

# Sex-specific differences in cardiac maladaptation to hypertension and arterial stiffening

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## Abstract

The overall prevalence of symptomatic heart failure (HF) is similar in men and women and constitutes about a quarter of the first manifestation of cardiovascular disease in both sexes. However, there is an important difference between the sexes in the type of HF. Whereas men more frequently develop HF with reduced ejection fraction, HF with preserved ejection fraction is especially frequent in women. The major risk factors for symptomatic HF are high blood pressure and arterial stiffness, which evoke a complex network of functional and structural changes in the heart in both men and women. In this review, we will discuss the recent epidemiological data on sex discrepancies in cardiac maladaptation to hypertension and arterial stiffening.

**Key words:** sex differences, heart failure, hypertension, arterial stiffening

Kardiol Pol 2018; 76, 9: 1303–1311

## EPIDEMIOLOGY OF SYMPTOMATIC HEART FAILURE

The major burden of symptomatic heart failure (HF) on public health and national healthcare systems highlights the pressing need for better diagnosis and management of this disorder [1, 2]. Currently, symptomatic HF affects nearly 15 million Europeans [3] and its prevalence is expected to increase over the next decades due to extending life expectancy and rising presence of risk factors such as hypertension and diabetes mellitus [1]. Moreover, in recent years, the actual burden of HF has exceeded the one predicted by the American Heart Association [4, 5]. At the age of 40 years, the lifetime risk of developing HF is approximately one in five, in both men and women [6].

While traditionally associated with the concept of pump failure or reduced left ventricular (LV) ejection fraction (EF), it has become widely recognised that HF can occur even when EF is preserved, constituting the syndrome of HF with preserved EF (HFpEF) [7]. Symptomatic HF has a poor prognosis, regardless of whether EF is reduced or not [8–10]. For instance, a recent meta-analysis of 41,972 HF patients reported 121 deaths per 1000 patient-years in those with HFpEF and 141 deaths per 1000 patient-years in those with HF with reduced EF (HFrEF) [10].

In comparison to patients with HFrEF, those with HFpEF are typically older, are more often women, and have a history

of hypertension (Fig. 1) [10, 11]. The sex discrepancy in the prevalence of HFrEF and HFpEF might originate from differences in the major risk factors for HF in men and women. Indeed, whereas men more frequently develop HFrEF as a complication of coronary heart disease, HFpEF is especially frequent in women with risk factors such as hypertension, obesity, and diabetes [10, 11]. Of note, HFpEF is often underdiagnosed in elderly women even if it is already symptomatic. Moreover, due to diagnostic difficulties, women have often been underrepresented in randomised clinical trials testing the effect of treatments on HF, even though this disease often affects elderly women.

## HYPERTENSION AND ARTERIAL STIFFENING AS RISK FACTORS FOR HEART FAILURE

In both men and women, hypertension plays a prominent role in the development of symptomatic HF, in particular of HFpEF [9, 11]. In the Framingham study, hypertension was observed in 75% of new HF cases [6]. According to community-based data, hypertension contributes more to development of HF in women than in men. For instance, the adjusted risk for HF was approximately twofold higher in hypertensive men, but threefold higher in hypertensive women as compared to their normotensive counterparts [12]. The population-attributable risk of hypertension for symptomatic HF was 39% in men

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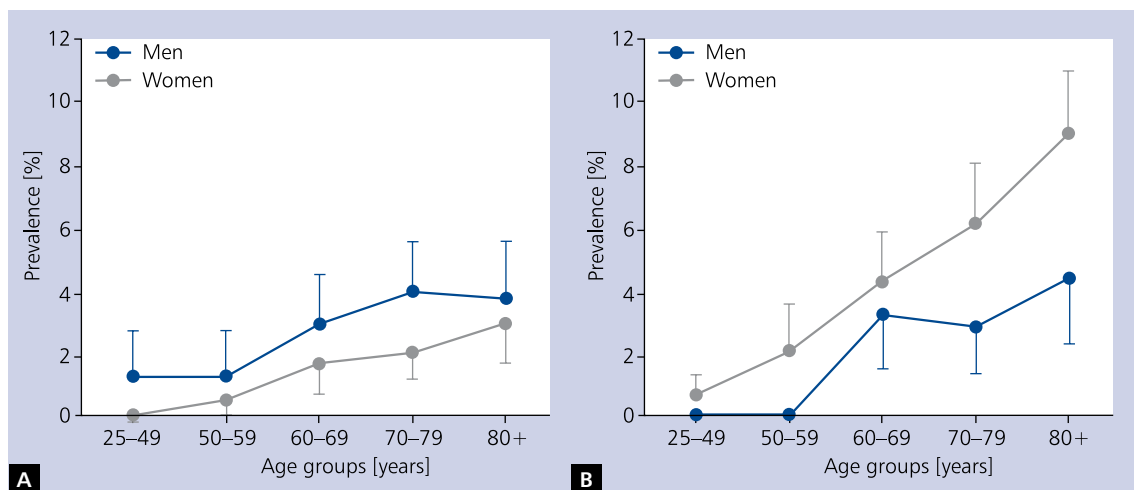
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Received: 26.07.2018

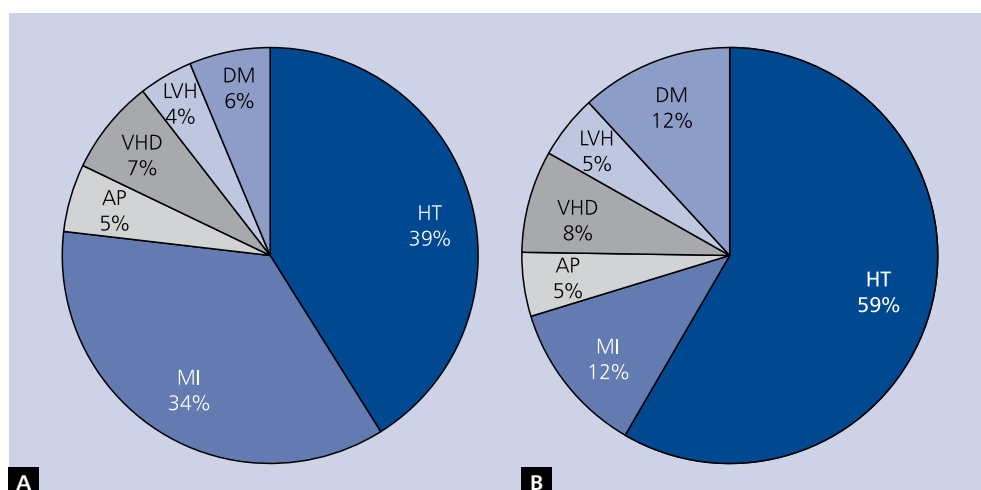
Accepted: 26.07.2018

Available as AoP: 6.08.2018

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**Figure 1.** Sex differences in the prevalence of heart failure with reduced ejection fraction (HFrEF) (A) or preserved ejection fraction (HFpEF) (B). Age- and sex-specific prevalence of HFrEF and HFpEF in a general population cohort from southwest Europe. Prevalence of HFrEF and HFpEF increased with age in both sexes. HFrEF was more prevalent in men and HFpEF more prevalent in women at any given age. Reproduced from Ceia F et al. [88] with permission

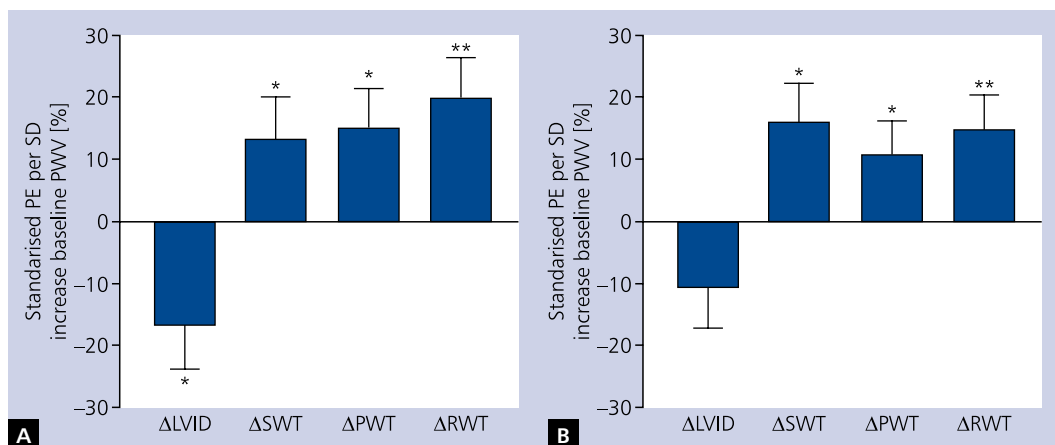


**Figure 2.** Population-attributable risk for the development of congestive heart failure in 5143 Framingham Study participants by sex; **A.** Men; **B.** Women. The population-attributable risk of hypertension (HT) for congestive heart failure was 39% in men and 59% in women; AP — angina pectoris; DM — diabetes mellitus; LVH — left ventricular hypertrophy; MI — myocardial infarction; VHD — valvular heart disease. Reproduced from Levy et al. [12] with permission

and 59% in women (Fig. 2) [12]. Women have lower blood pressure (BP) than men during the reproductive years, but not in the older age, when HFpEF typically develops [13]. From the menopause on, the cardioprotective effects of female sex hormones are lost and BP levels start to rise in older women and even surpass those of men [13].

In addition, arterial stiffening, a common feature of vascular ageing, might accelerate the development of HF and exacerbate its symptoms [14, 15]. Indeed, HF patients have greater aortic stiffness than healthy controls [16]. Moreover, even asymptomatic subjects with higher arterial stiffness as assessed by aortic pulse wave velocity (PWV) were found to

exhibit a higher risk for all-cause death, [17] cardiovascular events [17, 18], and symptomatic HF [19] beyond traditional cardiovascular risk factors. For instance, one standard deviation increase in aortic PWV was associated with a 29% higher adjusted risk for incident symptomatic HF [19]. To date, no prospective population study has reached sufficient statistical power to study the independent predictive value of arterial stiffness for the development of HF separately in women and men. For instance, Tsao et al. [19] did not find a significant interaction between arterial stiffness and sex for HF incidence, but their sex-specific analysis has been questioned due to the low number of events per group [20]. Future studies will need



**Figure 3.** Arterial stiffness as a mediator of left ventricular concentric remodelling in both men (A) and women (B). In 607 FLEMENGHO participants, higher arterial stiffness (PWV) at baseline independently predicted stronger left ventricular concentric remodelling (RWT) in both sexes during a five-year follow-up period; LVID — left ventricular internal diameter; PE — parameter estimate; PWT — posterior wall thickness; PWV — pulse wave velocity; RWT — relative wall thickness; SD — standard deviation; SWT — septal wall thickness; \* $p < 0.05$ ; \*\* $p < 0.01$ . Reproduced from Cauwenberghs et al. [24] with permission

to be larger and with long-term follow-up, in order to include a higher number of incident HF events that will have to be dichotomised by sex and by type of HF.

Because of the risk factors such as hypertension, arterial stiffness, insulin resistance, and myocardial ischaemia, the LV progressively remodels [21, 22] and its systolic and diastolic functions gradually worsen [23–25] years to decades before HF symptoms present. Using echocardiography, the non-invasive and easily accessible technique for the assessment of cardiac structure and function, subclinical LV maladaptation was observed in subjects free from HF symptoms, but with cardiovascular risk factors [21, 23, 24, 26, 27]. Indeed, in patients with hypertension and increased arterial stiffening, LV afterload is chronically elevated, opposing LV ejection, and the heart is forced to work at a high performance level [28]. In the long run, the chronic rise in LV workload will increase the heart's energy expenditure and oxygen consumption and trigger asymptomatic yet adverse myocardial remodelling and dysfunction [16, 29]. Over time, these adverse LV changes gradually diminish the cardiac reserve, until they evoke HF symptoms, disability, and death [16, 29]. Within this context, better understanding and targeting of the risk factors for early subclinical LV remodelling and dysfunction (e.g. hypertension, arterial stiffening, etc.) may be the most cost-effective strategy to reduce the burden of symptomatic HF on our society [30].

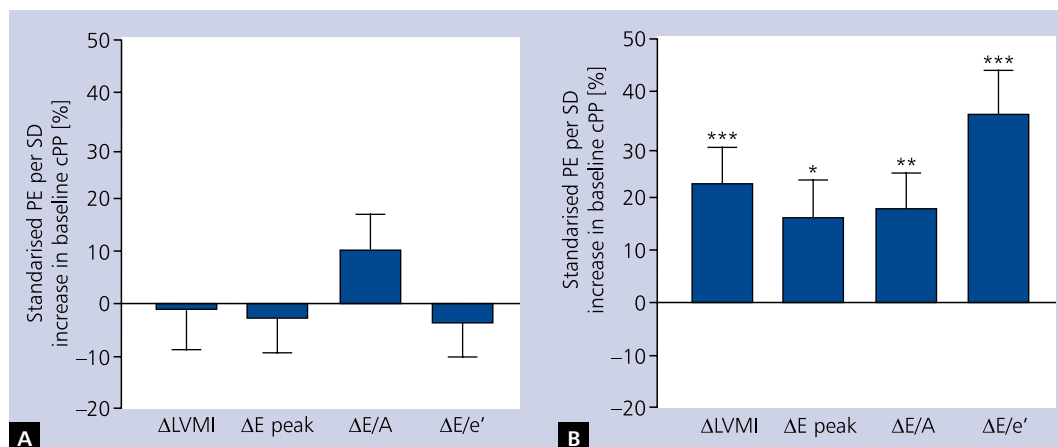
### SEX-SPECIFIC CARDIAC MALADAPTATION TO HYPERTENSION AND ARTERIAL STIFFENING

#### LV remodelling

To better understand cardiac remodelling induced by hypertension and arterial stiffening, one should consider

the law of Laplace, describing the relationship between LV pressure, volume, and wall stress. According to this equation, LV wall stress is directly proportional to the LV pressure and internal radius, and inversely proportional to its wall thickness. Higher pressure can cause thickening of LV walls to accommodate an increased load and maintain normal wall tension. Indeed, patients with hypertensive heart disease usually present with concentric (inward) LV remodelling and/or hypertrophy. On the other hand, LV chamber volumes and EF could be preserved for a longer time in such patients [31]. Of note, under hypertensive conditions, women are more likely to present LV concentric remodelling/hypertrophy, whereas men more commonly develop eccentric LV hypertrophy (LVH) [32, 33].

Previous population studies reported cross-sectional and longitudinal associations of LV remodelling with hypertension and arterial stiffness. In the Framingham study, exposure to elevated BP at baseline was associated with future development of LVH as assessed by echocardiography in both men and women [21]. Moreover, in line with a small study in 100 subjects free of overt cardiac disease [34], a cross-sectional magnetic resonance imaging study in 2093 MESA participants showed that higher proximal aortic stiffness was associated with LV concentric remodelling [35]. Furthermore, in 607 FLEMENGHO participants, in both men and women, we observed similar associations of longitudinal increases in LV wall thickness and relative wall thickness (a marker of concentric remodelling) with higher baseline PWV during a five-year follow-up period, independent of other important covariables (Fig. 3) [24]. In contrast to a cross-sectional study reporting a relation between concentric remodelling and arterial stiffness only in postmenopausal women [36], we



**Figure 4.** The left ventricular (LV) diastolic function of women is sensitive to increased central haemodynamics and arterial stiffness; **A.** Men; **B.** Women. In 607 FLEMENGHO participants, higher central pulse pressure (cPP) (reflecting aortic compliance) at baseline independently predicted a stronger increase in LV mass and LV filling pressure (E/e' ratio) in women at five-year follow-up examination. LVMI — left ventricular mass index; PE — parameter estimate; SD — standard deviation; \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ . Reproduced from Cauwenberghs et al. [24] with permission

confirmed the importance of aortic stiffening as a mediator of LV concentric remodelling in both men and women [24].

Previous population studies have demonstrated the link between adverse LV remodelling and future cardiovascular events [21, 37]. In a meta-analysis including 48,545 participants from 20 prospective studies, the presence of LVH implied a 2.3- and 2.5-fold higher weighted risk for future cardiovascular morbidity and all-cause mortality, respectively [37]. The authors also reported a trend toward a worse prognosis among women with baseline LVH compared with men [37]. Furthermore, in the Framingham Heart Study, developing an abnormal LV geometric pattern (concentric remodelling) during four years of follow-up was associated with a 1.6 times greater risk for developing cardiovascular disease in a subsequent follow-up period of 12 years [21]. Several mechanisms may explain why adverse LV remodelling and hypertrophy can lead to poor cardiovascular outcome. First, an abnormal LV geometry can lead to diastolic filling disturbances, a harbinger of congestive HF. Second, structural LV maladaptation can damage the autonomic nervous system, reduce the coronary reserve, and increase the oxygen requirements of the heart. Lastly, it increases the risk for ventricular arrhythmias and sudden death.

#### **LV diastolic dysfunction**

Parallel to cardiac remodelling, LV diastolic function progressively worsens throughout life [23]. Diastolic dysfunction stands central in the development of HFpEF. Conventional echocardiography and tissue Doppler imaging (TDI) allow to detect subclinical deterioration of LV diastolic function [38]. Impaired LV myocardial relaxation is initially characterised by decreased early (E peak) and enhanced late (A peak) diastolic blood velocities over the

mitral valve as well as by less vigorous mitral annulus motion (e' peak) during early diastole. The more advanced stage of diastolic dysfunction presents also with increased LV filling pressure at end-diastole because of increased LV stiffness. Combining the early transmitral flow velocity with the early mitral annular TDI velocity (E/e' ratio) allows a non-invasive evaluation of LV filling pressure [39].

Previous population studies demonstrated that LV diastolic function is sensitive to increased central haemodynamics and arterial stiffness, particularly in women [24, 40, 41]. For instance, in our community-based sample, higher central pulse pressure (reflecting aortic compliance) independently predicted a stronger increase in LV mass and LV filling pressure (E/e' ratio) during five years of follow-up, but only in women (Fig. 4) [24]. This higher sensitivity of LV diastolic function of women to increased pulsatile load might be explained by the fact that women, as compared to men, present on average higher aortic stiffness [40, 42], enhanced LV systolic performance [43–45], higher preload sensitivity, and lower LV compliance [43]. First, BP, aortic stiffness, and wave reflection increase more prominently with age in women than in men [44, 46]. Second, women have on average smaller heart chamber volumes, even after standardisation for body size [44], with higher LVEF [45] and global longitudinal deformation (strain) [47], and a steeper slope of the stroke work/end-diastolic volume relationship (Starling curve), suggesting overall enhanced LV performance as compared to men [44]. Third, the passive LV diastolic elastance, a major determinant of LV filling pressure, also appears to be higher in women than in men [44, 46]. These observations might conjointly explain why HFpEF appears to affect twice as many women as men [48–50].

### ***LV systolic dysfunction***

In clinical practice, LV systolic function is often evaluated by the fraction of blood that is ejected by the LV during systole (i.e. EF). However, reductions in EF seem to appear only late in HF development [25, 51], questioning its usefulness in detecting early stages of cardiac dysfunction. Instead, changes in the relative deformation (or strain) of the LV might better reflect preclinical worsening in LV systolic performance [25]. The heart is a complex three-dimensional structure with myocytes laid out in different directions. Longitudinal deformation of the heart results from the contraction and relaxation of longitudinally-stretched subendocardial and subepicardial fibres, whereas LV wall thickening along the radial axis mainly originates from the contraction of circumferential fibres located in the midwall [52]. It should be noted that longitudinal, circumferential, and radial strains are not interchangeable and might hold different diagnostic and prognostic information [53, 54]. Separate analysis of LV deformation along the various axes might thus help us to better understand the progression of LV systolic dysfunction induced by risk factors [25, 55].

### ***LV longitudinal strain and afterload***

The average deformation of the LV in the longitudinal direction (referred to as LV global longitudinal strain or global LS) has been validated as a reproducible and valuable marker of LV systolic function that could be more sensitive than EF [25, 47, 56]. In fact, longitudinal systolic dysfunction is already observed in the early stages of myocardial maladaptation following a chronically increased load [42, 57].

High systemic arterial pressure particularly elevates LV wall stress in the endocardium, predominantly consisting of longitudinally oriented fibres, and might thus specifically burden the long-axis deformation. Theoretical models already predicted that longitudinal LV deformation decreases with an increase in the mean arterial pressure (MAP) [58]. In line with this model, clinical studies demonstrated that hypertensive patients had significantly lower LV longitudinal strain than normotensive controls [59–61]. Moreover, in community-based cohorts, in both men and women LV longitudinal strain declined independently with an increase in the steady BP component (i.e. MAP) in continuous analysis [42, 62]. Also, several measures of aortic stiffening were associated with worse LV longitudinal deformation, even after accounting for important confounders. For instance, in a large Framingham cohort, lower global LS was independently associated with higher aortic pulse wave velocity similarly in both men and women [63].

Several community-based studies [47, 64, 65] have demonstrated that low global LS is associated with a greater risk for future cardiovascular and cardiac events [47]. For instance, FLEMENGHO participants belonging to the lower quartile of global LS distribution (i.e. reduced global LS) exhibited a significantly higher adjusted risk than the average population

for future cardiovascular (128%) and cardiac (94%) events [47]. Of note, in the Copenhagen City Heart study global LS was a stronger prognosticator for incident HF in men than in women [64].

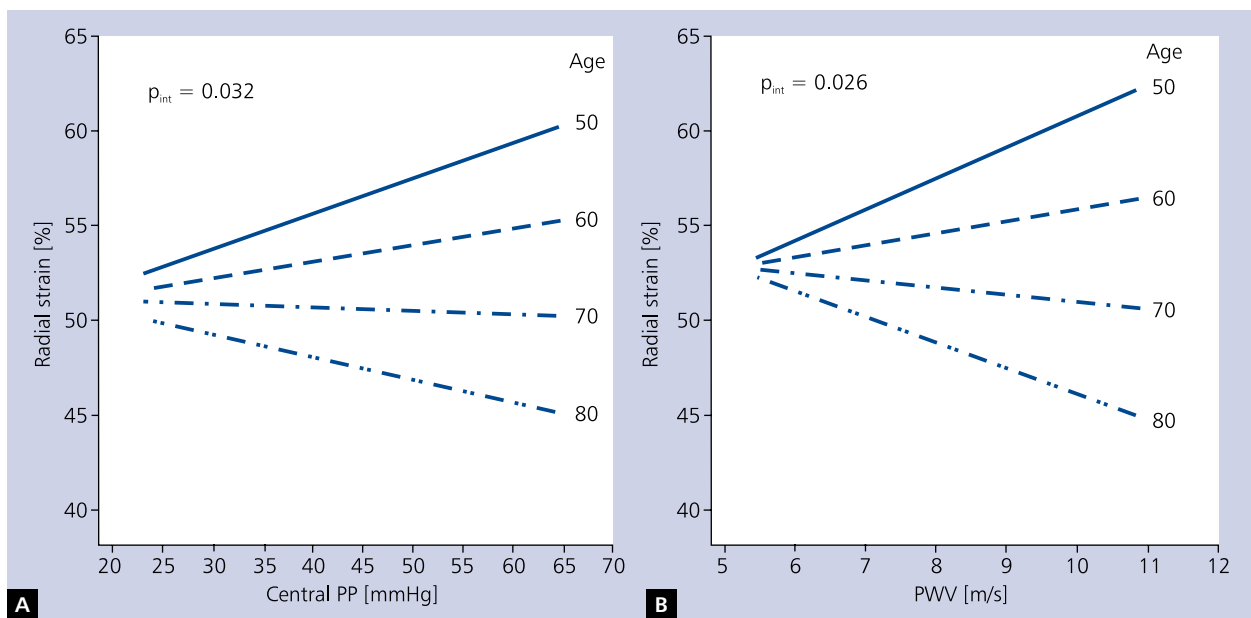
### ***LV radial strain and afterload***

Overall, LV wall stress is suggested to be higher longitudinally than circumferentially due to differences in LV curvature [66]. Therefore, an increased afterload might less affect the circumferential fibres within the midwall than the longitudinal fibres in the subendocardium [57, 66]; an experimental aortic banding model showed disparate changes in longitudinal and radial deformation in response to an acute increase in LV afterload [67]. Whereas longitudinal systolic function decreased dramatically, LV radial strain was still preserved upon mild aortic banding [67]. Similarly, in both hypertensives and diabetics at early stage of disease, decreased LV longitudinal deformation was compensated by an increase in LV radial function [59–61, 68].

Along these lines, we reported an age-dependent relationship of changes in LV radial systolic deformation with early and late systolic load in a general population (Fig. 5) [42, 69]. Radial strain increased significantly with higher central pulse pressure, haemodynamic load components, and PWV in middle-aged participants only, whereas it decreased with these indexes in subjects above 70 years old [42, 69]. Overall, a chronic rise in afterload and, in turn, LV load might thus enhance the circumferential/radial systolic performance of the left ventricle initially as a compensation for the decline in longitudinal deformation and might only lead to an impairment of radial (and circumferential) deformation in the long run [25]. To date, however, there is a compelling need for serial imaging studies in the general population to clarify to what extent a long-term LV overload, e.g. due to hypertension and arterial stiffening, contributes to subclinical impairment of the different LV strain components and whether this happens in a sex-dependent way.

## **ANTIHYPERTENSIVE AND DE-STIFFENING STRATEGIES FOR HEART FAILURE PREVENTION**

Targeting the risk factors of preclinical LV remodelling and dysfunction may be the most cost-effective strategy to reduce the massive burden of HF on societal health and healthcare [30]. As such, BP reduction is important in primary prevention of symptomatic HF. Indeed, it has been shown to decrease the risk of HF by reversing adverse myocardial remodelling processes related to hypertension. For instance, Verdecchia et al. [70] undertook a meta-regression analysis of 31 eligible trials, including 225,764 patients and 6469 new cases of symptomatic HF, to study the effects of antihypertensive drugs in the prevention of congestive HF in patients with hypertension or at high cardiovascular risk. Overall, the risk of new-onset HF significantly decreased by 24% per 5-mmHg reduction in



**Figure 5.** Extrapolation from a multivariable-adjusted model of radial strain in relation to indexes of arterial stiffness at fixed levels of age. Radial strain increased significantly with higher central pulse pressure (PP) (**A**) and pulse wave velocity (PWV) (**B**) in middle-aged participants only, whereas it decreased with these indexes in subjects above 70 years old. The number at the extrapolation line indicates the level of age.  $p_{int}$  indicates the p-values for interaction between the arterial indexes and age. Reproduced from Cauwenberghs et al. [42] with permission

systolic BP. Moreover, BP-lowering drugs were shown to reduce LV mass [71] and improve LV diastolic function [72] thus reversing two major cardiac consequences of hypertension. Studies investigating sex-specific effects of anti-hypertensive treatment on LVH came to discrepant and inconclusive findings so far [73–76]. As such, more research is required to elucidate a potential sex-dependent response of the heart to antihypertensive therapy, but optimal BP control appears to be an effective strategy to diminish subclinical maladaptation of the heart in both men and women.

As reviewed elsewhere [77, 78], antihypertensive drugs might also reduce arterial stiffness, especially calcium channel blockers and those targeting the renin-angiotensin system [79]. However, current non-invasive measures of arterial stiffness are BP-dependent, making it hard to distinguish the beneficial BP-lowering effects from those caused by de-stiffening of the arterial wall. In addition to BP-lowering drugs, statins, anti-diabetic drugs, advanced glycation end-products, cross-link breakers, and anti-inflammatory drugs have been proposed to lower arterial stiffness, but are still under development or validation [80]. On the other hand, favourable effects of physical activity [81–85] and weight reduction [86] on arterial stiffness have been described in both healthy individuals and in patients with cardiovascular risk factors. So far, large-scale, long-term, randomised controlled trials remain essential to investigate the protective effects of pharmacological interven-

tion or lifestyle modification on arterial stiffness and, in turn, on (sub)clinical LV maladaptation in both men and women.

## CONCLUSIONS

Subclinical LV abnormalities such as impaired LV longitudinal deformation, diastolic dysfunction, and LVH are highly prevalent in the general population and predispose to cardiovascular morbidity and mortality in both men and women. Hypertension and arterial stiffening initiate and accelerate the progression of early LV remodelling and dysfunction and, in the long run, contribute to the development of heart failure. Elevated BP and stiff arteries are important mediators of LV concentric remodelling and hypertrophy in both men and women. However, women appear to be more susceptible to the detrimental effects of increased pulsatile load on LV diastolic function. Overall, women have a higher aortic pulsatile load and stiffness, enhanced LV systolic performance, and a lower LV compliance as compared to men, which might explain the female predominance in HFpEF. A comprehensive assessment of cardiac function and structure for risk stratification is important in both men and women. Likewise, preventive strategies such as BP control and management of arterial stiffness hold great potential to reduce the development and surging burden of HF on our society.

**Conflict of interest:** none declared

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**Cite this article as:** Cauwenberghs N, Kuznetsova T. Sex-specific differences in cardiac maladaptation to hypertension and arterial stiffening. *Kardiologi Pol*. 2018; 76(9): 1303–1311, doi: [10.5603/KPa2018.0158](https://doi.org/10.5603/KPa2018.0158).