

What Do Women Have in Their Hearts?

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Heart failure has traditionally been thought of as a typically male problem. However, while women with heart failure have been little represented in clinical trials (0%-32%) and are not so often seen in cardiology units, over half of all patients with this syndrome - including over half of those admitted to hospital because of it - are women.¹ Women with heart failure are usually older than men²; increasing age is not just associated with an increased prevalence of heart failure but with more women patients suffering this problem. Currently over 60% of the mortality associated with heart failure is borne by women, despite their better chances of survival compared to men of the same age (in heart failure age is the foremost prognostic factor). This situation, along with the ever more apparent peculiarities of heart failure in women, has spawned a large number of studies with the aim of redressing the lack of data corresponding to this sex.

Studies of patients with systolic heart failure have unanimously shown lower mortality rates among women than among men, with sometimes marked differences in the case of non-*ischaemic* dilated cardiomyopathy.³ The reasons behind this better prognosis for women are unclear. There is evidence that left ventricular systolic dysfunction has no value as an independent prognostic marker in women. The HOLA study (Heart failure: Observation of Local Admissions) reported the interaction sex-left ventricular ejection fraction (LVEF) to be significant, such that systolic dysfunction in men - but not women - predicts mortality in heart failure.⁴ It is important to underline here that feminine sex has been associated with a better prognosis in studies of patients with systolic heart failure,⁵ but that there is no difference between the sexes when heart failure is accompanied by a normal LVEF.⁶ It is also well known that right

ventricular dysfunction is associated with a poorer prognosis in patients with systolic heart failure. A possible explanation of the better prognosis for women with this syndrome is that the right ventricle is less affected for the same degree of left ventricular dysfunction and pulmonary pressure.⁷ In addition, in healthy subjects the right ventricular ejection fraction (RVEF) is clearly larger in women than in men, while the LVEF is similar in both sexes.⁸ This suggests there are some sex-related biological differences in the anatomy and physiology of the right ventricle.

Why is the right ventricle of women (and the heart as a whole) more resistant to systolic heart failure? In normal subjects there are profound sex-related anatomical and physiological differences. For example, women have smaller hearts than men, as well as smaller coronary arteries, end-diastolic pressures and ventricular volumes, and they show a smaller increase in the ejection fraction with exercise (compensated by a greater increase in the end-diastolic volume). For the same age, the diastolic function variables of women are better, and men experience a deterioration in contractile function that women are spared (this may be related to the greater annual loss of myocytes seen in men).⁹ The sex hormones also have a clear effect on the cardiovascular system - this is most apparent in premenopausal women. Estrogen and androgen receptors have been detected in the aorta, coronary arteries, and cardiac tissue (in myocytes and fibroblasts). Sex hormones could influence contractile function by affecting the release of calcium to contractile proteins. Estrogens modulate proinflammatory cytokines, including tumor necrosis factor, and increase the activity of nitric oxide synthase, which promotes an endothelium-dependent vasodilatory effect. They also favor the growth of heart tissue fibroblasts, and may therefore directly influence ventricular remodeling.¹⁰

With respect to pathological situations of heart failure and systolic dysfunction, many studies have shown women's hearts to have a better response than those of men. This has been reported in terms of ventricular remodeling, myocardial ion channel activity, skeletal muscle function, protection against ventricular arrhythmia, and sympathetic and neurohormonal activation (women with systolic dysfunction have lower atrial natriuretic peptide and B-type natriuretic peptide levels than men).⁴

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TABLE 1. Adaptation of the Cardiovascular System to Exercise and Pregnancy

Exercise		Pregnancy	
Morphological Changes	Functional Changes	Morphological Changes	Functional Changes
Ventricular hypertrophy	Increased heart rate	Increased LV and RV end-diastolic diameter	Increased heart rate
	Increased venous return (increased preload)	Increased atrial size	Arterial and venous dilation
	Reduction of peripheral vascular resistance (reduced afterload)	Ventricular hypertrophy	Increased blood volume (increased preload)
	Increased systolic volume	Possible dilation of atrioventricular rings	Reduction of peripheral vascular resistance (reduced afterload)
	Increased contractility	Reduction in elasticity	Increased ejection volume
	Increased cardiac output		Increased contractility
			Increased cardiac output

RV indicates right ventricle; LV, left ventricle.

Also, in animal models of dilated cardiomyopathy, female hearts have been found to show advantages in terms of the myocardial expression of tumor necrosis factor RNA receptor expression and in their hypertrophic reserve.⁴ Experiments have shown that female animals respond better to volume and pressure overloads, developing concentric ventricular hypertrophy, while males develop dilation of the left ventricle and suffer greater mortality. These sex-related differences in ventricular remodeling could be associated with the lesser degree of myocyte necrosis and apoptosis seen in women with terminal heart failure.¹¹ It has even been proposed that women are protected against genetic mutations; in men, an alteration in the gene coding for angiotensin converting enzyme is associated with an increased heart size and increased cardiovascular risk, yet the same mutation in women is associated with no increased risk.

It is not clear to what point these pathophysiological differences explain the better prognosis for women with heart failure. What is known is that only women undergo a non-pathological situation in which profound anatomical and physiological changes in the heart occur: pregnancy. During pregnancy the heart rate increases, along with the blood and ventricular volumes (both can increase 50% over baseline) and cardiac output, and ventricular hypertrophy occurs. In addition, vascular resistance declines (via arterial and venous dilation and because of the development of the low resistance blood circuit of the placenta).¹² The pressure in the pulmonary artery is therefore not affected, although there is an increase in the pulmonary blood flow and a reduction in pulmonary vascular resistance. The quantity of atrial natriuretic peptide increases during pregnancy, and is one of the mechanisms (along with hormonal activation) of the changes described.¹³ Many of these changes are maintained for at least a year, and some authors suggest that the persistence of this

cardiovascular remodeling might reduce the risk of heart failure/cardiovascular disease faced by women over the remainder of their lives.¹⁴ The hemodynamic changes observed during pregnancy are similar to those seen in sportspersons (Table 1), and the benefit of exercise in patients with heart failure is well known. Pregnancy might be understood as a kind of “training” with benefits for women, who would then be better prepared to tolerate and adapt to future situations of myocardial stress.

The presence of XY cardiomyocytes in the hearts of women who have had male children has recently been reported by Bayes-Genis et al.¹⁵ Although the implications of this important finding are still unclear, it cannot be ruled out that the heart undergoes some degree of rejuvenation during pregnancy, which would be advantageous in a future situation of systolic heart failure. Further, since female stem cells are more potent than male stem cells,¹⁶ even more benefit might be gained from having had a female child.

No discussion of the relationship between pregnancy and heart failure is complete, however, without the mention of peripartum cardiomyopathy. This enigmatic situation has been considered a consequence of myocarditis, nutritional deficiencies, hormone alterations, and even volume overload, but the radical, negative changes seen in the heart suggest some deep relationship between the heart and pregnancy.

In the present issue of the *Revista Española de Cardiología*, Redondo-Bermejo et al¹⁷ report a study based on a cohort of patients with heart failure, all of whom were hospitalized in a cardiology unit. This work confirms the known clinical profile of women with heart failure,¹⁸ with more comorbidity than men and less coronary disease (despite their greater age and their more commonly suffering high blood pressure and diabetes). As in earlier studies¹⁹ the results show the

prevalence of a normal ejection fraction in women double that seen in men. An important finding of this work is the low number of coronary angiography studies performed in women (22% compared to 37% of men underwent such an examination). Although there could be several reasons for this,²⁰ there is evidence that other non-invasive diagnostic tests such as echocardiography are also less often employed in women patients.¹⁹ It is true, however, that with advancing age fewer complementary diagnostic tests are requested - and since women presenting with heart failure are usually older than men they have been less studied during their time in hospital.²¹

Unfortunately, the study by Redondo-Bermejo et al provides less information with respect to the independent influence of sex on prognosis. The work analyses 412 patients, 157 of whom were women, selected via their admission to a cardiology unit. Follow-up, however, was for a short time only and was very variable (16 [9] months). Cardiovascular causes accounted for about 15% mortality in both sexes, despite the fact that the women patients were clearly older (75 years compared to 71 in men) and suffered greater comorbidity (which agrees with the idea of women enjoying a certain degree of protection). With respect to overall mortality, the hazard ratio for each sex had a very wide 95% confidence interval range, preventing any conclusions being drawn. In fact, this confidence interval includes a possible greater mortality in men of 1.4-fold compared to women. Although studies focusing on patients with very advanced systolic heart failure and with an LVEF of <20% report a hazard ratio of 2.2-2.5 for men with respect to women, those that have focused on patients with less advanced disease and larger ejection fractions (such as the patients of Redondo-Bermejo et al) report more modest hazard ratios (always <1.63 and therefore compatible with the findings of the Murcia group).

Finally, the authors provide different markers of mortality for men (only age) and women (age and the presence of anemia), but they do not report whether there is any significant interaction of sex with these predictors (which would be of particular interest with respect to anemia); this prevents our knowing whether anemia has a particularly pernicious effect in women. Since women have lower hemoglobin and hematocrit concentrations than men this is a hypothesis worth testing. It also remains to be determined what the correct management of patients with anemia (which is frequently multifactorial) and heart failure is²²; hopefully results will soon be published that will throw some light on this.

So, what is in a woman's heart? Everything but weakness. It is unknown, however, whether all women enjoy a certain protection against systolic heart failure. It may be a result of a genetic/hereditary capacity to adapt to volume overload and the development of reversible ventricular hypertrophy during pregnancy. Maybe such protection is exclusive to, or is at least predominant in,

women who have been pregnant. Hopefully, future work will provide the answers to these questions.

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