Hypertensive Cardiac Remodeling in Males and Females
From the Bench to the Bedside

Christian F. Deschepper, Bastien Llamas

Cardiovascular diseases affect women and men differentially: there are sex-dependent differences in the age at which they become manifest, in the pathophysiologic consequences of various insults, in the relative importance of risk factors, and in the responses to several treatments (as reviewed recently).1,2 Although many of these differences may relate to modifications of the lipid profile, as well as differences in the functions of endothelial and/or vascular smooth muscle cells, it is becoming clear that direct actions within the heart itself must also be considered. The current review will, therefore, focus on sex-specific differences in the remodeling responses of cardiac ventricles to various challenges.

Sex-Dependent Differences in Cardiac Remodeling

At baseline, male and female hearts display several differences: (1) coronary artery size is smaller in women; (2) there are differences in the electrophysiological properties of the hearts, as females have faster resting heart rates and longer rate-corrected QT intervals4,5; (3) male and female hearts differ in terms of the pattern of expression of certain genes6; and (4) there are differences in the contractile properties of male and female hearts.7,8 More importantly, there are significant differences in the way male and female hearts respond to various challenges. In rodents, aortic banding-induced pressure overload increases left ventricular mass to the same extent in males and females, but function is better preserved in females.11 Differences in the remodeling responses can also be seen after myocardial infarction (MI), because female rats develop less thickening of noninfarcted regions and less pronounced diastolic dysfunction than their male counterparts,12 and post-MI rupture of the left ventricle is less frequent in female than in male mice.13,14 Aging (arguably the most common type of insult on human hearts) may also affect cardiomyocytes in a sex-specific fashion. For instance, various biochemical characteristics (including telomerase activity and several components of the insulin-like growth factor system) vary differently across the lifespan in male and female cardiomyocytes.15,16 Finally, there are several examples where modification of the cardiac expression of specific genes (either by transgenesis or inactivation) induces cardiac remodeling in male but not in female mice.17,18 With the exception of longer QT intervals (which increase the risk of “torsades-de-pointe” in females), males generally develop greater remodeling responses than females.2 The sex-related differences in remodeling of the whole heart are mirrored by differences in intracellular signaling pathways and/or patterns of gene expression. First, rat cardiac myocytes display sex-dependent differences in intracellular calcium concentrations under either baseline or stimulated conditions (which is important in light of the central role that calcium exerts on cardiac growth and function19), possibly because of differences in the capacity of the sarcoplasmic reticulum to handle calcium.20,21 Second, many genes respond to pressure overload in a sex-specific manner in rat hearts.22

The evidence listed above has been derived from experiments performed in animals. Direct comparisons with humans are not always possible, because clinical studies often enroll aged patients, where participating women are postmenopausal. Nonetheless, there is evidence that left ventricles remodel differently in women and men. For instance, women with aortic stenosis display more marked concentric hypertrophy, better preservation of systolic function, and less fibrosis than men.23,24 Likewise, hypertension induces mostly concentric hypertrophy in women but eccentric dilated hypertrophy in men.25 It also has been reported that left ventricular mass decreases in an age-dependent fashion in men but not in women.26 These age-related changes are paralleled at the cellular level, because the number of cardiomyocytes decreases with age and their volume increases in men but not in women.27 Microarray experiments have also revealed that sex had a greater effect than heart failure on the cardiac transcriptome in human hearts.6 Of note, premenopausal women do not always fare better than men. When cardiac complications do develop in women, they often have more negative consequences than in men.1 Women are also more vulnerable than men to specific pathologies, such as idiopathic dilated cardiomyopathy or alcohol-induced cardiac disease.17

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From the Experimental Cardiovascular Biology Research Unit, Institut de Recherches Cliniques de Montréal, Montréal, Quebec, Canada; and the Université de Montréal, Montréal, Quebec, Canada.

Correspondence to Christian F. Deschepper, Institut de Recherches Cliniques de Montréal, 110 Pine Ave West, Montréal, Quebec, Canada H2W 1R7. E-mail christian.deschepper@ircm.qc.ca

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Several lines of evidence suggest that differences in the steroid environment may be (at least in part) responsible for some of these sex-dependent differences. First, there is no sex-related difference in heart size before puberty. Second, in young premenopausal women, cardiovascular risk increases when estrogen production stops, for instance, as a result of surgery. Of note, the presence of functional estrogen receptors on both cardiac myocytes and fibroblasts, as well as that of functional androgen receptors in cardiomyocytes from several species, are compatible with the notion that sex steroids may exert direct effects on the hearts, as will be discussed in the following paragraphs.

Cardiac Effects of Estrogens
In young adult rats, ovariectomy abolishes the female-specific protection against volume overload–induced adverse remodeling and attenuates the effect of age on ventricular remodeling. Conversely, administration of estradiol to ovariectomized female rodents attenuates the remodeling induced by either pressure overload or aging. The effects of estrogens on postmyocardial infarct remodeling are a bit more controversial. Some have reported in Sprague–Dawley rats that estradiol had deleterious effects on ventricular mass and acute mortality but prevented later dilated remodeling. Others have found no evidence of such effects of physiological replacement of estrogens in Wistar rats but found that high pharmacological doses of estradiol prevented post-MI remodeling. In C57Bl/6J mice, others have reported that, despite diminished infarct size and reduced cardiomyocyte apoptosis, estradiol-treated mice had greater increases in left ventricular mass and enhanced post-MI mortality. Finally, systemic deletion of estrogen receptor (ER)β increases mortality and aggravates clinical and biochemical markers of heart failure in the post-MI period.

In addition to its effects on cardiomyocytes, estradiol also affects age-induced changes in collagen isoforms and metalloprotease activity, indicating that the antiremodeling effects of estradiol are not limited to cardiomyocytes but may also affect noncardiac cells, as well as the extracellular matrix. The latter finding is compatible with the observation that estradiol inhibits the proliferation of cardiac fibroblasts and their capacity to produce collagen. Mast cells constitute other types of noncardiac cells that are postulated to play important roles in ventricular remodeling. The effect of either pressure overload or age on ventricular remodeling has been shown to be greatly attenuated in genetic rodent models that are devoid of mast cells. The cause–effect relationship among myocardial mast cells, matrix metalloprotease activity, and volume overload–induced ventricular remodeling has also been demonstrated by pharmacological inhibition of mast cell degranulation. Importantly, estrogens also inhibit cardiac mast–cell–mediated extracellular matrix degradation, an effect that probably participates in the protective effect of ovarian hormones against volume overload–induced hypertrophy. In humans, transdermal estradiol has been shown to increase the effect of standard antihypertensive therapy on left ventricular mass reduction. Despite all of the evidence listed above, the effects of estrogens on left ventricular remodeling cannot be considered as consistently positive, as shown for instance in some models of post-MI remodeling.

In keeping with the many cardioprotective effects of estrogens identified mostly in animal models, these compounds have been reported to recruit several protective mechanisms and to activate protective signaling pathways, as well as to inhibit several potentially harmful mechanisms or pathways, as summarized in the Table. For instance, estradiol inhibits pressure overload–induced hypertrophy via induction of the production of atrial natriuretic peptide and, thus, via activation of intracellular cGMP, which has been shown to be sufficient to inhibit pressure overload hypertrophy.

The Presence of Estrogens or the Absence of Androgens?
When considering the causes of reduced cardiovascular risk in premenopausal women, much more attention has been paid to the potential protective effects of estrogens than on the possible deleterious effects of androgens. However, the absence of a clear and sharp break point in the rise of female cardiovascular risk at menopause has led some to challenge the estrogen protection hypothesis. The fact that the prospective Hormone and Estrogen/progestin Replacement Study (HERS) Trial of estrogen replacement therapy actually increased cardiovascular risk in healthy postmenopausal women has reinforced this thinking. Several lines of evidence indicate that androgens may be (at least in part) responsible for some differences in the cardiovascular systems of males and females. For instance, the higher plasma concentration of high-density lipoprotein in women is because of the fact that androgens decrease high-density lipoprotein cholesterol and not because of the fact that estrogens increase it. In male mice, the increased risk of post-MI rupture of the ventricular wall is because of testosterone; however, estrogens may decrease the risk in males by virtue of their testosterone-lowering effects. Likewise, much of the sex-dependent differences in adult mouse cardiac repolarization are because of the effects of androgens. There are also several rat models where higher levels of blood pressure in males are explained by a deleterious effect of testosterone but not by a blood pressure–lowering effect of estrogens.

### Table: Mechanisms Possibly Involved in the Cardioprotective Effects of Estrogens

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>References</th>
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<tr>
<td>Increased production of atrial natriuretic peptide</td>
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<td>Upregulation of NOS synthases</td>
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<td>Increased nuclear Akt activity</td>
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<td>Decrease apoptosis of cardiomyocytes</td>
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<td>Decreased phosphorylation of p38 mitogen-activated protein kinase</td>
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<td>Decreased B-type endothelin receptors in cardiomyocytes</td>
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<td>Decreased expression of the cardiac L-type calcium channel</td>
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<td>Decreased production of tumor necrosis factor-α</td>
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</tr>
<tr>
<td>Decreased angiotensin-converting enzyme</td>
<td>95</td>
</tr>
<tr>
<td>Decreased angiotensin AT1 receptors</td>
<td>41, 96</td>
</tr>
</tbody>
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Likewise, there is evidence that antiandrogen treatment of hypertensive rats with flutamide decreases end-organ damage in heart and kidneys\(^{55}\); however, the interpretation of these data is not clear cut, because flutamide has also been found to have cardiovascular actions that are androgen receptor independent.\(^{56}\) In vitro, androgens have been reported to induce apoptosis in cardiomyocytes.\(^{57}\) The possible effects of androgens on cardiac remodeling are compatible with the report that cardiomyocytes contain functional and responsive androgen receptors.\(^{58}\)

Despite the findings listed above, there is no clear-cut evidence that androgens are deleterious from a cardiovascular standpoint: (1) in males, there is evidence that physiological levels of testosterone participate, via its conversion to estrogen in target tissues by aromatase, to the maintenance of normal vascular tone in males\(^{59}\); (2) in men, there is an inverse relationship between testosterone levels and the incidence of coronary heart disease\(^{60}\); and (3) there is no evidence that administration of testosterone at physiological doses has any effect on cardiovascular risk.\(^{60}\) However, the possibility remains that androgens may exert adverse effects in certain particular backgrounds and/or conditions. For instance, it has been reported recently that postmenopausal women with type 2 diabetes have evidence of androgen excess that might contribute to increased cardiovascular risk.\(^{61}\)

**Mechanisms of Actions of Sex Steroids and Gene–Environment Interactions**

The effects of estrogens are mediated via 2 distinct types of ER, that is, ER\(_{\alpha}\) and ER\(_{\beta}\). Each ER appears to contribute differently to the various cardioprotective effects of estrogens. In the vasculature, the protective effects of estrogens have been shown in knockout mice to be mediated predominantly via ER\(_{\alpha}\). In contrast, the protective effect of estradiol against pressure overload–induced hypertrophy is abolished only after inactivation of ER\(_{\beta}\).\(^{62,63}\) Interestingly, recent data indicate that ER\(_{\beta}\) gene polymorphisms associate with left ventricular mass and wall thickness in women but not in men.\(^{64}\) However, the molecular machinery mediating cellular responses to estrogens is complex and involves both genomic and nongenomic effects, is regulated by numerous coregulatory proteins, and is still far from being understood.\(^{65,66}\) The actions of activated androgen receptors are modulated by an equally large number of coregulators,\(^{51}\) but their mechanisms of action and their potential roles within the cardiovascular system have been studied in less detail than that of ERs. When considering the effects of steroids on the heart, one should also take into account their actions on different cell types and/or processes. For instance, estrogens and androgens have been suggested to have adverse and beneficial effects on inflammatory processes in cardiomyocytes and/or immune cells, respectively.\(^{57,68}\)

We have shown recently by linkage analysis that genetic loci linked to left ventricular mass under baseline conditions in males are different and distinct from those found in females in a normotensive rat cross.\(^{69}\) However, when the hearts are challenged by volume overload, a particular locus that showed linkage to baseline left ventricular mass in males only was linked to transition toward congestive heart failure both in males and females, thus showing that the effect of loci may be modulated by environmental conditions.\(^{70}\) Some of these gene–environment interactions may actually result from differences in the response of individuals to sex steroids. For example, androgens increase left ventricular mass to a much greater extent in mice where the gene coding for natriuretic peptide receptor A was inactivated than in their wild-type counterparts.\(^{71}\) In rats, we have made similar observations, because orchidectomy did not decrease the size of cardiomyocytes in Wistar–Kyoto male rats but did so in congenic Wistar–Kyoto rats containing a hypomorph variant allele of the gene coding for atrial natriuretic peptide precursor (B.L. and C.F.D., unpublished observations, 2006). In some instances, steroids themselves may constitute the environmental factor, which is then modulated by gene variants within the steroid-responsive machinery. For instance, recent data in humans show that variants of the ER\(_{\alpha}\) gene associate with MI in men,\(^{72}\) whereas variants of the ER\(_{\beta}\) gene associate with left ventricular mass in women.\(^{64}\) Thus, when considering the actions of sex steroids, one should remember that their effects can be modulated by the genetic background of individuals, as well as by environmental conditions (including age and/or postmenopausal condition).

**Role of Sex Chromosomes**

The mechanisms responsible for sex-based differences in ventricular remodeling are not entirely clear, but differences in sex chromosomes constitute an undisputable difference between males and females. One of the attributes of maleness in humans and laboratory rodents is the presence of chromosome Y. Interestingly, several chromosome substitution experiments have been performed between normotensive (Wistar–Kyoto, Brown Norway, and King Holtzman) and hypertensive (spontaneously hypertensive and spontaneously hypertensive stroke-prone) rat inbred strains.\(^{73,74}\) In several cases, the presence of chromosome Y from the hypertensive strain was associated with a 20- to 25-mm Hg difference in blood pressure. Of note, this is not a genetic characteristic of all hypertensive strains, because transfer of chromosome Y from other hypertensive strains did not yield the same effect.\(^{73}\) When present, the effect of chromosome Y was found to depend on the presence of testosterone and of androgen receptors.\(^{74}\) Although the effect of chromosome Y on left ventricular mass has not been tested directly, allelic variants of this chromosome also associate with sympathetic nervous system activity, salt sensitivity, and lipid phenotypes, all of which may (in addition to blood pressure) affect cardiac remodeling.\(^{73,74}\) Recently we have measured the shape of cardiomyocytes from 2 mouse strains displaying marked differences in cardiac mass, that is, A/J and C57Bl/6J mice.\(^{75,76}\) In keeping with the differences in cardiac mass, cardiomyocytes from C57Bl/6J mice were much larger than that from there A/J counterparts. However, substitutions of chromosome Y between the 2 strains revealed that chromosome Y from C57Bl/6J was associated with an increased size of cardiomyocytes, despite the fact that blood pressure was within the normotensive range in all of the strains.\(^{77}\) Further analyses are underway to decipher the mechanisms responsi-
Steroids and Perinatal Programming

Beyond the role of postpubertal steroids, early life exposure to steroids may also have important consequences on late-life cardiovascular diseases. For instance, excess exposure of developing fetuses to glucocorticoids increases their blood pressure later during adult life. A key event in early male life is the perinatal androgen surge, a period that is critical for hormonal imprinting and sex differentiation of the brain and the prostate, and possibly also other tissues, including cardiovascular ones. Neonatal androgen imprinting has been reported to determine the sex-specific susceptibility of rats to cafeteria diet–induced hypertension. Importantly, the environment contains numerous agents that may disrupt the function of steroid hormones by acting as either agonists or antagonists and, thus, disturb the normal mechanisms of perinatal imprinting. One example is that of soybean-derived phytoestrogens (PE), that is, the isoflavones daidzein and genistein. Most commercial rodent chows are soybean derived and, thus, contain PEs at sufficiently high concentrations to affect the physiology of several organs. Therefore, compared rats fed with standard PE-rich rodent chow with others receiving a PE-free casein-based diet to test whether the diet would have an impact on cardiac morphology and/or function. We found that the hearts of rats fed with a PE-free casein-based diet developed features of dilated eccentric hypertrophy and (unlike the hearts of their counter-parts fed with PE-rich soy-based diet) progressed toward congestive heart failure when further challenged by volume overload. Importantly, the effect of dietary PE was restricted to their presence in the maternal diet during perinatal development, thus demonstrating that receptors recognized by PE (presumably steroid receptors) play an important role in the perinatal programming of cardiac morphology and function. Of note, whereas some have confirmed that dietary PEs protect rats against volume overload, others have reported different and divergent effects of dietary PEs, because a soy-based diet appears to worsen cardiac function in male transgenic mouse models of hypertrophic cardiomyopathy. However, it is unknown whether the latter effect is related to perinatal or adult exposure to PE.

Clinical Consequences

As summarized in the Figure, there are many ways and mechanisms by which sex can modulate the cardiac phenotype, and much remains to be learned about each of them. These pathways themselves are modulated by other factors, including the genetic background of individuals and age. The modulatory actions of sex steroids on inflammatory processes are of particular interest; because those are likely to become more prevalent as age increases, it might explain in part why the protective effects of estrogens in young women turn into adverse effects when replacement therapy is given to older postmenopausal women.

Although the cardiovascular effects of estrogens and androgens are not uniformly positive or negative, respectively, the evidence reviewed above has led to the widely held perception that women are protected against cardiovascular diseases. This has led to the unfortunate consequence that women are protected against cardiovascular diseases. This has led to the unfortunate consequence that cardiovascular diseases are less diagnosed in women and that they are less likely to receive appropriate treatment. However, cardiovascular diseases typically manifest themselves during middle age, at a time when women are postmenopausal and even more vulnerable to cardiovascular problems than men. One consequence of the HERS Trial is that there is currently no safe and accepted hormonal replacement therapy to reduce cardiovascular risk in postmenopausal women. It is, therefore, critical not to minimize the diagnosis and treatment of cardiovascular disease in women. This
should also serve as an impetus to better understand how steroids exert their potential cardioprotective action and use that knowledge to design proper strategies for hormonal replacement (provided that sex steroids are the main cause of sex-specific differences). Because genetics have shown that different genes may be responsible for ventricular remodeling in males and females, it is also possible that the efficacy of some drugs will be different in men and women. So far, differences in the use of cardiovascular drugs have been mostly justified by differences in pharmacokinetics and/or in the activity of drug-metabolizing enzymes. However, because women are still underrepresented in studies on arterial hypertension and heart failure, we still do not appreciate fully whether drugs work differently in men and women. If differences are found, a better understanding of the mechanisms of sex-specific cardiovascular differences should be helpful in the optimization of therapies according to the sex of the patients.

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Disclosures
None.

References