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The influence of sex on left ventricular remodeling in arterial hypertension

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Abstract

Hypertension represents one of the most important and most frequent cardiovascular risk factors responsible for heart failure (HF) development. Both sexes are equally affected by arterial hypertension. The difference is lying in the fact that prevalence of hypertension as well as hypertension-induced target organ damage varies during lifetime due to substantial variation of sex hormones in women. Left ventricular (LV) structural, functional, and mechanical changes induced by hypertension are well-known complications that occur in both sexes and they are responsible for HF development. However, their prevalence is significantly different between women and men, which could potentially explain the variation in HF occurrence and prognosis between the sexes. Studies have shown that the prevalence of left ventricular hypertrophy is higher in men. The data are not consistent regarding LV diastolic dysfunction and a similar report has been given for LV mechanical changes. Most investigations agree that LV longitudinal strain is lower among hypertensive men. However, even in the healthy population, men have lower LV longitudinal strain and the cutoff values are still missing. Therefore, it would be difficult to draw the conclusion that LV mechanical dysfunction is more prevalent among men. The main mechanisms responsible for sex-related LV remodeling are sex hormones and their influence on biohumoral systems. This review provides an updated overview of the available data about sex-related LV remodeling, as well as potential mechanisms for these changes, in the patients with arterial hypertension.

Keywords Arterial hypertension · Sex · Left ventricular hypertrophy · Diastolic function · Strain · Pathophysiology

Introduction

Arterial hypertension represents the most prevalent and one of the most important risk factors for development of cardiovascular diseases. Women are significantly protected during the premenopausal period; however, after menopause (usually after 50 years of age) the incidence of hypertension suddenly increases and hypertension becomes more prevalent among women [1]. This large study has shown that hypertension control is better in women due to better awareness and compliance to the treatment [1].

Using Joint National Committee's (JNC) eight definitions of hypertension, 34% of adults older than 20 years of age in the USA have hypertension: 34.5% of men and 33.4% of women [2]. This means that approximately 51% of the hypertensive population in the USA are women. However, the prevalence is not equal in different age groups. Men are more prevalent in the period between 45 and 54 years of age; the prevalence of hypertension is similar between the sexes in the period from 20 to 44 and from 55 until 74, and finally becomes higher in women than in men at the age > 75, when they are also under higher risk of hypertension-related cardiovascular diseases [2].

Sex hormones such as estrogen and testosterone have the central role in cardio protection by changing the balance between vasodilators and vasoconstrictors, which involves important biohumoral systems such as the renin-angiotensin-aldosterone system (RAAS), the autonomic nervous system, and the endothelin system [3].

Previous studies have reported significant difference in left ventricular (LV) remodeling induced by arterial hypertension

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in different sexes [4, 5]. At the beginning, the authors were concentrated on LV hypertrophy (LVH), but soon they discovered that changes influenced by gender in hypertension referred also to LV systolic and diastolic function [6], and only recently even to LV mechanics [7–9]. Sex hormones are again considered as the most important mechanism responsible for these differences [10].

We aimed to provide a comprehensive review of the current data regarding sex influence on overall LV structural and functional remodeling in the hypertensive patients, including detailed description of mechanisms, as well as inclusion of the data regarding LV strain. This article also summarized the mechanisms that might explain LV changes in arterial hypertension induced by sex.

Pathophysiology of sex-related cardiac remodeling

The most important mechanisms that underlie changes of the cardiovascular system between the genders are sex hormones. Blood pressure elevation in postmenopausal women occurs due to significant alterations in sex hormones. Estrogen impacts the vascular system provoking vasodilatation, increasing nitric oxide bioavailability, changing the RAAS and the sympathetic system, and regulating vascular remodeling and the response to vascular injury [11–13]. Progesterone is involved in vascular dilatation and therefore responsible for blood pressure regulation [11]. Nitric oxide, vasopressin, endothelin, and the immune system are also important factors that induce cardiovascular remodeling in arterial hypertension in both sexes [3].

It has also been reported that androgens induce the increase in endothelin and catecholamines, which is leading to elevation of renal uptake of sodium and consequent induction of vasoconstriction [11]. Testosterone decreases the high-density lipoprotein level (HDL), increases low-density lipoprotein cholesterol (LDL), and elevates production of angiotensin II and homocysteine [11]. Figure 1 illustrates pathophysiological mechanisms that explain the association between sex hormones, arterial hypertension, and LV remodeling.

Sex hormones are not the only factor responsible for sex-specific cardiovascular changes. Some other factors, such as body size and composition should also be stressed. There is no agreement regarding the influence of sex hormones on body size and composition. Animal models showed sex-related effects on blood pressure. However, these effects were not always related with sex hormones. The Dahl salt-sensitive rat showed increases in blood pressure after ovarectomy [14]. On the other hand, Reckelhoff et al. reported that the blood pressure in the spontaneously hypertensive rat was independent of estrogens [15]. Additionally, treatment with estradiol enabled the reduction of blood pressure in the postmenopausal period only transitorily [16] or even induced the increment of blood pressure, especially after longer use of hormone replacement therapy [17].

The influence of body size on cardiac remodeling and the role of sex is another important issue. In a large study, the authors showed that body mass index (BMI) has important independent impact on systolic and diastolic blood pressure in both sexes [18]. The Norwegian longitudinal study showed that the baseline BMI was associated with systolic and diastolic blood pressure in both genders [19]. However, BMI change during the follow-up period was associated with elevation in systolic blood pressure in both sexes, but the relationship between BMI change and diastolic pressure was found only in women [19].

There are also indications that some other biohormonal systems could be responsible for sex-specific regulation of blood pressure and cardiac remodeling: estrogen/androgen ratios, renin-angiotensin-aldosterone and the activated sympathetic nervous system, endothelin systems metabolic syndrome, inflammation, increased vasoconstrictors, and anxiety [20].

Pathophysiology of sex-related left ventricular hypertrophy

The development of hypertension-induced LVH could be divided into two stages: increased preload and normal afterload are typical for the first stage, while normal preload and elevated afterload are characteristic for the second stage. The LV adaptation follows these changes in pre- and afterload. Therefore, the initial phase consists of mild LV dilatation, which occurs as the result of the Frank-Starling law which reads that increased stretching of myofibers provides force for ejection of higher stroke volume [5, 21, 22]. The second phase is characterized by elevated afterload which induces LVH according to the LaPlace's law which claims that LVH represents a compensatory mechanism to reduce wall stress and oxygen demand [5, 21, 22]. Norton summarized all the factors that contribute to preload and afterload [23]. Afterload depends on total peripheral resistance, stroke volume, and arterial compliance as well as ventricular properties [23].

The role of estrogen and androgens in cardiac pathophysiology is still unclear and it represents the topic of ongoing discussion. Sex-related differences in LVH might be related to estrogen effects. Estrogen has an antiproliferative effect on vascular or ventricular smooth muscle [24, 25]. This could explain age-related LV mass increase in women, particularly during menopause [26]. However, LV mass in women never reaches LV mass in men, even in the post-menopause period [26].

The role of testosterone is even more controversial. On the one hand, studies indicate that testosterone induces LVH [27, 28]. On the other hand, another investigation reported that antiandrogenic therapy induced attenuation of LVH and improvement of LV function [29]. A more recent investigation showed the inverse relationship between the total testosterone

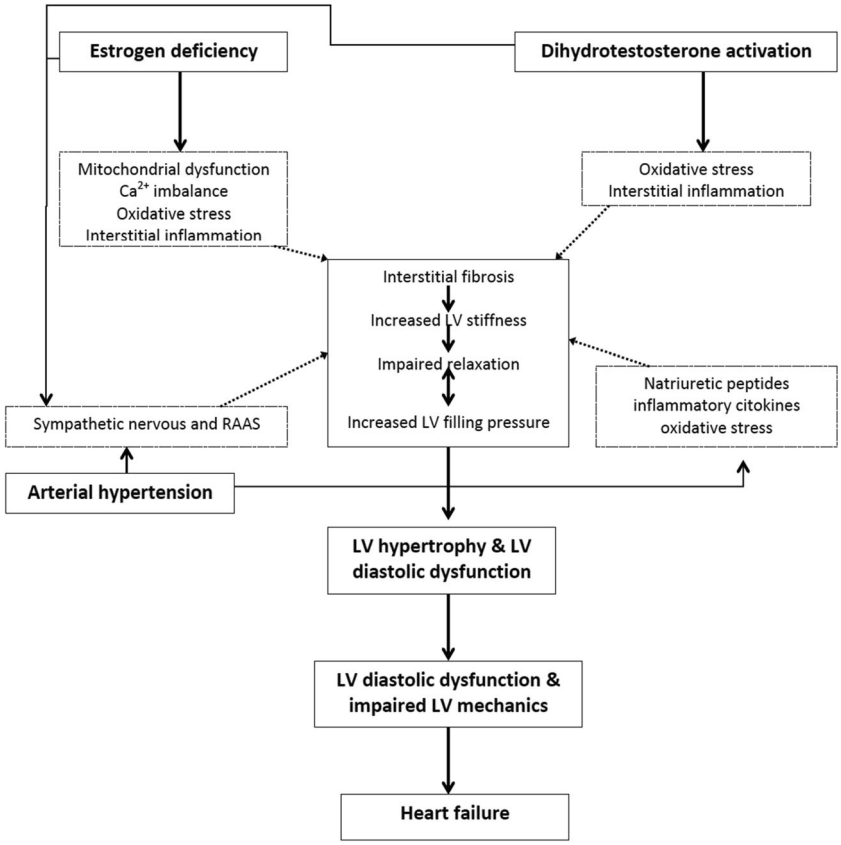

Fig. 1 Pathophysiological mechanisms that explain the association between sex hormones, arterial hypertension, LV remodeling, and heart failure. Footnotes: LV, left ventricle; Ca, calcium

level and LV mass and higher cardiovascular risk in men with the lower level of total testosterone [30]. However, one should be careful in interpretation of these findings because the authors measured only the level of total and not free testosterone, which represents an active form of testosterone responsible for its main effects.

Hypertension-induced LVH in women is more resistant to antihypertensive therapy and its regression is more difficult to achieve in women than in men despite effective antihypertensive treatment and good blood pressure control [31]. This might be explained by the lack of estrogen effects after menopause. The lack of estrogen, but not testosterone levels, could be the essential risk factor for LVH and concentric cardiac adaptation response to increased afterload in postmenopausal women [32].

Pathophysiology of sex-related left ventricular diastolic dysfunction

Estrogen deficiency could induce cardiac inflammation and fibrosis that further provoke cardiac remodeling and, consequently, LV diastolic dysfunction [33]. LV diastolic dysfunction occurred together with an elevated LV end-diastolic pressure and LV filling pressure [33]. The low testosterone level was related with more impaired parameters of LV diastolic function (increased E/e′, decreased E/A, and prolonged DT) in men when compared with the men with the normal testosterone level [34]. The study which included young women with polycystic ovary syndrome, characterized with the increased level of free testosterone, revealed significantly higher LV mass and lower E/A ratio (the parameter of impaired LV diastolic function) in these patients comparing with the healthy controls [35].

Ventricular–vascular coupling has a very important role in development of LV diastolic dysfunction in both genders. It seems that sex could also impact the ventricular–vascular relationship [7]. However, there is still no consensus regarding the influence of gender on ventricular–vascular relationship in arterial hypertension. Redfield et al. in the community-based study showed that advancing age and female gender were associated with increases in vascular and ventricular systolic and diastolic stiffness even in the absence of cardiovascular disease [7]. Vascular, ventricular systolic, and ventricular diastolic elastance were significantly higher among women than in men [7]. In hypertensive patients, Faconti et al. showed that main determinants of ventricular elastance were arterial elastance and gender [36]. All parameters of arterial elastance were higher in women. Interestingly, the ratio between arterial and ventricular elastance was similar between the genders. However, pressure augmentation was independently associated with ventricular elastance only in men [36]. Cost-Hong et al. reported that hypertensive women had higher reflected

aortic pressure waveform and central blood pressure indexes than hypertensive men, and these findings were worsened by the menopausal status [37].

Pathophysiology of sex-related left ventricular systolic dysfunction

Studies have reported that women have higher LV ejection fractions [38, 39] and greater systolic elastance than men, which confirms better myocardial contractility [7]. In the normal ventricle, the helical fiber orientation of cardiomyocytes enables efficient contraction during systole. Hearts with smaller ventricles, typical for women, show greater torsion, suggesting that increased torsion is required to maintain an adequate cardiac output in women hearts [40]. Redfield et al. suggested an additional potential mechanism for sex differences in LV structure and function which referred to higher arterial stiffening in advanced age in women, but not in men [7]. Differences in arterial function could also underlie sex-related variations in LV function and mechanics.

Salem et al. recently showed that LVEF and LV global longitudinal strain were negatively associated with bioavailable testosterone levels in men, whereas midventricular radial strain was positively associated with the bioavailable testosterone level [10]. The follicle-stimulating hormone (FSH) was positively correlated with circumferential strain in men. The authors hypothesized that different effects of FSH and testosterone on cardiac systolic function were the consequence of the multilayered cardiac fiber orientation constituted of cardiomyocytes with different electro-physio-mechanical properties and hormone receptors [41].

However, one should not forget other sex-related lifestyle and environmental factors that could significantly impact LV structure and function in arterial hypertension. Diet, prevalence of obesity (particularly abdominal obesity), physical exercise, alcohol consumption, and smoking habits are substantially different among the sexes over the lifetime and they could also contribute to LV remodeling in both sexes [3].

Clinical data regarding sex-related LVH in hypertension

The comparison of LV linear dimensions, mass, and volumes between the sexes is challenging due to significant difference in body size and different cutoff normal values that are adjusted to the sex [42]. Therefore, it is more informative to consider the prevalence of LVH and different LV geometry patterns. A large meta-analysis of our study group included 40,444 treated and untreated hypertensive patients and showed no significant difference in the average prevalence of electrocardiographically detected LVH between the sexes (24% in men vs. 16% in women, $p = 0.11$) [43]. The main limitation of this large study is that LVH was assessed only by electrocardiographic and not echocardiographic criteria, which are not accurate for LVH evaluation. The Campania Salute Network revealed that the risk of incident LVH was substantially higher in hypertensive women [44]. The Framingham Heart Study detected LVH in 15.5% of women and 21% of men [45], and our study group found similar results in patients with concomitant hypertension and metabolic syndrome (58.6% women vs. 48% men) [46]. The data regarding the influence of sex on LVH are summarized in Table 1.

There is no agreement regarding LV geometric patterns in the hypertensive population. Some studies do not show any difference in the prevalence of different LV geometric patterns between the sexes [5, 48], whereas the investigation that included patients with isolated systolic hypertension reported that concentric and eccentric LVH was more prevalent among women than among men (4 vs. 29% and 9 vs. 14%, respectively) [49]. Significant limitation of these studies represents a small sample size. However, large studies did not investigate sex-related differences in the LV geometry pattern among hypertensive patients.

The Strong Heart Study showed that LVH regression was found in only 3% of men and 10% of women during a 4-year follow-up [50]. Simultaneously, new LVH was diagnosed in 14% of men and 15% of women. This implied that hypertension-induced LVH in women is more resistant to antihypertensive therapy and its regression is more difficult to achieve in men than in women. On the other hand, the Campania Salute Network reported that female sex was an independent predictor of lack of LVH regression in hypertensive patients [52].

LVH is a well-known independent predictor of cardiovascular and overall morbidity and mortality in the hypertensive population [45, 53, 54]. Recent findings demonstrated that women without LVH had a 35% lower risk of major cardiovascular events than men without LVH after the 4-year follow-up [51]. However, there was no difference in cardiovascular risk between the sexes in hypertensive subjects with LVH [51]. The LIFE study, which included only hypertensive patients with electrocardiographic-defined LVH, showed women experienced more adverse events during the follow-up [55]. However, it should be emphasized that echocardiographic LVH confirmation was not available for this study.

The Multi-Ethnic Study of Atherosclerosis (MESA) showed that the presence of LV fibrosis, recognized as a scar in cardiac magnetic resonance, was associated with 3% decrease in LVEF and 0.7% larger LV end-diastolic volume only in men over the period of 10 years [47]. Initially, the study included 29% hypertensive women and 27% hypertensive men. Over the period of 10 years, this percentage increased to 50% in both sexes. Sustained hypertension over 10 years was associated with increased LV mass index and higher diffuse fibrosis at the follow-up in both sexes [47]. Over a 10-year period, replacement

Table 1 The impact of sex on left ventricular hypertrophy in arterial hypertension

Reference	Sample size	Women/men (%)	Study type and type of LVH assessment	Main findings
Masiha et al. [5]	922 patients	50/50	Follow-up Echo	No difference in prevalence of different LV geometric patterns between elderly women and men (> 70-year-old)
Ambale Venkatesh et al. [47]	1813 subjects	48/52	10-year CMR follow-up	Replacement fibrosis was associated with increased concentric LV hypertrophy in women and LV dilatation in men, whereas diffuse fibrosis was related with reduced LV mass index in both sexes
The Campania Salute Network [44]	4290 hypertensives	40/60	1-year follow-up Echo	LVH was substantially higher in hypertensive women, independently of age, systolic blood pressure, and LV mass index
Framingham Heart Study [45]	4073 subjects	57/43	Follow-up Echo	No significant difference in LVH prevalence between sexes (15.5% women and 21% men, $p > 0.05$)
Cuspidi et al. [46]	3752 hypertensives	47/53	Cross-sectional Echo	LVH in women than in men with concomitant hypertension and metabolic syndrome (58.6 vs. 48%), but without statistical significance
Cipollini et al. [48]	162 untreated hypertensives	38/62	Cross-sectional Echo	LV mass variance explained by systolic blood pressure was much higher in females than in males. No difference in LV geometric patterns between women and men
Heesen et al. [49]	244 participants	36/64	Cross-sectional Echo	Concentric and eccentric LVH were more prevalent among women than among men (4 vs. 29% and 9 vs. 14%, respectively)
Strong Heart Study [50]	851 hypertensives	57/43	4-year follow-up Echo	LVH regression was found in 3% men and 10% women during 4-year follow-up. New LVH was diagnosed in 14% men and 15% women
The Campania Salute Network [51]	12,329 hypertensive patients	44/56	4-year follow-up Echo	Women without LVH had a 35% lower risk for major cardiovascular events than men without LVH after adjustment for cardiovascular risk factors and antihypertensive treatment. Women with LVH have similar risk as men

CMR cardiac magnetic resonance, *LVH* left ventricular hypertrophy

fibrosis was associated with increased concentric LV hypertrophy in women and LV dilatation in men, whereas diffuse fibrosis was related with reduced LV mass index in both sexes. Hypertension-induced remodeling was related to diffuse LV fibrosis and hypertrophy in both sexes.

The same study showed that over this period the change in LV mass was positively associated with systolic blood pressure and body mass index and negatively associated with the treated hypertension and the high-density lipoprotein cholesterol level [56]. In men, the longitudinal LV mass increase was in contrast to a cross-sectional pattern of LV mass decrease, which emphasized the importance of conducting longitudinal studies [56].

Clinical data regarding sex-specific LV diastolic dysfunction in hypertension

The growing body of evidence regarding different echocardiographic values among the sexes recently initiated the idea of echocardiographic reference values specific for each sex, even for LV diastolic function parameters [42]. This is of importance because LV diastolic dysfunction represents "*conditio sine qua non*" of heart failure with preserved ejection fraction that is more prevalent among women and very frequent in the hypertensive population [57]. The data regarding the influence of sex on LV diastolic function are presented in Table 2.

The investigation that included the subjects with the increased risk profile including hypertension showed significantly more impaired LV diastolic function in women than in men [58]. However, the prevalence of LV diastolic dysfunction was similar between the sexes. The other study involving only the subjects without structural heart disease or systolic dysfunction found that LV diastolic function correlated with the parameters of arterial stiffness only in women [59].

Foconti et al. did not find any difference in the main parameters of LV diastolic function between women and men with hypertension [36]. Fujimoto et al. investigated elderly patients with the early stage of hypertension and reported more impaired parameters of LV diastolic function in women [60]. The ARIC study included the elderly of whom > 70% had hypertension and showed a correlation between female sex and increased LV filling pressure only in women [8]. Hayward et al. conducted invasive measurement of LV systolic and diastolic function in a small population of subjects

Table 2 The impact of sex on left ventricular diastolic and systolic function in arterial hypertension

Reference	Sample size	Women/men (%)	Study type	Main findings
Tadic et al. [6]	283 subjects	43/57	Cross-sectional	Female sex was not associated with impaired LV diastolic parameters or reduced LVEF
Kuznetsove et al. [9]	650 subjects	51/49	4.7 years follow-up	The magnitude of decrease in most of diastolic indexes was greater in men than in women
Russo et al. [58]	983 patients	62/38	Cross-sectional	More impaired echocardiographic parameters of LV diastolic function in women than in men. The prevalence of LV diastolic dysfunction was similar between sexes. LVEF was higher in women than in men
Shim et al. [59]	158 subjects	50/50	Cross-sectional	LV diastolic function correlated with the parameters of arterial stiffness only in women
Faconti et al. [36]	102 subjects	31/69	Cross-sectional	No difference in the main parameters of LV diastolic function between hypertensive women and men. No difference in LVEF between sexes
Fujimoto et al. [60]	151 subjects	55/45	Cross-sectional	Women exhibited faster E, slower e′ and greater average E/e′. No difference in LVEF between sexes
Copenhagen City Heart Study [61]	1296 participants	58/42	11-year follow-up	Women had shorter deceleration time, higher E/e′ ratio and similar E/A ratio than men. Reduced LVEF more frequently among men (1.3 vs. 0.3%, $p = 0.030$)
GENOA Study [62]	1172 black participants	72/28	Cross-sectional	Late transmitral diastolic velocity was slightly higher and isovolumic relaxation time was slightly lower in women comparing with men. LVEF was higher in women than in men
Krzesiński et al. [63]	144 hypertensives	31/69	Cross-sectional	No difference in LV diastolic and systolic parameters between women and men
Strong Heart Study [64]	1351 participants	64/36	Follow-up	No significant difference in average LVEF between sexes, but reduced LVEF was more frequent in men than women (16.7 vs. 4.7%, $p < 0.001$)

E/A ratio between early and late diastolic transmitral velocities measured by pulsed Doppler, *E/e′* ratio between early diastolic velocities measure by pulsed and tissue Doppler, *LV* left ventricle, *LVEF* left ventricular ejection fraction

with high prevalence of arterial hypertension and showed greater LV systolic function and lower diastolic compliance in women than in men [65].

In the Copenhagen City Heart Study that included individuals from the normal population with average 40% prevalence of hypertension reported that women had more impaired parameters of LV diastolic function than men [61]. Other studies did not find statistically significant difference in LV diastolic parameters in different subgroups of hypertensive patients [5, 6, 62, 63].

Kuznetsova et al. followed 650 subjects from the general population for 4.7 years and found that male gender was associated with significant reduction in a large number of LV diastolic function parameters (E, A, E/A ratio, and e′/a′), but interestingly not with E/e′ ratio [9]. The authors concluded that the magnitude of decrease in most diastolic indexes was greater in men than in women [9]. The same group of authors showed that mitral E/e′ ratio was significantly higher among women, whereas there was no difference in E/A ratio [66]. They showed that there was no significant difference in the association between LV diastolic function indexes and central hemodynamics load between the sexes [66].

A study that investigated 1760 individuals of both sexes from the Framingham study reported normal-to-mild LV diastolic dysfunction in 1615 participants at the baseline. Progression to at least moderate LV diastolic dysfunction was observed in 12% patients during the period of 6 years [67] and it was more likely to occur in older women. Female sex, besides changes in blood pressure, body mass index, serum triglycerides, and diabetes, was associated with worsening of LV diastolic function. Presence of moderate and severe LV diastolic dysfunction was related with higher mortality risk in both genders [67].

In conclusion, changes in LV diastolic function in women could be ascribed to the following: (i) more prominent elevation of blood pressure, aortic stiffness, and wave reflection that occurs with aging more frequently in women than in men [65]; (ii) steeper Starling curve slope, the relationship between stroke work/end-diastolic volume, which indicates increased LV performance [65]; (iii) passive LV diastolic elastance, an important indicator of LV filling pressure, is also higher in women comparing with men [65].

Clinical data regarding sex-specific LV systolic function in hypertension

LV systolic function in clinical practice is usually defined by ejection fraction (LVEF). In the last several years, other parameters, primarily LV longitudinal strain, with better reproducibility and higher predictive value have emerged [68]. LV global longitudinal strain was a better predictor of mortality than 2D and 3D LVEF [67]. Nevertheless, LVEF still remains the "holy grail" of LV systolic function in everyday clinical practice in hypertensive patients.

The current echocardiographic guidelines recognized the difference in LVEF cutoff values and therefore lower cutoff for men is 52% and for women 54% [69]. The main problem of LVEF is that this robust parameter remains preserved for a long time and therefore other indexes of LV systolic function, such as LV longitudinal strain, have been recommended nowadays [64, 70]. The data regarding the influence of sex on LV systolic function are provided in Table 2.

The ARIC study with a large percentage of hypertensive patients (> 70%) showed a positive correlation between LVEF and female sex, who had higher LVEF than men [8]. Some studies found similar results with increased LVEF in women [5, 58, 62, 64], whereas other did not find any significant difference between the sexes [6, 36, 60, 63, 65, 71].

Fujimoto et al. for instance found that female sex was associated with reduced LV systolic function estimated by the tissue Doppler in hypertension, even though there was no difference in LVEF [50]. The Strong Heart Study did not show any significant difference in average LVEF between the sexes, but reduced LVEF was more prevalent among men than women (16.7 vs. 4.7%, $p < 0.001$) [72]. The authors showed that parameters of LV systolic function were higher in women than in men, even after adjusting for fat-free mass, which suggested that sex-specific alterations were independent of body size [72].

Clinical data about sex-specific LV mechanics in hypertension

Left ventricular mechanics is complex in order to provide an efficient cardiac cycle and satisfy the body needs in all circumstances. These cardiac motions include shortening, lengthening, thickening, rotation, and twisting. The best echocardiographic method for evaluation of the complex cardiac motion is strain that represents a percentage in change of myocardial longitudinal diameter, circumference, and thickness—longitudinal, circumferential, and radial strain, respectively [73, 74]. Apical and basal rotations are supplementary essential cardiac motions that facilitate effective cardiac contraction. The cardiac base rotates clockwise, while the apical segment rotates counterclockwise. The mathematical twist represents the sum of the absolute values of both basal and apical ones [75].

LV global longitudinal strain has been particularly studied and it was revealed that even in the hypertensive population it had an important predictive role for major adverse cardiac events in an asymptomatic hypertensive population [76]. Studies have already shown the sex influence on LV mechanics in the general population, as well as in the hypertensives. The data about the impact of sex on LV mechanics are summarized in Table 3.

Our investigation showed that female sex was significantly associated with LV longitudinal and circumferential strain, as well as LV twist, in hypertensive patients [6]. The findings from the ARIC study that included a large percentage of hypertensive patients among elderly individuals showed that women had higher global longitudinal and circumferential

Table 3 The impact of sex on left ventricular mechanics in arterial hypertension

Reference	Sample size	Women/men (%)	Study type and type of strain assessment	Main findings
Tadic et al. [6]	283 subjects	43/57	Cross-sectional Echo study	Female sex was significantly associated with LV longitudinal and circumferential strain, as well as LV twist, in hypertensive patients
ARIC study [8]	1105 subjects	61/39	Follow-up Echo study	Women had higher global longitudinal and circumferential strain and reported a more pronounced increase of torsion and twist in comparison with men
Kuznetsova et al. [9]	791 participants	52/48	Follow-up Echo study	Sex-specific values of global and layer-specific strain longitudinal strain predicted future cardiovascular events independently of conventional risk factors
MESA study [40]	1478 subjects	46/54	Follow-up CMR study	Significant association between female sex and circumferential shortening and torsion
Kuznetsova et al. [77]	627 subjects	51/49	Follow-up Echo study	LV longitudinal strain during follow-up period was associated with male sex, higher baseline mean blood pressure, increase in mean blood pressure, and changing of antihypertensive treatment

CMR cardiac magnetic resonance, *LV* left ventricle

strain and demonstrated a more pronounced increase of torsion and twist in comparison with men [8]. The MESA study also included a substantial number of hypertensive subjects (around 50% in the whole population) investigated by cardiac magnetic resonance and reported significant association between female sex and circumferential shortening and torsion [40]. Furthermore, fiber orientation is dependent on LV shape and this study reported that women had more spherical hearts comparing with men before and after the adjustment for other clinical parameters [40]. Higher arterial stiffness and impaired arterial–ventricular coupling in women in advanced age could also be the reason for higher torsion in women.

The Danish study included the subjects from the general population with prevalent hypertension and found that the sex changed the relationship between LV global longitudinal strain and the composite outcome and the incident of heart failure alone [61]. Therefore, LV longitudinal strain was a stronger predictor of adverse outcomes in men than in women [61]. On the other hand, the sex did not impact the relationship between LV longitudinal strain and occurrence of acute myocardial infarction or cardiovascular death [60]. It should be emphasized that the authors did not use cutoff values for LV longitudinal strain specific for each sex, as some authors recently proposed [9, 78].

Kuznetsova et al. showed that sex-adjusted values of global and layer-specific strain longitudinal strain predicted future cardiovascular events independently of conventional risk factors in the global population. However, the authors did not particularly investigate the influence of sex on the outcome [9]. In a recent study of the same group, the authors reported that significant decrease in LV longitudinal strain during the follow-up period of 4.7 years was associated with male sex, higher baseline mean blood pressure, increase in mean blood pressure, and alteration in antihypertensive treatment [77].

Conclusion

The increasing amount of evidence confirms sex-specific left ventricular remodeling in arterial hypertension. However, the extent and clinical importance of these differences are still poorly understood, with many persisting questions. Studies have confirmed significant difference in LV structural, functional, and mechanical changes among the sexes with arterial hypertension. It has also been reported that these adaptations influenced by sex could be partly responsible for different cardiovascular morbidity and mortality in the hypertensive population. Sex hormones and their influence on biohumoral systems such as RAAS and the sympathetic nervous system have been blamed for these LV changes so far. Nevertheless, many other potential factors responsible for these changes remain to be enlightened. The future directions of investigation should provide critical information regarding the potential effect of various therapeutic approaches to different sexes.

Compliance with ethical standards

Conflict of interest The paper "The influence of sex on left ventricular remodeling in arterial hypertension" has not been submitted elsewhere, it is not under review, or published previously. There is no possible conflict of interest. All authors are aware of and approve the manuscript being submitted to this journal.

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