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. As a consequence, HF patients are characterized by a high comorbidity profile and high cardiovascular risk. 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.

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 mineralocorticoid receptor antagonists (MRAs), are directed against those mechanisms. Two main patterns of HF can be described: 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%, HFrEF), 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.

Gender differences in mechanisms, clinical manifestations and responses to therapy exist in specific HF patterns. They will be analyzed and discussed in this review.
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\(^11\).

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**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 myocardiacities 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.
References


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