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Arterial stiffness in metabolic syndrome: sex-specific differences, clinical consequences, how to prevent?

Sztywność tętnic w zespole metabolicznym — różnice płci, konsekwencje kliniczne, jak zapobiegać?

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Abstract

Non-invasively assessed arterial stiffness has been recently growing interest as a novel marker of cardiovascular (CV) risk. The effects of risk factors on the progression of arterial changes and the development of CV diseases seem to be different in women and men. Arterial stiffness was shown to be primarily determined by age and mean arterial pressure (MAP). Hyperglycaemia and resistance to insulin were identified as contributors to increased arterial stiffness. Metabolic syndrome (MS) accelerates age-related arterial stiffening, leading to the so-called early vascular ageing. Arterial stiffness was also shown to increase with the number of MS components. The effects of MS and its components on arterial stiffness are stronger in women than in men. The sex-specific differences in age-related changes within the cardiovascular system might explain why heart failure with preserved ejection fraction occurs more often in older women than in men. Published evidence suggests that arterial stiffness may be associated with left ventricular diastolic dysfunction in MS patients. Hence, a question arises whether a therapy aimed at optimal control of glycaemia and reduction of arterial stiffness could slow down the development of diastolic heart failure? Lifestyle modifications and pharmacological interventions(de-stiffening) may exert a beneficial effect on arterial stiffness independently from the reduction of blood pressure.

Key words: arterial stiffness, metabolic syndrome

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Introduction

Arterial stiffness is determined by cellular processes, the function of the endothelium and vascular smooth muscle cells and the extracellular matrix's integrity. Stiffening of the arteries was shown to be associated with the risk of cardiovascular diseases (CVD) and all-cause mortality, regardless of the presence of conventional risk factors. Moreover, published evidence suggests that the effects of the risk factors on the progression of vascular changes and development of CVD may be different in women and men [1–4].

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Metabolic syndrome (MS), a cluster of disorders including obesity, resistance to insulin/hyperinsulinemia, dyslipidaemia and arterial hypertension, plays a significant role in the development of CVD through the promotion of inflammation, thrombosis and atherosclerosis. These unfavourable effects of MS lead to vascular damage, and as a result, to a worse prognosis. In MS endothelial dysfunction, the inflammatory response of cytokines, sympathetic overdrive and the renin-angiotensin system's activation contribute to an increase in vascular tone, promote hyperplasia and hypertrophy of smooth muscle cells, enhance the synthesis of collagen and eventually lead to increased arterial stiffness. However, the role of MS as a contributor to arterial stiffness is a matter of debate. The question of whether metabolic syndrome itself as an interplay of several risk factors exerts an additional effect on the progression of arterial stiffening, or the latter is rather associated with the co-existence of various conventional CVD risk factors being components of MS, still raises some controversies [1]. The increase in arterial stiffness is postulated to be an intermediate stage in the development of cardiovascular complications, and recent evidence points to non-invasively assessed arterial stiffness as a novel marker for cardiovascular risk [1–3].

Measurement of a regional parameter, carotid-femoral pulse wave velocity (cfPWV) through applanation tonometry constitutes the gold standard in the assessment of arterial stiffness. The measurement is most often taken with the Complior or Sphygmocor system. Other frequently determined regional parameters of arterial stiffness include cardio-ankle vascular index (CAVI), which is independent of blood pressure (BP) and brachial-ankle PWV (baPWV). Local arterial stiffness can be determined with the Esaote method or through echo-tracking [1, 4–7]. The latter technique allows for simultaneous assessment of arterial stiffness and intima–media thickness (IMT) and hence, provides information about both functional and structural changes within the arteries [1, 4].

Arterial stiffness: sex-specific differences

It is still unclear whether the effects of risk factors on pulse wave velocity (PWV) and augmentation index (AI), a measure of wave reflection, are modulated by sex. Due to the cardioprotective effect of oestrogens, premenopausal women are less likely to suffer from CVD and they develop this condition one decade later than men. Oestrogen deficiency associated with menopause harms cardiovascular function and metabolism, promoting unfavourable changes in adipose tissue distribution, vasculitis, increased sympathetic drive and resistance to insulin. Younger women typically present with lower arterial stiffness than men, but their stiffness indices increase dramatically during the perimenopausal period. The question of whether hormone replacement therapy could reduce arterial stiffness in women is yet to be answered. The sex-specific differences in age-related changes within the cardiovascular system, including changes in arterial stiffness, might explain why older women present with isolated systolic hypertension and heart failure with preserved ejection fraction (HFpEF) more often than men [3, 8–10].

Effects of metabolic syndrome and its components on arterial stiffness

Arterial stiffness was shown to depend primarily on age and mean arterial pressure (MAP). Age is a key determinant of arterial stiffness. Other factors that were demonstrated to contribute to increased arterial stiffness include hyperglycaemia, and/or insulin resistance. According to literature, an increase in arterial stiffness is mediated by advanced glycation end-products (AGEs), tobacco smoking and leptin. The role of the autonomic nervous system and increased heart rate has been postulated as well [1, 2, 4].

Some evidence suggests that premature arterial stiffening can be observed already in persons with increased fasting glucose (IFG) and resistance to insulin associated with prediabetes. In Hoorn study, conducted in a Dutch population (n = 2,500), elevated fasting glucose level was associated with increased arterial stiffness after adjustment for age and blood pressure [11].

A large body of evidence suggests that type 2 diabetes mellitus may be associated with increased arterial stiffness [12, 13]. Increased arterial stiffness, expressed as cfPWV, was shown to be a predictor of mortality in a population of patients with type 2 diabetes [12]. Cardiovascular mortality risk in women with diabetes is 3.3-fold higher than in the general population, compared with "only" 1.8-fold increase in diabetic men. This sex-related difference is postulated to be associated with more rapid arterial stiffening in diabetic women. Enhanced arterial stiffening in diabetes may be a consequence of the increased activity of AGEs and endothelial dysfunction [12, 14, 15]. The question of whether the effect of diabetes on arterial stiffness in women is stronger than in men is yet to be answered and requires further research.

Impaired metabolism of glucose plays a key role in the increase in arterial stiffness in MS. In Bogalusa Heart Study, a growing prevalence of MS components in the young population (24–44 years) was associated with an increase in arterial stiffness. This implies, that MS may accelerate the stiffening processes associated with age, leading to the so-called early vascular ageing (EVA) [16]. In hypertensive perimenopausal women components of MS are stronger predictors of subclinical organ damage than MS itself [17].

The effects of MS and its components on vascular stiffness in various populations are summarized in Table 1. The results of many previous studies suggest that MS has

Table 1. The effects of metabolic syndrome (MS) and its components on arterial stiffness in various populations

No.	Reference	Study population and method	Results
1	Li S et al. Atherosclerosis 2005 [16]	baPWV in 806 asymptomatic healthy young adults (22–44 years, white and black), participants of Bogalusa Heart Study	Arterial stiffness increased with the number of MS components; MS was shown to modulate arterial stiffness in young adults
2	Lin HF et al. Atherosclerosis 2010 [18]	Effects of MS, age and sex on IMT and arterial stiffness determined by means of echotracking in Chinese population from Taiwan (1,245 patients, 22% with MS)	MS contributed to an increase in IMT and arterial stiffness, as shown by higher values of Ep, β and PWVβ; the relationships were more evident in younger women
3	Kim HL et al. J Cardiol. 2015 [19]	Sex-specific differences in the effects of MS components on arterial stiffness determined based on baPWV in Korean population (537 patients, 22.7% with MS)	The association between MS components and arterial stiffness determined based on baPWV was stronger in women aged < 55 years than in men; while the effects of SBP, DBP and TG on baPWV were similar regardless of sex, the significant effect of waist circumference on baPWV was observed solely among women and the effect of fasting glucose only in men
4	Protogerou AD. Atherosclerosis 2007 [20]	Effects of MS on arterial stiffness determined based on PWV and AI in European patients with arterial hypertension (41% with MS)	The effects of MS on PWV and AI were modulated by sex; MS proved to be an independent determinant of arterial stiffness and wave reflection solely in hypertensive women
5	Weng Cet et al. Int J Med Sci. 2012 [21]	Age- and sex-specific differences in the effects of MS on arterial stiffness determined based on baPWV in Chinese population (12,900 patients, 19.4% with MS)	The effects of MS on arterial stiffness differed depending on age and sex; blood pressure turned out to be the strongest predictor of arterial stiffness determined based on baPWV; TG correlated with increased baPWV in middle-aged women and younger men
6	Scuteri A et al. Atherosclerosis 2014 [22]	Effects of MS and its components on arterial stiffness determined based on cfPWV in European and American population (MARE Consortium Metabolic Syndrome and Arteries Research; 20,570 patients, 24.2% with MS)	MS accelerated age-related arterial stiffening in both women and men
7	Gomez-Sanchez L et al. Cardiovasc Diabetol. 2016 [23]	Sex-specific differences in the effects of MS and its components on arterial stiffness determined based on CAVI and baPWV in the European population (MARK study; 2,351 patients, 51.9% with MS)	Among patients with MS, CAVI and baPWV values were higher in men than in women; the effects of MS components on arterial stiffness were sex-specific, with stronger impact observed among men
8	Della-Morte D. Int J Stroke 2010 [24]	Effects of MS on arterial stiffness in 1,133 patients participating in Northern Manhattan Study (older multiethnic population with a mean age of 65 ± 9 years, 49% with MS)	Higher BP and waist circumference had a significant effect on arterial stiffness; MS contributed to higher arterial stiffness, which explains why patients with this condition are at increased risk of stroke
9	Topouchian J et al. J Hypertens. 2018 [25]	Effects of age and MS on arterial stiffness determined with two methods, based on CAVI and cfPWV, in the European population (Triple A — Stiffness Study; 2,224 patients, including 1,664 with MS)	The effects of age and MS differed depending on whether arterial stiffness was determined based on CAVI or cfPWV; age exerted a stronger effect on CAVI while MS had a greater impact on cfPWV; TG and HDL cholesterol levels correlated with cfPWV but not with CAVI; waist circumference correlated positively with cfPWV and inversely with a CAVI
10	Kruszyńska E et al. Diabetes Metab Syndr Obes. 2020 [26]	Sex-specific differences in the effect of MS on arterial stiffness determined by means of echotracking in the European population (419 patients, including 51% with MS)	The effect of MS on arterial stiffness was stronger among women; MS exerted a significant effect on the pulsatile component of blood pressure (PP) in women and steady component (MAP) among men; a paradoxical relationship was found between waist circumference and arterial compliance (AC) in women

baPWV — brachial-ankle pulse wave velocity; IMT — intima-media thickness; Ep — pressure-strain elastic modulus; β — β-stiffness index; PWVβ — one-point pulse wave velocity; TG — triglyceride; PWV — pulse wave velocity; AI — augmentation index; cfPWV — carotid-femoral pulse wave velocity; CAVI — cardio-ankle vascular index; SBP — systolic blood pressure; DBP — diastolic blood pressure; TG — triglycerides; HDL — high-density lipoproteins

a substantial contribution to enhanced arterial stiffening in middle-aged and older populations, especially women, especially Asians [18–21]. As already mentioned, the reasons behind the sex-specific differences in arterial stiffening are still not fully understood. It is postulated that MS contributes to preterm loss of oestrogens' protective effect on the cardiovascular system. However, the effect of MS on arterial stiffening in the European and American population (MARE Consortium) was similar regardless of sex, the number of MS components present in a given patient had a more profound effect in men than in women [22]. Individual components of MS also had a greater contribution to arterial stiffening in males than in female patients in another European population, participants of the MARK trial. These discrepancies might at least in part result from differences in the characteristics of studied populations and methods used to assess arterial stiffness [16, 18, 19–26]. (Table 1).

The relationship between arterial stiffness and hypertension is bidirectional and is referred to as a "vicious circle" in literature, as the two processes accelerate one another. However, the question of which of them, arterial stiffening or hypertension, is a primary component of the circle is still a matter of debate. Elevated blood pressure promotes arterial wall thickening and fibrosis, the two processes involved in the pathogenesis of arterial stiffening [27]. On the other hand, higher arterial stiffness contributes to an increase in blood pressure and pulse pressure (PP), microcirculatory disorders and impaired vasodilation, which leads to the progression of arterial hypertension [27]. In the MARK trial [23] elevated blood pressure, either systolic blood pressure (SBP) or diastolic blood pressure (DBP), turned out to be the strongest determinant of increased arterial stiffness in European patients with MS. Similar results were also obtained in American and Korean populations [19, 24].

Recently, blood pressure is being described with two components, the so-called "steady component" expressed as MAP and the "pulsatile component" expressed as PP. MAP was shown to be a predictor of CVD events, heart and kidney failure, whereas PP is known primarily as a predictor of atherosclerotic changes [28].

Only a few published studies verified whether the link between PP and arterial stiffness depends on patient sex. In this context, particularly interesting is the observation that in a population exposed to risk factors, the pulsatile component of blood pressure PP was associated with the indices of local stiffness determined through echo-tracking in women, but not in men [29]. An association between the echo-tracking determined parameters of local stiffness and PP was also found in women with MS. Meanwhile, in men with this condition, the measures of local stiffness correlated with MAP [26].

Published evidence points to a likely link between blood lipids and arterial stiffness in healthy subjects. Blood triglycerides were identified as an independent predictor of both regional cfPWV and local echo-tracking arterial stiffness in a group of 210 healthy Brazilians [30]. However, the results of some prospective studies imply, that the association between the lipid profile of the blood and arterial stiffness may be different in women and men. In a Swiss observational study SAPALDIA, including 2,545 persons without symptomatic CVD, but with risk factors, higher arterial stiffness was associated with elevated blood triglycerides in women, elevated low-density lipoprotein (LDL) cholesterol in men and increased body mass index (BMI) regardless of sex [31].

Available data on the relationship between obesity and increased arterial stiffness are inconclusive. In pathophysiological terms, the link between the two conditions can be explained by insulin resistance and the overactivation of the renin-angiotensin-aldosterone system in obese persons. Abdominal obesity was shown to be associated with increased arterial stiffness and a higher risk of CVD in young women, counterbalancing the protective effect of hormones. In a study of young Polish women, obesity was associated with increased arterial stiffness indices [32]. Interestingly, in the TRIPLE study, waist circumference correlated positively with cfPWV, but an inverse correlation was found between this parameter and another measure of arterial stiffness, CAVI. The latter relationship was particularly evident in older women [25]. Such a paradoxical association between waist circumference and arterial compliance was also observed in the present study involving the group of middle-aged women [26]. Further research is needed to address the discrepancies mentioned above.

Arterial stiffness and left ventricular diastolic dysfunction

A cardiac complication of MS can be diastolic heart failure. A growing body of evidence suggests that an increase in arterial stiffness may play a vital role in the pathophysiology of heart failure with preserved ejection fraction (HFpEF). To understand the pathophysiology of HFpEF, a concept of ventricular-arterial coupling (VAC) was developed, according to which an increase in arterial stiffness is associated with the increase in the stiffness of the left ventricle. HFpEF is twice as common in women as in men. Women are predisposed to HFpEF because of higher aortic stiffness, lesser arterial compliance and increased pulsatile load [33]. However, little is known about the relationship between the heart and arteries at the early stages of heart failure. An increase in arterial stiffness results in a premature return of wave reflection, which is associated with a raise of central systolic pressure and afterload, eventually leading to

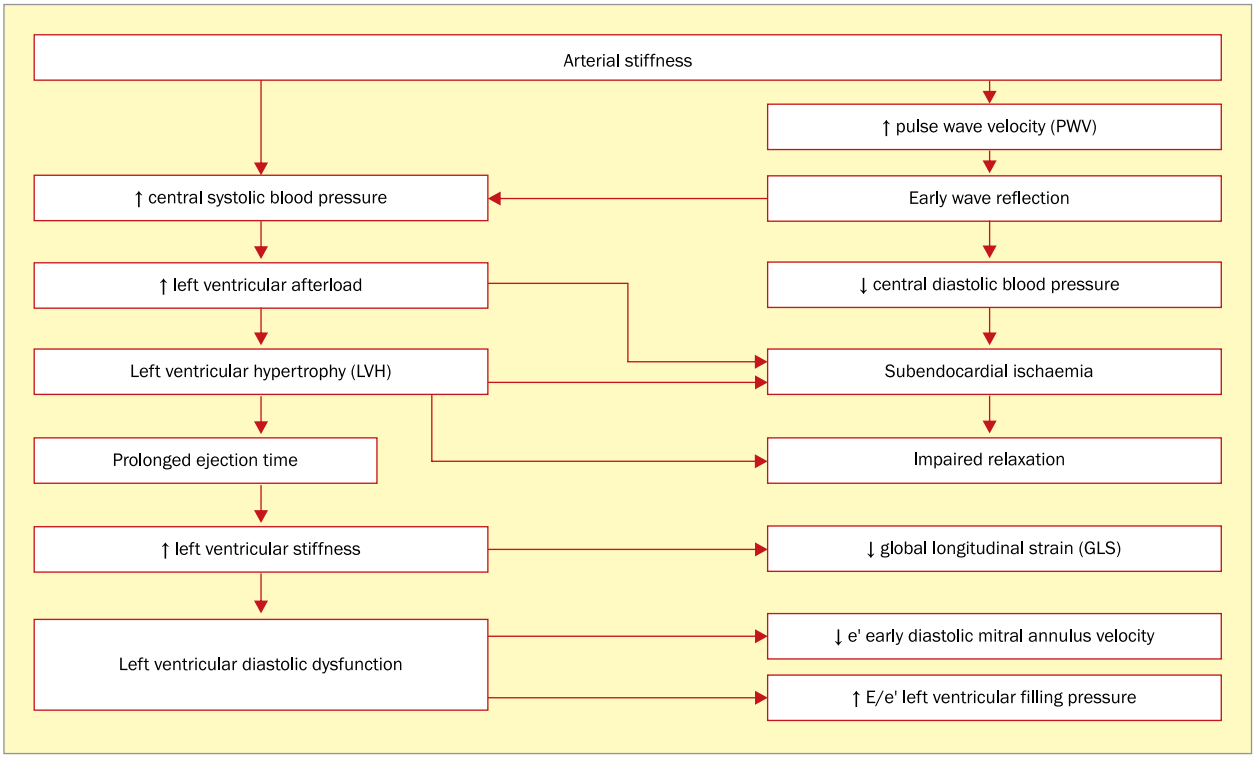

Figure 1. Relationship between arterial stiffness and left ventricular diastolic dysfunction

left ventricular hypertrophy (LVH), prolongation of ejection time and impairment of ventricular relaxation. A concomitant decrease in diastolic pressure contributes to the reduction of coronary perfusion, left ventricular ischemia and relaxation impairment, with a subsequent increase in the stiffness of the left ventricle and its diastolic dysfunction [8, 33] (Figure 1). Recently, tissue Doppler imaging (TDI) has been applied to assess left ventricular diastolic dysfunction. A decrease in global longitudinal strain (LGS) on TDI reflects an increase in left ventricular stiffness. In turn, a decrease in early diastolic mitral annulus velocity (e') is a marker of impaired left ventricular relaxation, and an increase in E/e' ratio (the ratio of early diastolic mitral inflow to early diastolic mitral annulus velocity) reflects an increase in left ventricular filling pressure (Figure 1).

The results of some published studies suggest that the link between arterial stiffness and left ventricular diastolic dysfunction might occur in different populations. In a group of older women without structural heart disease (n = 819), arterial stiffness expressed as baPWV was shown to be associated with some TDI indices. Namely, an inverse correlation was found between baPWV and e' wave as a measure of left ventricular relaxation, along with a positive correlation between baPWV and E/e', a marker of left ventricular filling pressure [34]. In another study, including 127 asymptomatic persons with risk factors for heart failure (stage A), a significant association was observed between increased vascular stiffness determined through echo-tracking and left ventricular diastolic dysfunction [35]. A significant relationship between the local stiffness index (PWV beta) determined with echo-tracking and left ventricular diastolic dysfunction was also demonstrated in a study of patients with untreated arterial hypertension [36].

In a group of 1,119 patients with MS and left ventricular diastolic dysfunction, a significant determinant of the latter turned out to be cfPWV determined through applanation tonometry [37]. In another study of 131 patients with MS, arterial compliance (AC) was an independent predictor of left ventricular diastolic dysfunction in men, but not in women [38]. Finally, in patients with diabetes mellitus, glycated haemoglobin level was shown to correlate with left ventricular mass and aortic stiffness [39]. Considering all the above, a question arises, if a therapy aimed at optimal control of glycemia and reduction of arterial stiffness could slow down the progression of diastolic heart failure?

Pharmacological and non-pharmacological strategies to improve arterial stiffness

Many previous studies demonstrated that lifestyle modifications and pharmacological interventions might exert a beneficial effect on arterial stiffness independently from the reduction of blood pressure. A concept of de-stiffening, i.e., reduction of arterial stiffness and/or wave

reflection, has been proposed as a way to prevent arterial hypertension and cardiovascular diseases. This concept has been derived from the observation that the renin–angiotensin–aldosterone system's (RAAS) blockade exerts an antiproliferative effect on vascular smooth muscle cells. The inhibition of the RAAS was shown to contribute to a decrease in PWV and wave reflection. Research showed that aside from anti-atherosclerotic, anti-inflammatory and anti-proliferative action, angiotensin-converting enzyme inhibitors (ACEI) and sartans can also target the mechanisms involved in arterial stiffening. Reduction of MAP was identified as a primary mechanism contributing to a decrease in arterial stiffness. However, the reduction of central SBP and central PP should be considered important de-stiffening mechanisms independent of MAP changes. Modulators of the renin-angiotensin system, Ca blockers and insulin were shown to reduce both wave reflection and central SBP [3, 28]. Moreover, some drugs, such as ACEI, angiotensin receptor II inhibitors, aldosterone antagonists and calcium antagonists are known to increase arterial compliance. Also, cardio-selective beta-blocker nebivolol and statins were shown to exert a beneficial effect on arterial function. Main non-pharmacological strategies that were proven to decrease arterial stiffness include regular physical activity and the reduction of dietary salt intake [3].

Conclusions

To summarize, published evidence suggests that the effects of metabolic syndrome and its components on arterial stiffness are stronger in women than in men. An increase in arterial stiffness plays a crucial role in the development of diastolic heart dysfunction. Lifestyle modifications and pharmacological interventions (de-stiffening) may exert a beneficial effect on arterial stiffness independently of blood pressure reduction.

Conflict of interest

The authors declare no conflict of interest.

Streszczenie

Ostatnio zwiększa się zainteresowanie nieinwazyjną oceną sztywności tętnic jako nowym markerem ryzyka sercowo-naczyniowego (CV). Zwraca się uwagę na odrębny wpływ czynników ryzyka na postęp zmian naczyniowych i rozwój chorób CV u kobiet i mężczyzn. Udowodniono, że sztywność tętnic w głównej mierze zależy od wieku i średniego ciśnienia tętniczego. Wykazano wpływ hiperglikemii i oporności na insulinę na wzrost sztywności naczyń. Dowiedziono, że zespół metaboliczny (MS) akceleruje procesy sztywności związane z wiekiem, tak zwany wczesny wiek naczyniowy. Zanotowano wyższe wartości sztywności ze wzrostem komponent zespołu metabolicznego. Wpływ MS i jego komponent na sztywność tętnic jest silniej zaznaczony u kobiet niż u mężczyzn. Odmienny przebieg zmian w układzie CV z wiekiem i płcią, w tym także dotyczących sztywnienia tętnic, może odpowiadać za częstsze występowanie niewydolności serca z zachowaną frakcją wyrzutową u starszych kobiet niż u mężczyzn. W literaturze pojawiają się prace, których autorzy wskazują na zależność między sztywnością tętnic a dysfunkcją rozkurczową lewej komory w MS. Czy zatem terapia zmierzająca do optymalnej kontroli glikemii i ograniczenia sztywności naczyń może opóźnić rozwój rozkurczowej niewydolności serca? Zmiana stylu życia i interwencje farmakologiczne mogą korzystnie wpływać na sztywność tętnic (*de-stiffening*) niezależnie od obniżenia ciśnienia tętniczego.

Słowa kluczowe: sztywność tętnic, zespół metaboliczny

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