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Gender differences in heart failure

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Background

Heart failure (HF) is defined as a systemic condition where the heart is unable to properly meet the peripheral tissues' needs. The HF prevalence is approximately 1-2% of the adult population in developed countries. It is continuously increasing, mostly due to the aging of the population. In elderly (i.e. over 70 years old) HF affects more than 10% of the population[1]. As a consequence, HF patients are characterized by a high comorbidity profile and high cardiovascular risk[2]. Therefore, despite the progress in knowledge, therapy and technology, HF maintains a worse prognosis than most of the commonest cancers, such as bowel, breast and prostate cancer[3].

The marker of HF is the cardiac remodelling. The heart goes through several changes in its dimensions, mass and shape in order to counter pressure overload (i.e., systemic hypertension, aortic stenosis), volume overload (i.e., valvular regurgitation) or primary cellular damage (i.e., myocardial infarction, myocarditis). The pathophysiological leading systems of the heart remodelling are mainly neuro-hormonal stresses, such as the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). Therefore, the cornerstones of HF therapy, beta-blockers (BB), angiotensin-converting-enzyme inhibitors (ACE-i) and mineralcorticoid receptor antagonists (MRAs), are directed against those mechanisms. Two main patterns of HF can be described[1]: HF with reduced ejection fraction (i.e. ejection fraction <40%, HFrEF), mostly linked to chronic volume overload and cellular injury, and HF with preserved ejection fraction (i.e., ejection fraction >49%, HFpEF), more frequent in chronic pressure overload. Moreover, an intermediate pattern of HF with mid-range ejection fraction (i.e. ejection fraction 40-49%, HFmrEF) has been recently described[1].

Gender differences in mechanisms, clinical manifestations and responses to therapy exist in specific HF patterns. They will be analyzed and discussed in this review.

Gender differences in heart failure

Compared to men, women have a lower left ventricular mass, however it is more frequently preserved with aging in women than with men. Women have a greater contractility, a lower rate of apoptosis, smaller coronary vessels, higher heart rate at rest, higher incidence of left bundle branch blockage, lower catecholamine mediated vasoconstriction. All the above mentioned characteristics contribute to the different clinical expression of HF in the two genders. Moreover, concerning clinical differences between male and female, sex hormones, their receptors and sexual chromosomal gene products are considered to be responsible for mediating such mismatches. Estrogen receptor a (ERa) and estrogen receptor b (ERb), which are the nuclear receptors of the most effective female sex hormone 17 beta estradiol (E2), are located in the vascular endothelial cells and smooth muscle cells of blood vessel walls, as well as in cardiac fibroblasts and myocytes. They are considered to be the mediators of the positive effects on the cardiovascular system that can be identified in women: vasodilatation, decreasing the development of atherosclerosis, and preventing apoptosis in cardiac myocytes in HF[4]. On the other hand, testosterone increases inflammation and cholesterol blood levels. To underline the importance of sex hormones in cardiovascular disease, what should also be noted is the higher rate of heart attacks among women at about 10 years after menopause[4].

Globally, women show a better prognosis in heart failure compared to men. In fact, the lifetime risk of HF at 55 years old is 33% for men, and 28% for women[1]. However, HF is a severe syndrome that affects negatively the quality of life, which is even worse for women compared to men. From this point of view, women seem not to be as aware as they should about the severity of this disease. In fact it seems that other diseases, with relatively better prognosis (i.e., breast cancer), are more important sources of concern for women than HF. Finally, a paramount factor that may play a crucial role in worsening the prognosis of a female with HF, is that women are consistently less represented in HF trials; the highest share of the female

population in a HF clinical trial is 40%[5]. It may be due to clinical features (HF is more frequent in the male sex) and also social issues.

HFrEF – post-myocardial infarction HF

Even though women are protected against ischemic heart disease until menopause, afterwards, ischemic heart disease becomes the most common cause of HF for both genders in developed countries.

In the population under 75 years old, myocardial infarction (MI) in women is characterized by a higher risk of death during hospitalization compared to men. Moreover, the clinical presentation of MI is different between male and female: women have more frequently atypical symptoms, such as sleep disturbance (48%), abdominal discomfort (39%), dizziness (39%). It is worth noting that women have a relatively lower rate of chest pain (43%) at clinical presentation. Consequently, the symptoms-to-balloon time, which is one of the most important predictors of outcome, in women is generally prolonged. At the first medical contact, women have more frequently a higher Killip class (pulmonary oedema, cardiogenic shock), with a subsequent important impact on prognosis. New onset atrial fibrillation during MI is more frequent in women compared to men[6]. It may be a consequence of the higher prevalence of hypertension in women or the delay in treatment.

Additionally, the long-term prognosis is also different between women and men. Indeed, women have a higher risk of developing HF after myocardial infarction, after adjusting for age and comorbidities, independently from the extent of the left ventricular systolic dysfunction[7]. It seems to be linked either to differences in the sex hormones or to differences in the clinical management.

Moreover, women have a worse prognosis in ischemic heart disease requiring a surgical approach. In fact, women also have a higher intra-hospital death rate and worse outcomes after coronary artery bypass surgery.

HFrEF – non-ischemic cardiomyopathies

Some aetiologies of HFrEF are definitely more frequent in women than in men: peri-partum cardiomyopathy, chemotherapy induced and Tako-Tsubo syndrome. Tako-Tsubo, also called "broken heart" syndrome because of its close linkage with emotional stress, in 90% of cases where it affects women and it is characterized by an apicalventricular dysfunction with a moderate release of troponin in the absence of significant coronary artery disease[8].

Peri-partum cardiomyopathy is obviously peculiar in young women and its risk is increased in later pregnancy, multiparity, multiple gestations and has a strong association with pre-eclampsia and hypertension in pregnancy; nevertheless, the exact physiopathology is not yet explained[9]. Post-chemotherapy dilated cardiomyopathy seems to be more frequent in women due to the wide use of antracyclines in breast cancer.

The natural history of idiopathic dilated cardiomyopathy is generally less malignant in women: they have less cardiovascular events and a longer survival free from death or heart transplantation. Nevertheless, at diagnosis women show features of more severe disease in terms of left ventricular ejection fraction and dimension[10]. Moreover optimal medical treatment is more effective in women than in men, with a higher rate of left ventricular reverse remodelling, and they are better candidates for cardiac resynchronization therapy when indicated[11].

HFpEF

In the past, we focused our attention on HFrEF with a consequently significant reduction in mortality. Over the past several years, the cardiology community began studying HFpEF, which is going to become a major public health issue because of the aging population[12]. This phenotype is more frequent in women. In fact, HFpEF is frequently characterized by hypertensive heart disease or diabetic heart disease. Therefore, HFpEF is predominant in the elderly and affects mostly women compared to men. Similar to non-ischemic HFrEF, HFpEF is more malignant for men than for women in terms of prognosis[12]. The exact mechanisms at the basis of the better outcomes for women are not well known yet.

Conclusion

In conclusion, it is desirable that further research should be focused on improving the knowledge of the differences between men and women in the context of cardiovascular diseases and, especially, HF. Future studies are needed in order to understand the different aetiologies, pathophysiology, and how pathogenic stimulus affects myocardiocities in men and women.

This process should be finalised to establish an optimized therapy, that accounts for the differences between the sexes and moves us toward more precise medical responses. A critical step will be to enrol a higher percentage of women in clinical trials. In this way, the gaps in the evidence will be reduced and more women will be treated properly, narrowing the current sexual disparities.

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