: transporting blood to tissues and converting pulsating blood flow into continuous flow. Arterial stiffness, in particular the aorta and its large branches, causes a loss of elasticity and buffer capacity during left ventricular systole and leads to reduced blood flow during diastole. Arterial stiffness significantly increases the risk of numerous cardiovascular complications [1]. Currently, we use several methods to accurately determine the degree of arterial stiffness. The most commonly used method is determining the pulse wave velocity (PWV). In young and healthy people the PWV is 5-7 m/s (10-20 times faster than blood flow). It has been assumed that PWV greater than 10-12 m/s indicates stiffness of large vessel [2]. Determining the difference between systolic and diastolic pressure, i.e., the so-called pulse pressure, is very easy and gives the doctor the possibility of an approximate but quick assessment of the severity of arterial stiffness [3]. Detailed description of numerous methods of assessing arterial stiffness can be found in publications [2,4].

2. Causes of arterial stiffness

2.1. Aging

Aging is the most common cause of arterial stiffness. The alternating pulsation caused by the ejection of blood from the left ventricle to the aorta, which is repeated many times

throughout life, leads to mechanical damage to the vessel walls. Arterial stiffness mainly concerns the aorta and its large branches containing many elastic elements. It begins with endothelial dysfunction, and in particular, when nitric oxide availability is reduced [5,6]. Over time, elastin fragments, which are essential for proper vascular compliance, as well as collagen, glycosaminoglycans, and connective tissue fibers accumulate in place of damaged elastin. In the final period of stiffness, calcium salt deposition may occur in the arterial wall [6]. The rate of vascular stiffening under physiological conditions depends to a large extent on genetic predisposition. Particular attention is paid to genes affecting the renin-angiotensin-aldosterone system, the structure of elastic fibers, vascular endothelial cells and vascular smooth muscle cells [5,6]. Although vascular stiffness is believed to be inevitable with aging, only slight arterial stiffness has been observed in the elderly in certain populations [7]. Bruno RM et al. introduced the concept of supernormal vascular age or SUPERNOVA where the vascular age is much younger than the patient's age would suggest. Patients with the SUPERNOVA phenotype have a 40% lower risk of cardiovascular disease [8]. Recently, the early vascular aging (EVA) syndrome, first described by Nilsen, has been of particular interest. In this syndrome, much more advanced arterial stiffness is found than what should result from the age of the patients [9].

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2.2. Hypertension

Hypertension and especially high central pressures rapidly lead to accelerated vascular stiffness [5]. It also turned out that the prognosis based on the degree of vascular stiffness is independent of the prognosis based on hypertension alone and predicts numerous complications, such as heart attacks, strokes, kidney damage, intermittent claudication, cognitive impairment, and orthostatic hypotension [10]. It has been shown that the relationship between arterial hypertension and vascular stiffness is bidirectional, i.e., arterial hypertension increases vascular stiffness and at the same time vascular stiffness promotes the development of arterial hypertension [11]. It is known, for example, that vascular stiffness may precede the onset of hypertension. Accelerated arterial stiffness also occurs in obesity, diabetes [12], and renal failure [13].

2.3. Chronic inflammation and oxidative stress

There is abundant evidence that chronic inflammation and oxidative stress are also important factors in accelerating vascular stiffness [14,15,16].

2.4. Abnormal lipid metabolism

Abnormal lipid metabolism is important in the development of arterial stiffness. Lipids induce the production of cytokines and adhesive molecules. As a result, leukocytes adhere more closely to the endothelium, penetrate the intima, leading to an increase in vascular resistance [17]. Many studies involving people of different ages and ethnicities have shown a close relationship between total cholesterol and the degree of arterial stiffness. They found a significant positive correlation between pulse wave velocity (PWV) and total cholesterol [18]. Studies on the relationship between the concentration of LDL cholesterol in the blood serum are, however, inconsistent. In a meta-analysis [19] by Reiner et al., the relationship between LDL cholesterol and PWV disappears when individuals with normal serum cholesterol levels are included. However, many researchers agree that between HDL-C and PWV, there is a significant negative correlation between these parameters. The lower the concentration of HDL-C, the greater the arterial stiffness [20]. High blood triglycerides are significantly associated with a greater degree of stiffness, even after accounting for multiple confounding factors [21].

For this reason, it is recommended to evaluate triglycerides at each lipid metabolism test. Wang et al. [21] believe that aiming to lower triglycerides may be a promising strategy for the treatment of arterial stiffness.

2.5. Elevated uric acid

Elevated uric acid often accompanies hypertension, metabolic syndrome, and chronic kidney disease [22,23]. Elevated uric acid causes oxidative stress, endothelial dysfunction, and stimulates vascular inflammation and fibrosis. [24].

Many studies have shown elevated levels of uric acid in patients with stiffness of large vessels, both in men and women [25]. Other researchers found these relationships stronger in women [26] or only in women [27]. However, several studies have shown no relationship between uric acid concentration and vascular stiffness [28]. In conclusion, the results evaluating the relationship between uric acid concentration and vascular stiffness are divergent. Perhaps they are related to the study population, the presence of risk factors for cardiovascular diseases or the method of assessing vascular stiffness. Recently, it has been suggested that serum homocysteine concentration may be important. Patients with high levels of homocysteine and uric acid develop arterial stiffness rapidly, whereas in patients with low levels of homocysteine and high levels of uric acid do not show symptoms of arterial stiffness [29].

2.6. Homocysteine

In hypertension the concentration of homocysteine in the blood serum is elevated and very high level this compound is a significant risk factor for accelerated atherosclerosis and cardiovascular diseases [30]. In a number of studies, a statistically significant relationship between the concentration of homocysteine and increased PWV was observed. Mantjoro et al. demonstrated such a relationship in a prospective study on men [31]. Sheng et al. also observed a higher degree of arterial stiffness in men, but not in women [32].

2.7. Vascular calcification

Vascular calcification is usually a late form of vascular stiffness. There are several stages of calcification of the vascular walls, namely calcification of the intima, then calcification of the media, and finally, calciphylaxis [33]. Vascular calcification develops most rapidly in patients with renal failure. Calcium and hydroxyapatite deposition in the vascular wall significantly increases morbidity and mortality [34]. Calcification is the result of an imbalance between factors that promote calcification and factors that inhibit calcification [34]. Calcification aggravating factors include inflammation, oxidative stress, and the presence of uremic toxins in the blood serum [34,35,36]. Calcification inhibitors have also been identified; these include the Klotho protein, pyrophosphatases and, above all, the factor known as Matrix Gla Protein (MGP inhibitor calcification) [34]. The MGP factor belongs to the family of vitamin K-dependent proteins [34].

3. Prevention and treatment of arterial stiffness

Stiffening of large arteries increases with age and is an inevitable process. So, is it possible not only to inhibit but also to achieve a significant reduction in arterial stiffness? In some clinical situations it is possible, for example, long-term improvement of arterial stiffness has been observed in patients with chronic advanced uremia after successful kidney transplantation [37].

Lifestyle modification and appropriate drug treatment can also significantly slow down the progression of arterial stiffness.

3.1. Various diets

Various diets are recommended for the prevention and treatment of arterial stiffness. According to a meta-analysis by Chu et al., high fish consumption and a Mediterranean-like diet have a beneficial effect on PWV [38]. Weight loss in obese people significantly reduces arterial stiffness [39]. Reductions in arterial stiffness have also been reported after bariatric procedures [40]. Whole body vibration has been used for twenty years in some centers for weight loss. Several studies have shown a significant reduction in the PWV after the application of such vibrations [41].

3.2. Diet in obesity and diabetes

It has been shown that postprandial hyperglycemia significantly increases arterial stiffness [42]. A low glycemic index diet, similar to the Mediterranean diet, contains a lot of vegetable, oils, fish, lots of fruits, and a minimum amount of red meat, is indicated for patients with diabetes and vascular stiffness [42]. Detailed recommendations on the use of a diet to prevent obesity and vascular stiffness can be found in the comprehensive work of Stanek A et al. [43].

Many publications indicate the relationship between high consumption of table salt and increased arterial stiffness [44], while reducing the consumption of table salt leads to a decrease in arterial stiffness [45]. A study by Jin et al., including over 36,000 subjects, showed that the consumption of more than 10 grams of table salt per day compared to people whose daily consumption of table salt is below 6 g/day, it statistically significantly increases the PWV to 1400 cm/s [44]. In contrast, Garcia-Ortiz et al. showed that the relationship between sodium intake and arterial stiffness was J-shaped, that is, arterial stiffness increased with both high and very low sodium intake [46].

3.3. The influence of cigarette smoking

The influence of cigarette smoking on arterial stiffness is important. PWV in chronic smokers was 0.64 m/s faster than in non-smokers $p < 0.001$ [47,48]. Most of studies agree that even single smoking (or passive smoking) increases arterial stiffness in both smokers and non-smokers [49,50]. Smoking cessation significantly reduces arterial stiffness [51]. According to research by Szoltysek-Boldys [52], smoking electronic cigarettes does not increase arterial stiffness. Other authors observed that smoking electronic cigarettes increases arterial stiffness, but to a lesser extent than smoking regular cigarettes [47]. Nilson suspects that one risk factor in the development of EVA syndrome in teens is their mothers' heavy smoking during pregnancy [9].

3.4. Alcohol, coffee, energy drinks

A number of studies have evaluated the effect of alcohol on the degree of arterial stiffness. These papers were collected in a Del

Giorno meta-analysis, and its results were published one year ago [53]. According to this meta-analysis, the effect of alcohol on vascular stiffness is bidirectional. Low alcohol consumption reduces arterial stiffness, while high alcohol consumption statistically significantly increases the stiffness of large vessels.

Coffee lovers will probably be interested to know that heavy coffee drinking slightly reduces arterial stiffness, while the consumption of energy drinks has an adverse effect on large arteries stiffness [54,55,56,57]. Dietary antioxidants inhibited vascular remodeling in experimental animals, but results in humans are inconsistent.

3.5. Vitamin K

Vitamin K deficiency predisposes to faster build-up of calcifications in the vessel wall [58,59,60]. Supplementation with other vitamins did not bring the expected benefits [61]. The use of non-steroidal anti-inflammatory drugs increases arterial stiffness [62].

3.6. Physical exercise

Physical exercise reduces the number of free radicals, reduces oxidative stress and inflammation, and improves endothelial function. All these elements have a positive effect on the function of large blood vessels. A number of studies have shown the beneficial effect of physical exercise on arterial stiffness. In both healthy and hypertensive subjects, strenuous exercise on a cycle ergometer slowed down the PWV compared to pre-exercise values [63]. According to Figero et al., mild exercise reduces arterial stiffness in young people but does not improve arterial stiffness in middle-aged and elderly people [64]. Other authors had different observations and physical exercise is also highly recommended in the elderly. In the Korean Yoo study, the relationship between physical activity of seniors (average age 72 years) and the degree of arterial stiffness was assessed [65]. The cited authors showed not only a significant relationship between the intensity of physical activity and a slower PWV, but also suggested that the lack of physical activity may be a predictor of the development of hypertension. According to a meta-analysis by Cheng et al., after interval training, arterial stiffness and intima-media thickness can be significantly reduced and endothelial function significantly improved, while endurance training is ineffective [66]. In contrast to regular interval exercise, severe endurance training may even increase vascular stiffness [67].

Not all authors observed a beneficial effect of physical exercise on arterial stiffness. Hinrichs et al. investigated whether walking capacity was assessed by 10-meter habitual walking speed, 10-meter maximum walking speed, and six-minute walk distance in seniors affected by arterial stiffness. It turned out that the ability to walk faster in the subjects had no effect on the degree of arterial stiffness [68].

3.7. Pharmacological treatment of arterial stiffness in patients with hypertension

Hypertension is an important reversible factor significantly affecting arterial stiffness; therefore, the prevention or treatment of hypertension is an important component of the therapy of arterial stiffness. Since we know that central pressure has a much greater effect on arterial stiffness than peripheral pressure, it is likely that drugs that reduce central pressure more than peripheral pressure will be more effective in preventing large arterial stiffness. Drugs that reduce central pressure to a greater extent than peripheral pressure include angiotensin converting enzyme inhibitors, sartans, and calcium antagonists. This was demonstrated by the ASCOT and CAFE studies [69,70]. Many studies to date assessing PWV pre- and post-treatment have indicated that ACE inhibitors, sartans, and calcium channel blockers are superior to other antihypertensive drugs in the prevention or treatment of arterial stiffness [70,71].

However, not all studies have confirmed the superiority of angiotensin converting enzyme inhibitors, sartans, and calcium antagonists in the treatment of arterial stiffness. In 2017, a meta-analysis by Xie et al. compared the effect of atenolol and angiotensin converting enzyme inhibitors on arterial stiffness assessed by PWV. The cited researchers did not find any advantage of the effect of convertase inhibitors on arterial stiffness compared to atenolol. [72]. In 2020, another meta-analysis by Li et al. was published, evaluating the effect of angiotensin converting enzyme inhibitors on arterial stiffness, based only on randomized and controlled studies. Seventeen of these studies involving 1,458 people measured PWV. The authors did not show a significant difference in the reduction of arterial stiffness between ACE inhibitor therapy and other antihypertensive drugs [73]. A meta-analysis of 15 randomized trials by Ong et al. showed a decrease in PWV in 294 patients who were chronically treated with ACE inhibitors (75 patients), calcium channel blockers (75 patients), beta-blockers (30 patients) or diuretics (26 patients) compared to the control group. However, in short-term therapy, angiotensin-converting enzyme inhibitors proved to be more effective than other drugs. [71]. Other studies have shown that spironolactone and doxazosin are also effective drugs for reducing vascular stiffness [74,75].

Two meta-analyses assessed the effects of statin treatment on arterial stiffness. In a meta-analysis by Upala et al., statin administration (simvastatin, rosuvastatin, fluvastatin, lovastatin, and atorvastatin) was found to reduce vascular stiffness at the borderline of significance and a decrease in the PWV was < 0.07. [76] A year later, a meta-analysis by D'lelia et al. showed that statins slightly but statistically significantly reduce arterial stiffness by 6.8% [77]. This effect appears to be at least in part independent of the changes in blood pressure and lipid profile. Ezetimibe and PCSK9 inhibitors also improve vascular stiffness [78].

Since triglycerides correlate better with PWV than blood cholesterol concentrations, it seemed that administration of fibrates would have a better effect on arterial stiffness. This was confirmed by the study by Yamaguchi et al. who observed a decrease in PWV after treatment with bezafibrate 400 mg/day in 66 diabetic patients with hypertriglyceridemia [79].

Allopurinol lowers oxidative stress, reduces inflammation and reduces advance glycation end product, and above all, lowers the concentration of uric acid in the blood. The results of these studies were summarized in Deng's meta-analysis, which showed no significant difference in PWV after treatment with allopurinol, but only a decrease in amplification index [80].

Metformin is still one of the main drugs in type II diabetes. However, the results of studies on the effect of metformin on arterial stiffness are inconsistent. Some authors observed a beneficial effect of metformin on arterial stiffness parameters [81,82]. Resveratrol in the study by Imamura et al. reduces arterial stiffness [83].

Increasingly, patients with diabetes are treated with flozins. These drugs have not only improved the treatment of diabetes and heart failure but are probably the most effective in reducing arterial stiffness of all antidiabetic drugs. Currently, three meta-analyses have been published confirming the beneficial effects of these drugs on endothelial function or vascular stiffness [84,85,86]. According to meta-analysis Wei I et al., SGLT2 was superior to other antidiabetic agents in improving arterial endothelial function but not arterial stiffness [85]. Batzias believes that newer antidiabetic drugs differentially affect endothelial function and arterial stiffness, as assessed by FMD and PWV, respectively [86].

Vitamin K deficiency can lead to cardiovascular events [87] and advanced arterial stiffness, and namely, calcification of the vessel walls may occur [88].

Several authors have observed an inhibition of the development of vascular stiffness after the administration of vitamin K in patients with renal failure [59,89,90,91]. But other authors did not confirm the beneficial results after using vitamin K. Increased supply of vitamin K does not slow down the progression of vascular calcification in patients not on dialysis with renal failure in stages 3-5 in the study by Kurnatowska and al. [92]. Lees et al. administered vitamin K to patients after kidney transplantation and did not observe a beneficial effect of this vitamin [93]. In a meta-analysis by LEEs et al., vitamin K supplementation significantly reduced vascular calcification but had no effect on the degree of arterial stiffness [94]. Finally, in the last meta-analysis from this year, Li et al. indicate the beneficial effect of vitamin K on increased risk of calcification but consider further research necessary in larger numbers of patients [95]. It has long been known that warfarin, as a compound that lowers the concentration of vitamin K, promotes vascular calcification [95]. Patients with atrial fibrillation who use warfarin as an anticoagulant are at high risk of accelerated vascular

calcification. Ikari Y et al. showed that discontinuation of warfarin in patients with atrial fibrillation and administration of new oral anticoagulants significantly reduces arterial stiffness [96].

3.8. Activation of baroreceptors and denervation of renal arteries

Activation of baroreceptors not only lowers blood pressure but also reduces the tone of the sympathetic system. In the study by Walbach et al., after six months of baroreceptor activation, the PWV decreased from 10.3 m/s to 8.6 m/s [97]. Gronda et al. decided to evaluate whether arterial stiffness would improve in nine patients with heart failure treated with baroreceptor activation for three months. As a control, nine other patients with heart failure were treated without baroreceptor activation. Despite the improvement in the severity of heart failure symptoms, arterial stiffness did not change in the group treated with BAT [98].

There are several papers in the literature reporting the beneficial effect of renal artery denervation in patients with arterial hypertension on arterial stiffness. For example, in the study by Brandt et al., six months after successful renal denervation, the PWV decreased from 11.6 m/s to 9.6 m/s (<0.001) [99]. Berukstis A et al. reported a decrease in the PWV after renal artery denervation as early as 48 hours after denervation, and this effect was also maintained after six months [100]. The beneficial effect of renal sympathetic denervation on vascular stiffness was also observed by Mortensen et al. [101].

Renal arterial denervation does not reduce blood pressure in all hypertensive patients, despite the decrease in sympathetic tone. Until now, the selection of patients for whom renal artery denervation will lower blood pressure has been very unreliable.

In several studies, it was observed that in patients with a high PWV, the pressure drop after denervation of the renal arteries is statistically lower than in patients with a low PWV [102]. This relationship was also confirmed by the study with the acronym ASORAS [103]. That the baseline assessment of arterial stiffness allows to assess the effectiveness of renal artery denervation.

4. Conclusions

Advanced arterial stiffness significantly increases the risk of cardiovascular diseases. Early implementation of appropriate non-pharmacological and pharmacological treatments allows the slow-down or even reduction in the degree of arterial stiffness and thus prolongs the life of patients. Accelerated stiffening of vessels under the influence of warfarin makes it necessary to replace this drug with other anticoagulants. The assessment of the degree of arterial stiffness enables the selection of patients for renal artery denervation.

Authors' contribution

Jerzy Głuszek: research concept, original draft preparation and design, approval of the version for publication.

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Conflict of interest

The authors have no potential conflicts of interest to declare.

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