



Gender differences in cardiac hypertrophic remodeling

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Abstract

Cardiac remodeling is a complex process that occurs in response to different types of cardiac injury such as ischemia and hypertension, and that involves cardiomyocytes, fibroblasts, vascular smooth muscle cells, vascular endothelial cells, and inflammatory cells. The end result is cardiomyocyte hypertrophy, fibrosis, inflammation, vascular, and electrophysiological remodeling. This paper reviews a large number of studies on the influence of gender on pathological cardiac remodeling and shows how sex differences result in different clinical outcomes and therapeutic responses, with males which generally develop greater cardiac remodeling responses than females. Although estrogens appear to have an important role in attenuating adverse cardiac remodeling, the mechanisms through which gender modulates myocardial remodeling remain to be identified.

Key words

- gender
- hypertrophy
- pressure overload
- myocardial infarction
- myosin isoforms

INTRODUCTION

Cardiovascular diseases are the leading cause of death for both sexes in the world. In 2012 about 13% of deaths were due to ischaemic heart disease, and 11% to stroke. In Italy cardiovascular diseases are responsible for 37% of total deaths [1]. Preclinical and clinical data indicate that the female gender is less exposed to cardiovascular disease. Specifically, the incidence of cardiomyopathies and stroke is lower in premenopausal women than in men, whereas this trend decreases with age and rapidly disappears after menopause. The mechanisms responsible of these differences are not completely clear.

As it is well known, the anatomy and the physiology of the heart and the vascular system are similar in both sexes. However, minimal differences occur. In women, the heart is smaller, has an increased heart rate, has better performance indices, and is subjected to less control by the autonomic nervous system. Nevertheless, sex has a profound impact on the cardiac response to harmful insults such as ischemia and hypertension. Here we reviewed the literature comparing gender differences in cardiac response to high blood pressure or ischemia in humans as well as in animal models of post-infarction or hemodynamic overload-induced cardiac remodeling.

CARDIAC REMODELING INDUCED BY HEMODYNAMIC OVERLOAD

Cardiac remodeling develops in response to chronic hemodynamic overload, abnormal gene expression, or loss of cardiomyocytes caused by myocardial infarction or aging. The Framingham Heart Study, the first major epidemiological study by cohort to assess the risk of cardiovascular disease, indicated cardiac remodeling as a

negative prognostic factor, as the presence of hypertrophic echocardiographic signs was associated with an increased appearance of coronary ischemic events [2, 3], major incidence of stroke in an elderly cohort [4], and increased risk of sudden death [5]. Cardiac remodeling can be defined as a complex set of cellular, biochemical and molecular events that occur in response to cardiac injury or increased load (ischemia, pressure or volume overload) leading to chamber enlargement without a relative increase in its wall thickness (eccentric hypertrophy) or thickening of ventricular walls without chamber enlargement (concentric hypertrophy) (Figure 1).

Pressure overload is a common cause of cardiac remodeling and heart failure. Sustained pressure overload causes concentric cardiac hypertrophy. Conventional wisdom holds that pressure overload-induced hypertrophy represents a compensatory response aimed at countering the increased wall stress, to diminish oxygen consumption and to maintain cardiac systolic function (adaptive cardiac hypertrophy), but that unrelieved hemodynamic load can overwhelm these adaptive processes and result in heart failure.

Clinical studies suggest that sex-related factors influence the adaptive response of the heart to pressure overload. Garavaglia *et al.* evaluated sex differences in left ventricular adaptations to essential hypertension. Premenopausal women had smaller left ventricular thickness, diameter and mass and higher left ventricular performance indices compared with men with the same level of arterial pressure [6], which is in accordance with the results of other studies [7-11]. These sex differences tended to disappear after the menopause [6].

Sex differences in left ventricular (LV) remodeling

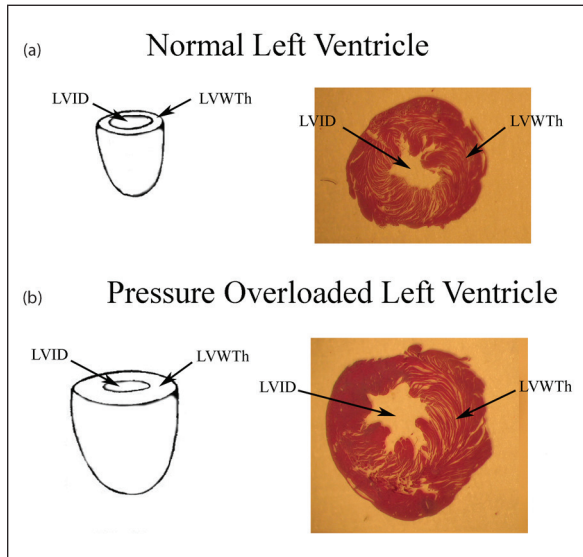


Figure 1

Aortic banding-induced cardiac hypertrophy. Representative hematoxylin and eosin staining of left ventricular cross sections from (a) sham-operated and (b) aortic banded mice, 2 weeks after surgery. Sustained pressure overload causes an increase in left ventricular wall thickness (LVWTh) whereas left ventricular internal diameters (LVVID) do not change. Consequently, the ratio of LV wall thickness to LV radius increases (concentric left ventricular hypertrophy).

and function preservation were also observed in patients with aortic stenosis. Despite a similar degree of left ventricular outflow obstruction (similar transvalvular aortic gradient and estimated aortic area), women developed more marked concentric hypertrophy, lower levels of wall stress, and higher indices of systolic function compared with men [12-16]. Similar results were also observed in premenopausal hypertensive women. Collectively, these results suggest that gender is a possible determinant of the cardiac adaptive response to chronic pressure overload. Additional evidence supporting the presence of sex related differences in LV adaptation to pressure overload derives from preclinical studies. In spontaneously hypertensive rats (SHR), Pfeffer *et al.* [17] observed that female SHR had better indices of systolic function and smaller end-diastolic and end-systolic dimensions compared with male SHR, which also developed LV dysfunction and heart failure after 12 months of age. In the aortic banding-induced pressure overload model, Douglas *et al.* [14] found that male but not female rats showed LV chamber dilation, loss of concentric remodeling and elevated wall stress 20 weeks after surgery. In line with this study, Weinberg *et al.* [18] reported that, in comparison with males, females developed higher LV pressures in the isolated heart 6 weeks after banding, despite a similar degree of LV hypertrophy and systolic wall stress.

Valvular heart disease is another cause of pathological remodeling. Volume overload leads to eccentric cardiac hypertrophy with increased ventricular diameter but reduced relative wall thickness and preserved systolic function. Rohde *et al.* [19] demonstrated that, in com-

parison with men, women with pure aortic regurgitation had smaller LV mass and volume indexes. In a preclinical model of volume overload induced by aortocaval fistula, Gardner *et al.* [20] found that female but not male rats showed minimal mortality and no significant LV dilatation after fistula surgery. Altogether, these results indicate that gender influences the evolution of the cardiac response to hemodynamic overload.

GENDER DIFFERENCES IN GENETIC MOUSE MODELS OF CARDIAC REMODELING

Important differences in the development of the hypertrophic process between males and females have also been observed in experimental models of genetically modified animals. In transgenic mice overexpressing phospholamban protein and with increased levels of circulating catecholamines, males have an earlier onset of hypertrophy, and die before females [21]. In addition, the genetic inactivation of FKBP12.6, a binding protein that modulates the activity of the cardiac ryanodine receptor, caused cardiac hypertrophy in male but not in female mice [22]. Finally, in a mouse model of hypertrophic cardiomyopathy associated with the mutation R403Q of α -myosin heavy chain, male mice developed a progressive dilatation of the left ventricle and a reduced heart systolic function. In contrast, female mice with a similar degree of cardiac hypertrophy showed preserved ventricular performance without chamber dilation [23].

GENDER DIFFERENCES IN POST-INFARCTION CARDIAC REMODELING

Cardiac remodeling after myocardial infarction (MI) is characterized by infarct expansion, hypertrophy of surviving myocardium, increased collagen deposition, geometric changes in chamber shape, and eventual progression to heart failure. Epidemiologic and animal studies suggest that sex significantly affects cardiac remodeling after MI.

Cavasin *et al.* [24] compared LV remodeling after MI in male and female mice. They reported that mortality and cardiac rupture during the first week after MI were significantly higher in males than females. In addition, male mice had more pronounced neutrophil infiltration at the infarct border zone with increased metalloproteinase activity and a higher infarct expansion index. During the 12 weeks after the ischemic insult, males showed worse LV function, and more extensive remodeling, with more cardiac chamber dilation and myocyte hypertrophy. In contrast, females had 3 times lower mortality despite similar infarct size and showed a better outcome during the development of heart failure. In line with these results, Wu *et al.* [25] found that female mice with MI underwent less extensive LV remodeling than males, with less chamber dilation and a better preserved LV systolic function. Additional evidence for sex impact on myocardial remodeling after MI derives from an experimental study performed in rats by Litwin *et al.* [26]. They demonstrated that male rats had a greater increase in LV posterior wall thickness, higher myocyte diameter in the non-infarcted region, and greater diastolic dysfunction compared to female rats 6 weeks af-



ter MI. A clinical study published by Crabbe *et al.* [27] supports preclinical results with women having less myocyte hypertrophy in post MI LV remodeling than men. Collectively, preclinical and clinical results suggest that in the presence of myocardial infarction sex affects adaptive cardiac responses and that in females the heart is protected from chronic remodeling and deterioration of function after MI. Although there is evidence that sex hormones play an important role in post-MI cardiac remodeling, the mechanisms responsible for cardioprotection are unclear. Since estrogens can inhibit apoptosis in many cell types, it cannot be ruled out that males and females have a different modulation of the apoptotic pathway in the peri-infarct region. Indeed, in a post-mortem study, Biondi-Zoccai *et al.* [28] showed that in the peri-infarct region, males had a 10-fold higher apoptotic rate and greater gene expression of the apoptotic promoter Bax than women. Further evidence supporting the role of apoptosis in sex-related differences comes from patients undergoing transplantation for cardiac failure. Indeed, Guerra *et al.* [29] found that the magnitude of apoptotic and necrotic myocyte death differed significantly in women and men. The reduced incidence of cell death in women was associated with a longer duration of the cardiomyopathy, a later onset of heart failure, and a longer interval between diagnosis of cardiac dysfunction and transplantation.

ESTROGENS IN CARDIAC REMODELING

The impact of hormone replacement therapy on cardiovascular morbidity is a subject of much controversy in medical literature. Some studies, such as the "Heart and estrogen / progestin Replacement Study (HERS)" [30] and the "Women's Health Initiative Clinical Trial" suggest that hormone replacement therapy in postmenopausal women can increase the possibility of myocardial infarction, deep vein thrombosis and pulmonary embolism [31, 32]. Conversely, other studies report that female sex hormones improve the performances of contractile postmenopausal women [33-35] and their prognosis in myocardial ischemia [36-38]. In addition, results from clinical trials indicate that hormone replacement therapy reduces cardiovascular risk only if it starts within the first years after menopause [39-41]. This suggests that age- and menopause-related vascular endothelial injury, changes in vascular estrogen receptors expression, intracellular signaling or genomics may alter the cardiovascular effects of sex hormones [42].

Although the mechanisms responsible for the sex-related differences in cardiac remodeling are not completely understood, preclinical and clinical studies indicate that circulating sex hormones have an important role. Pines *et al.* [43] studied 30 postmenopausal women with borderline to mild hypertension to evaluate whether hormone replacement therapy (HRT) affects cardiac morphology. They found that HRT causes a significant reduction in left ventricular cavity dimensions and mass, which is in accordance with the results of other studies [44-46]. Other evidence that estrogens have antihypertrophic effects comes from preclinical studies. van Eickels *et al.* [47] reported that administration of estrogens in ovariectomized rats reduces the develop-

ment of aortic banding-induced cardiac hypertrophy by 30%. Jazbutyte *et al.* [48] showed that administration of an agonist of estrogen receptor β in ovariectomized spontaneously hypertensive rats lowers blood pressure thus preventing the increase in cardiac mass. Patten *et al.* [49] reported that estrogen treatment promotes cardiomyocyte survival in a murine model of myocardial infarction. In addition, Pedram *et al.* [50] observed that treatment with 17- β -estradiol, the most important circulating estrogen, is able to prevent angiotensin II- or endothelin-1-induced hypertrophy of cultured cardiomyocyte. Together, these results imply that estrogens exert their cardioprotective action through indirect and direct effects on vascular and cardiac cells.

The mechanisms of antihypertrophic effects of estrogens remain to be determined. Vega *et al.* [51] found that estrogens increase the expression in the left ventricle of the antihypertrophic protein MCIP1, which is able to inhibit the activity of calcineurin, a well-known hypertrophic inducer, which is in keeping with the results of other studies [52, 53]. Ma *et al.* [54] reported that in ovariectomized mice there is an increase of δ isoform of CaMKII, and that estrogen administration prevented this increase. The inhibition of CaMKII in ovariectomized mice produced cardioprotective effects similar to those obtained with the administration of 17- β -estradiol, further suggesting a possible mechanism underlying cardioprotective effect of estrogen [54].

SEX INFLUENCE ON FETAL GENE EXPRESSION

With a few exceptions, cardiac hypertrophic remodeling is characterized by cardiomyocyte hypertrophy associated with the remodeling of extracellular matrix and the re-activation of the fetal gene program which includes myosin heavy chain (MHC) isoforms, skeletal α -actin (skACT), and atrial natriuretic peptide (ANP), the expression of which is repressed in adult ventricular myocardium. In conjunction with these changes, a decrease in the adult cardiac muscle-specific genes, α -myosin heavy chain (α -MHC) and sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA) also occurs [55].

These changes may be interpreted as indicating that the fetal gene program, or at least a part of it, is involved in a complex adaptive process aimed at limiting cardiac energy consumption and supporting cardiac output in the presence of an increased cardiac workload. This view is consistent with: a) the poor tolerance to pressure overload of hearts in which the fetal gene response is abrogated; b) the cardioprotective action of ANP, a peptide endowed with natriuretic and antihypertrophic properties; c) the lower ATPase activity of β -MHC, able to generate a cross-bridge force with a higher economy and energy consumption than α -MHC; and d) the significant positive correlation between skACT cardiac amount and cardiac contractile function.

Although gender influence on the left ventricular remodeling has been studied extensively, the influence of sex on fetal gene expression has been poorly investigated. Reiser *et al.* [56] studied whether there is a sex-related difference in the level of β -MHC in the right and left atria of humans with cardiomyopathy. They found

**Table 1**

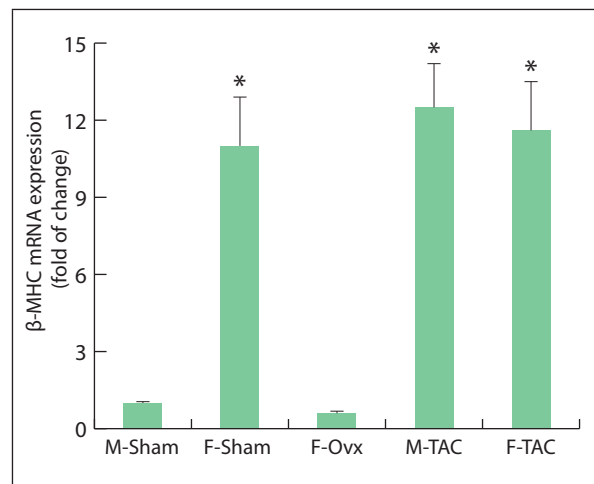
Sex-associated differences in cardiac remodeling responses to different injuries

Cardiac remodeling (females vs males)	
Clinical studies	Preclinical studies
Hemodynamic remodeling	
Hypertension	
Smaller left ventricular thickness, diameter and mass [6]	Better indices of systolic function in females SHR [17]
Higher left ventricular performance indices [6]	Smaller end-diastolic and end-systolic dimensions in females SHR [17]
Lower prevalence of LV hypertrophy [8]	Lower chamber dilation and wall stress after TAC [14]
Preservation of ejection parameters [10, 11]	Higher expression of β -MHC [57, 58]
Valvular heart disease	
More marked concentric hypertrophy [12]	Minimal mortality and no LV dilatation after fistula surgery [20]
Lower levels of wall stress [14, 15]	
Smaller LV mass and volume indexes [19]	
Higher indices of systolic function [13, 16]	
Postinfarction remodeling	
Smaller myocyte hypertrophy [27]	Lower mortality and cardiac rupture [24]
Lower apoptotic rate in the peri-infarct region [28]	Lower neutrophil infiltration and infarct expansion index [24]
	Smaller LV posterior wall thickness and diastolic dysfunction [26]
	Lower LV remodeling and better preserved LV systolic function [25]

significant differences in MHC isoform expression of failing atria between men and women and a twofold greater amount of β -MHC in the nonfailing left atrium of women compared with men. Villar *et al.* [16] determined the β -MHC gene expression in LV samples from patients with aortic stenosis and controls. They found no difference in MHC isoform expression between elderly men and woman. Sex-related differences have been reported by us [57, 58] in mice both in physiological conditions and under an increased pressure load induced by thoracic aortic coarctation (TAC), a preclinical model of pressure overload cardiomyopathy. We observed that in physiological condition β -MHC expression was tenfold higher in the LV of fertile female mice, compared to the age-matched males (Figure 2), whereas no difference was found in α -MHC expression [57, 58] (data not shown). However, gender difference in the β -MHC gene expression tended to disappear after ovariectomy or in the presence of hemodynamic overload induced by TAC [58] (Figure 2), as TAC increased β -MHC mRNA levels in males but not females.

CONCLUSIONS

There is evidence that gender affects cardiac response to pressure overload or ischemia in both humans and animals and that sex differences should be taken into account when studying cardiac remodeling in humans as well as in animal models (Table 1). Since cardiac remodeling is a prognostic negative factor in patients with chronic heart failure, a better understanding of the mechanisms through which gender regulates cardiac remodeling could open the way to innovative therapeutic strategies for heart failure therapy.

**Figure 2**

Sex-associated differences in cardiac expression of β -myosin heavy chain isoform. β -MHC mRNA expression in the left ventricles from male sham-operated (M-Sham), female sham-operated (F-Sham), and ovariectomized female (F-Ovx) mice of 12-weeks-old. M-TAC and F-TAC represent male (M-TAC) and female (F-TAC) mice subjected to thoracic aortic coarctation (TAC). * $p < 0.05$ = significantly different from M-Sham and F-Ovx.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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