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Sex differences in left ventricular remodelling and heart failure development

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Abstract

There are significant differences in physiology, hormonal influences, the type of coronary blood vessel network and clinical course of myocardial infarction between men and women. The purpose of this review is to describe sex differences during the remodelling process after myocardial infarction (MI) which is crucial for heart failure (HF) development. After MI, more adverse left ventricular dilatation is observed in men but it appears that women have a different way of unfavourable LV remodelling such as concentric LV remodelling or concentric hypertrophy and worse prognosis. Sex paradox is observed with higher 30-day mortality in women compared to men and therefore, women are more vulnerable to ischemia. Moreover, women have higher rates of microvascular dysfunction detected by impaired coronary flow reserve, higher rates of distal embolization and more cases of no-reflow phenomenon. Therefore, impaired myocardial perfusion after AMI is more frequent in women in comparison to men. Furthermore, female gender is the predictor of higher mortality, reinfarctions occurence and heart failure development in patients with ST elevation MI, regardless of age or other comorbidities. It seems that prolonged reperfusion time, less frequent restoration of TIMI 3, different plaque characteristics, pulmonary vascular function, endothelial inflammation, coronary microvascular dysfunction, more common secondary mitral regurgitation, all together driven by co-morbidities, contribute to poor prognosis in females. A better understanding of the underlying mechanisms of sex related differences in remodeling course after MI, will be one way to improve individual treatment modality, beneficial for both sexes.

Introduction

Risk factors of myocardial infarction

Numerous studies in the past and nowadays, including randomized clinical trials and registry data, have constantly reported significant gender-based differences in risk factors puzzle, clinical, angiographic and procedural characteristics as well as in the outcome in patients with myocardial infarction [1-3]. Females with coronary artery disease are older with higher prevalence of risk factors and co-morbid diseases, fewer prior MI, fewer revascularization procedures and less extensive epicardial coronary artery disease. However, they had worse outcomes, including post MI complications, higher incidence of heart failure (HF) and mortality rates [3].

Traditional risk factors

Aging: Recent studies showed unfavorable long-term prognosis in females after menopause and more frequent occurrence of heart failure after MI among female patients [4]. In general, when compared to men, women develop ischemic heart disease 7-10 years later. Acute MI occurs 3-4 times more frequently in men, but after 75 years of age female gender predominates [5]. However, the annual incidence of acute MI hospitalization (from 1995-2014) significantly increased for young women (p for trend=0.002) but decreased for young men (35-54 years) [6]. Although the trend of acute MI extends to younger patients, the gender differences in vulnerability are widely related to sex hormones. Compared to men, women at a younger age with acute MI had a greater co-morbidities burden especially cardio-metabolic risk factors such as hypertension, obesity, tobacco smoking; all of the above have more pronounced effects in women than in man and, according to ICACS-TC registry, with higher early mortality rate [6-9]. Diabetes mellitus was a relevant risk factor to predict death with statistical significance in younger patients where sex difference in mortality was largely apparent [9,10]. Women with diabetes mellitus (DM) had greater evidence of adverse LV remodelling after MI, with increased LV thickness and LV mass index earlier along the diabetic continuum [10].

There is also a significant difference between men and women in the secondary prevention of traditional risk factors, usually significantly less effective in women [11].

Additional female specific risk factors

Non-conventional, but very important and verified risk factors for LV remodelling and HF in female population are as follows: preterm delivery, hypertensive pregnancy disorder, gestation diabetes mellitus, breast cancer treatments by radiation or chemotherapy, autoimmune disease such as Rheumatoid arthritis or Systemic Lupus and depression [11].

Pregnancy related disorders are associated with CVD risk. Occurrence and severity of hypertensive and metabolic pregnancy disorders are correlated with severity of later CVD [12]. For most systemic autoimmune disorders there is a clear sex difference in their prevalence. The microvasculature injury in those patients may play an important role in accelerated ischemic heart disease [13].

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There is also a high risk of CAD in women after incidental exposure of the heart to ionizing radiation during radiotherapy for breast cancer [14]. Breast cancer patients treated with chemotherapy may be at risk of two types of cardiotoxicity (anthracycline like and trastuzumab like agents); the both types are dose dependent. Delayed cardiotoxicity can vary from LV dysfunction to overt HF, arrhythmias, or ischemia.

The impact of obesity or overweight and physical inactivity as a risk factors for ischemia, LV remodeling and HF are higher among women than among men [15].

Recent studies showed all of the mentioned risk factors to have been associated with higher risk of morbidity and mortality in women with ischemic heart disease [14-16].

Relevant Sections

Reperfusion: female specifics

Several contributing mechanisms have been proposed to explain different responses of ischemic injury in different sexes, such as modified sensitivity to platelet aggregation and ischemic preconditioning [17]. Females show greater resistance to ischemic injury, e.g., ischemic preconditioning and promising reperfusion pattern (18). On the other hand, prolonged reperfusion time, less frequent restoration of TIMI 3, different plaque characteristics (more diffuse and non-obstructive pattern) as well as impaired pulmonary vascular function, more extensive inflammation, more common secondary mitral regurgitation in females compared to males; all of the above do not result in higher rate of infarction in women but do contribute to poor prognosis in females [5]. In a prospective observational cohort study among 1465 young patients (aged from 18 to 54) women had more often reperfusion delays than similarly aged men [3,18]. Recently it has been shown that women had a distinct cardiovascular blood flow reactivity after p PCI regardless of time of hospital admission and higher rates of post p PCI TIMI flow grade 0-2 than man only in patients aged >60 years [19]. Smaller diameter of female epicardial coronary arteries with very high baseline myocardial blood flow could result in higher endothelial shear stress condition in woman. [5]. The WISE study highlights the importance of microvascular cardiac network after MI [20]. Higher prevalence of microvascular disease and a more diffuse pattern of atherosclerosis in coronary vasculature in women is probably responsible for more frequent anginal episodes after myocardial infarction and/or revascularization procedures in women [20,21].

According the "Virgo study, a more favourable response to reperfusion in young women is not accompanied by better clinical outcomes. The so-called «gender paradox» describes the fact that despite similar infarct size and left ventricular function, women have higher in-hospital complications, major bleeding and 1-year mortality from heart failure, as well as higher rates of re-hospitalization for a new acute coronary syndrome or heart failure [2,17,18]. Furthermore, sex is the predictor of higher mortality in STEMI patients, independent of age and risk factors [3]. Even with better angiographic status before pPCI (less obstructive coronary artery disease and better TIMI 3 flow) in younger females (below 60 years) with STEMI, after adjustment for cofounders, mortality rates stay twice higher than in age-matched men [21].

After effective reperfusion, myocardium in the infarction zone may increase its contractile function and recover regional and global LV function. While women may have lower rates of myocardial scar, fibrosis, wall thinning and dilatation to irreversible late remodelling, they have limited coronary reserve and microvascular disorders resulting in coronary vasospasm secondary to endothelial injury and/or distal embolization [22]. Functional and structural microcirculation injury after MI among females is associated with cardiomyocyte myocardial injury in IHD and consequently with diastolic dysfunction and HF p EF phenotype [23-25].

Therefore, optimal reperfusion and revascularisation must include not only early and sustained epicardial patency, but also optimal microvascular flow and tissue reperfusion.

Sex-related differences in remodelling

The cellular and extracellular response to myocardial infarction

By definition, in response to the hemodynamic changes and systemic neurohumoral activation associated with myocardial infarction (MI), the heart undergoes series of alterations in the geometric, cellular and extracellular composition, a process called remodelling [5]. Acute loss myocardial tissue is connected with structural and mechanical changes such as collagen deposition, excitation-contraction uncoupling, apoptosis, and fibrosis to preserve cardiac function and minimize myocardial stress. Immediately after the myocardial infarction the healing process occurs to compensate for the absence of regional function and is reflected in the complex interplay between inflammation and fibrosis.

Different characteristics of the normal myocardium suggest that different molecular response occurs between males and females in response to MI [10]. Furthermore, post mortem data studies suggested that males have 10-fold higher rate of apoptosis than men and females have different mechanisms of infarct healing, tissue repair, degradation of extra-cellular matrix and myocardial slippage [26,27,28]. Indeed, some gene mutations responsible for different remodelling phases and process are expressed at different levels among males and females [29].

Of the pathophysiological mechanisms aimed at explaining the gender-related differences in remodelling, the most investigated is the cardio-protective role of the main circulating female sex hormone-estrogen [30-33]. Deficiency of estrogen provides conditions for high vascular stiffness and consequently diastolic dysfunction, higher blood pressure as well as HFpEF development [33]. Moreover, estrogen is known to modulate natriuretic peptides and activates angiogenesis, which support elevated oxygen demand in hypertrophic heart [30-33].

Delayed deposition of fibrosis and apoptosis in females, excessive amount of collagen into the extracellular matrix, increased extent of inflammation, might be the reasons for cardiac dysfunction and late post-infarction complications in females [34-36]. All of the mentioned cardiac processes are underlying in different volume pressure LV remodeling pattern after MI.

Hemodynamic and functional patterns of LV remodeling after MI

The course of the remodelling process depends on the level of peri-infarction apoptosis and/or necrosis pathway. It has been proposed that the expansion lasts hours after the MI, but extension is due to changes in non-ischemic myocardium is ongoing during weeks and months after MI [35]. Heart remodelling can also be classified as a dynamic process with an adaptive and maladaptive phase; the initial adaptive phase enables the heart to normalize wall stress and preserve cardiac output, in the acute phase of cardiac injury. [36,37].

Hypertrophy and dilatation of spared myocardium in the chronic course, significantly contribute to the clinical outcome [34]. LV hypertrophy is possibly associated with structural, metabolic, and functional alteration, disturbance of myocardial flow and heart failure

development [37]. Volume and pressure overloads or a combination of both cause different LV geometric patterns with distinctive pathophysiologic modalities, which are very important for risk stratification in patients after MI [38,39]. In Valliant Echocardiographic study authors showed that concentric LV hypertrophy (increased basal LV mass and index of relative wall thickness) carries the greatest risk of advanced cardiovascular events after MI including death [39,40]. According to the recent findings, women better tolerate volume and pressure overload with less myocardial fibrosis, dilatation, and mass/volume ratio, but they may be related to higher wall stress and filling pressure [11,38]. Among post MI patients, the identification of any LVH pattern in women is associated with greater impact on outcome than in men [38]. Progression toward HFpEF occurs in women more often than in man through faster intermediate step between condition and disease [37-40].

The uncoupling of LV remodelling and heart failure in different sexes has not been sufficiently clarified in the literature so far.

Sex diversity in heart failure development

Recent study showed that women are at higher risk to develop de novo HF after STEMI and women with de novo HF have worse survival rate than their male counterparts [16].

Women are more likely to have a preserved systolic function, e.g. heart failure with preserved ejection fraction (HFpEF) while heart failure in man is more common with reduced ejection fraction (HFrEF). Indeed, half of the women and only one-third of men with HfpEF are presented with clynical symptoms of heart failure [42]. The latest studies showed that the central hypothesis for higher risk of HfrEF in man compared to women is their predisposition for dominant macrovessel coronary artery disease. However, coronary microvascular dysfunction plays a key role in remodeling proces and HFpEF development with dominant diastolic LV dysfunction in women [36,37]. Recent research has identified several contributing factors including limitation of systolic LV reserve,systemic and pulmonary vascular function, right ventricular function, autonomic tone and chronotropic reserve [16,40,43]. Microvascular injury (functional and structural), pro-inflammatory state and endothelial dysfunction transferred to cardiomyocites is followed on by final fibrosis and downstream of LV diastolic dysfunction [4,23,40]. Furthermore, women are more prone to develop stiffer heart with smaller stroke volume, consequent limitation of diastolic LV reserve including higher wedge pressure and LV filling pressure, impaired ventriculo-vascular coupling compared to men [23,32,35].

The patterns of LV hypertrophy have been reported to yield incremental prognostic information in patients with post MI HF [5,39]. All patients with HFpEF show an increase in end diastolic pressure; majority of females have concentric LVH with higher LVEF, worse diastolic filling and less co-morbidities (atrial fibrillation, 55% vs. 68%, anemia 61% vs. 73%, sleep apnea 5% vs. 20%, COPD 27% vs. 47%, in women vs. men, respectively) [23,37,39]. Duca et al. [24], also demonstrated that men with HFpEF have higher EDV and stroke volume but also a greater degree of RV involvement, e.g., RV dilatation and impaired RV function as well as lower aerobic capacity compared to women. Recent data from two clinical studies (CHARM, TOPCAT) showed that prior MI in patients with HF p EF is associated with greater cardiovascular and sudden death and worse HF outcomes [37]. In the meta-analysis of 10 randomized studies of patients with acute ST elevation MI treated with primary PCI, Kosmidou et al. showed that women had significantly higher LVEF measured by NMR technique, but there was no difference in infarction size, measured by SPECT, among men and women [5]. However, after adjustment for important baseline factors, women had a significantly higher risk of all death causes and HF hospitalization after a 12-month follow-up period. Authors did not focus on the influence of LV diastolic function during the reshaping or degree of mitral regurgitation after MI in men and women but noted that two-thirds of hospitalized HFs in women were HFpEFs.

Reverse LV remodeling is there any difference?

It was recently shown that long term neurohormonal blockade (sympathic, renin angiotensin aldosterone and inflammatory cytokine system) ameliorate the remodelling process or moderately restore LV structure and function (reverse remodelling) mostly based on the process known as "myocardial recovery [26,45]. Thus, the changes in LV volume occur secondary to the myocardial recovery process. Reverse remodelling (RR) is a complex process of restoration of chamber geometry and function including corrections of molecular and transcriptional abnormalities. It is already known that RR is associated with a decrease in myocardial cell size, reduction in total collagen content, increase of microvascular density, hemodynamic unloading as well as restoration of cardiac biomarkers and exercise capacity [26].

In patients with HF r EF reverse remodeling was projected and confirmed [26]. Beneficial effects of exercise, ACE inhibitors, beta-blockers have been shown to be very promising for attending or reversing changes in extracellular matrix (ECM), in particular collagen iso-forms modulations, during the process of RR [45].

It is observed that favorable clinical course with reverse remodeling occurs spontaneously or with myocardial revascularization, surgical, pharmacological, or device therapy [46]. The term "ventricular remodeling", described as progressive LV dilatation and diminished LV function after coronary artery occlusion has been changed over the years demonstrating clear dissimilarity in remodelling between HFrEF and HF p EF. Furthermore, therapeutic modality for RR should be different for HFpEF and more often present in females after MI [41,45].

Sex differences in risk factors, remodelling and heart failure are presented in Table1.

Variations in cardiovascular pharmacotherapy

The sex-related differences in prescription and adherence as well as the efficacy and safety of cardiovascular drugs are well established but underappreciated in everyday clinical practice. Biological differences among sexes in body composition, fluctuations in sex hormones, clinical characteristics and specificity of myocardial infarction and remodeling pattern significantly influence effective response of cardiovascular therapy [47,48]. On one side, some physiological differences in medication pharmacokinetics do not translate into clinically meaningful differences, while others can substantially affect pharmacodynamic and produce therapeutic outcomes differently in

Table 1. Sex differences in post infarction remodelling process

Types of remodelling	Females	Males
Structural and functional	Concentric	Eccentric
Cellular modulation	Extension (infarction zone)	Expansion (peri-infarction region)
Hemodynamic	Reverse	Non reversing
Heart failure development	HFpEF	HFrEF
Standard therapy responding	Lower	Better
Reperfusion responding	Lower	Better
Adaptive/Maladaptive	Late	Early

men and women. For instance, recent study suggested that women with HFrEF might need lower doses of ACE inhibitors or ARBs and β blockers then men. Furthermore, there are no additional benefits with increased doses or up titration to the peak value of all HFrEF medications [41]. In active controlled trial Paragon HF the authors showed the therapeutic benefit of sacubitril-valsartan (ARNI) in reducing the risk of heart failure hospitalization is more significant in women than in men. The same study showed that valsartan alone (without neprilisin inhibitor) in therapy of HFpHF reflected lower efficacy in women compared to men [24]. In patients with HFrEF women appear to obtain more benefit from cardiac re-synchronization therapy but less from digitalis [49]. Furthermore, the effect of digoxin therapy in patients with HFrEF is associated with an increased risk of death from any cause and worsening of heart failure among women, but not among men [50]. In patients with HF included in TOPCAT study, sex specific analysis showed that women appeared to benefit across the whole LVEF spectrum, whereas in men this was the case only at a lower LVEF [51].

There are indications that women are less likely to receive evidence-based medical therapy in primary and secondary prevention of atherosclerotic cardiovascular disease. Women with similar cardiovascular risk receive less often antiplatelet and lipid-lowering drugs than men but also neurohormonal antagonists (blockers of renin-angiotensin system, beta-blockers, and mineralocorticoid receptor antagonists) [49]. Some of the adverse drug reactions are more prevalent and more severe in women with the higher risk of bleeding and hemorrhagic stroke after PCI, diuretic-induced electrolyte abnormalities (hyponatremia and hypokalemia), antiarrhythmics-induced QT prolongation and torsades the pointes, which could be a piece in the puzzle for worse outcome after myocardial infarction in women (Table 1) [48,52,53]. Personalized pharmacological treatment with dose-adjustments in the female population would answer the question of true optimal therapy for men and women.

Conclusion and future directions

Existing differences in adverse LV post infarction remodelling are due to complex interaction of cellular, extracellular, molecular neurohormonal and inflammatory factors as well as gene vicinity expression. Substantial differences between men and women in a variety of cardiovascular risk factors and secondary prevention, cellular and hemodynamic response after myocardial infarction, different coronary macro and micro circulation modulations are the most important factors for diverse patterns of LV remodelling. An integrated assessment of these multiple parameters, together with the effectiveness of cardiovascular therapy, provides a better insight into the different types of HF in men and women. Better understanding of the factors and processes leading to differences in remodelling course after MI between men and women will be one way to adopt the novel individual treatment modalities and ultimately benefit patients of both sexes.

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