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The impact of gender in cardiovascular medicine: Lessons from the gender/sex-issue in heart failure

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Abstract

Heart Failure (HF) is a major healthcare issue, given its high prevalence and incidence, the rate of comorbidities, the related high health-care costs and its poor outcome. In the last years mounting evidence revealed several differences between men and women affected by this clinical condition. Apart from the well-known difference in phenotype (HF with reduced ejection fraction (HFrEF) occurs more commonly in men, and HF with preserved ejection fraction (HFpEF) is more frequent in women) other relevant sex-related issues dwell upon epidemiology, presentation, risk stratification and management. These differences shed new lights on the possibility to consider HF as a prototype of the impact of gender/sex issue in cardiovascular medicine. A call for action and future strategies might help in the achievement of a cleaver patient-care.

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Introduction

Heart Failure (HF) is a major healthcare problem with a global prevalence of more than 25 million, and this figure is estimated to grow in the forthcoming years [1,2], HF might represent the terminal stage of theoretically all cardiovascular diseases and is still burdened by a poor prognosis with a 5 years mortality of 50% and often patients are affected by concomitant comorbidity, which dramatically increase the related health-care costs [3,4]. Although HF affects equally men and women, the latter are remarkably underrepresented in clinical trials[5,6]. Moreover, is noteworthy the bimodal pattern of HF incidence, being higher in men at younger ages and higher in women after 80-years old [7]. On top of these observations, men and women present with different phenotypes of HF, being the latter more often affected by HF with preserved ejection fraction (HFpEF) than HF with reduced ejection fraction (HFrEF) [8]. Given this magnitude, the existing differences between the two sexes make the management of HF patients more challenging. In this review, we will focus on the main sex-related differences of heart failure pathophysiology, clinical features, and therapy and how this could impact the clinical practice of this condition.

Pathophysiological underpinnings of the different presentation of HF in men and women

HF is characterized by the overexpression of molecular and hormonal pattern (such as angiotensin-aldosterone pathways, adrenergic activation and inflammation) after an index event aimed at restoring the homeostasis of the cardiovascular system [9,10]. However, this process might ultimately result into a maladaptive remodeling of the left ventricle with long-term detrimental effects on the cardiovascular system [11-17].

As mentioned above, the age of HF-diagnosis is higher in women [7]. Moreover, risk factors act differently in female subjects compared with males. For instance, diabetes mellitus confers a 3-fold higher risk to develop HF in women, compared with a 2-fold risk in men [18]. Obesity is a more common comorbidity in women with HF than in men [19]. Moreover, systemic hypertension is more prevalent in women than in men at HF diagnosis [19]. On the other hand, the most

common cause of HF in men is ischemic cardiomyopathy [20]. Furthermore, hormones acts differently on the cardiovascular system of men and women [21-32]. All these factors ultimately lead to different structural phenotype of the left ventricle (LV). While female tends to present with reduced volumes, higher contractility and concentric remodeling, typically males HF patients are characterized by eccentric remodeling with higher volumes and reduced ejection fraction [33,34]. Usually women presents also with smaller right ventricles with concomitant RV systolic function similar to men which ultimately leads to reduced wall-stress [35-41]. However, although this paradigm (HFrEF in young/males, HFpEF in females) might be helpful to summaries, it does not prejudge the fact that young women/females may have HFrEF and old me/males may have HFpEF. Interestingly, some HF etiologies belong exclusively to female sex, such as peripartum cardiomyopathy, likewise other involves primarily women including connective tissue diseases, autoimmunity and chemotherapy [33]. Also, the so-called Takotsubo cardiomyopathy, a form of stress-induced cardiomyopathy, which leads to reversible acute HF, is predominant in post-menopausal women [42]. This body of evidence points to a higher prevalence of HFrEF phenotype in males, whereas females are more often affected by HFpEF. Symptoms also differ between the two sexes, with women more prone to develop shortness of breath associated with reduced exercise capacity and pulmonary edema [43]. Of note, also natriuretic peptides concentrations are higher in HF-females patients than in men [44,45].

Different effects of HF-treatment between the two-sexes and their impact on prognosis

While clinical trials brought about positive results in terms of reduction of hard clinical outcomes in HFrEF, we still did not develop a specific and targeted therapy for patients with HFpEF [46]. With regards to the use of angiotensin converting enzyme inhibitors (ACE-inh) and angiotensin receptor blockers (Arbs), they share similar effects in both sexes[47,48], with small differences in favor of a more noticeable positive effects in males according to post-hoc analysis of clinical trials [47]. Of note, women are more prone to develop angioedema and other side effects of ACE-inhibitors [49]. Beta-blockers showed similar positive results in men as well as in women, with a slightly more survival benefit in old-women [50]. However, when considering the effectiveness of implantable cardioverter-defibrillators (ICD) in women with heart failure (HF), several concerns arose in the last years. Pooled data of 5 trials showed no benefit in the prevention of sudden cardiac death in 934 women (HR: 1.01, 5-95% CI: 0.76-1.33) [51]. Another meta-analysis also demonstrated that women have a 70% increase in adverse events with ICD implantation compared to men [52]. Given these findings, it is surprising that no prospective trial has been ever implemented in women, also taking into account that 30% of ICD implantation are performed in the female population [53]. Surprisingly, women seem to benefit more than men from the use of cardiac resynchronization therapy (CRT). According to a post-hoc analysis of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial, women experienced a greater survival benefit and reduction of hospitalization, accompanied by a remarkable reverse remodeling of left ventricle when compared to the male counterpart [54,55]. In these regards, it is worth to mention that there are apparently no differences regarding prognosis in two sexes, although women without ischemic heart disease generally lives longer than men [56]. On the other hand, women are more prone to develop HF after myocardial infarction than men [5,6].

Heart Failure as a prototype for considering the importance of the sex/gender issue in cardiovascular medicine

The aforementioned evidence stresses the concept that an improved awareness of the gender/sex-issues in HF might represent a "flywheel" of a needed paradigm-switch, not only in HF-care, but in the full spectrum of cardiovascular medicine. This finding underlines again the concept that sex and gender differences should be considered as an important unmeet need of clinical research. Because of the lack of evidence, in part due to the circumstance that animal-models and large clinical trials classically have involved almost always males, in last few years a growing interest in this topic was recorded [57,58].

Indeed, even if greater efforts are eagerly needed to promote this topic in basic and clinical research, there is still a very poor knowledge about the proper role of the biological differences among male and female [58]. While it may be anticipated that the recent regulations of the National Institutes of Health may in all likelihood modify this trend in the future years, there is no doubt that such poor awareness of female differences in physiology, clinical features [59] and response to therapeutic interventions and drugs [60,61] led worldwide women to experience an inequitable health care assistance compared to men [62-64]. In this regard, it must be stressed that current guidelines are based on clinical trials that involved predominantly men.

In the age of personalized medicine, it is surprising that in clinical decision-making is still paid poor attention to the patient's sex, a concept that should represent a gold standard of clinical practice [65].

Another fundamental issue relates to the correct terminology, being sex and gender frequently used wrongly and considered as indicating the same term. On the one hand, the expression sex is related to biological characteristics including chromosomes, hormones, gene expression, and reproductive anatomy. On the other hand, gender is perhaps a more complex concept that includes the socially-constructed roles, behaviors, expressions, and identities of girls, women, boys, men and gender-diverse people [65]. Thus, gender identity may change over time, being not confined to a binary dichotomy. Compared to sex, gender could not be considered as static and it exists along a continuum. In this regard, a landmark study was recently published [66]. Pelletier *et al.* for the first time assessed the relevance of a composite measure of gender [67] as a tool to stratify the risk of death in a cohort of acute coronary syndrome (ACS) patients According to this interesting study, the presence of a feminine role accompanied by personality traits was more significantly associated with recurrent acute coronary syndrome than subjects with a masculine profile, and represented an independent predictor of ACS (hazard ratio from score 0 to 100: 4.50; 95% confidence interval: 1.05 to 19.27). These findings led to the speculation that feminine characteristics are more useful to assess the risk of hard outcomes in cardiovascular diseases than the sex (biological variable) itself.

According to several international societies, 4 interconnected aspects cover the gender concept: gender identity (*e.g.*, personality traits), gender roles (*e.g.*, child care), gender relationships (*e.g.*, social support), and what is termed "institutionalized gender" (*e.g.*, education level, personal income). Thus, gender-related factors should be included in the clinical study design, affecting clinical outcome or acting as mediating factors of the sex differences observed in clinical practice. The best recognized gender-related factors include: income, social status and supports, education, employment, social and physical environments, marital status, culture, and personal behaviors.

Sex and gender also affect health through several interactions: disease risk factors, symptoms, natural history, and outcomes as well as

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Table 1. Main differences related to sex/gender in heart failure.

	Females	Males
Age of presentation	Higher incidence in elderly	Higher incidence in younger
Phenotype	HFpEF	HFrEF
Remodeling	Concentric	Eccentric
Comorbidity	Obesity, diabetes, hypertension	Ischemic heart disease
Rare (etiology peripartum, autoimmune, Takotsubo)	Frequent	Uncommon
Pharmacological therapy	Beta-blockers has slightly better effect	ACE-Inh and ARBs has slightly better effect
ICD	Less effective	More effective
CRT	More effective	Less effective

HFpEF: Heart Failure with preserved ejection fraction; HFrEF: Heart Failure with reduced ejection fraction; ICD: implantable cardio defibrillator; CRT: cardiac resynchronization therapy.

the response to drugs and non-pharmacological strategies are strongly influenced by these differences. A better understanding of this issue is mandatory, in order to obtain equal opportunity and same high-quality health care among people. Of note, gender impact remarkably on several cardiovascular conditions [6,68-71]. A hot topic is the need of a good and widely accepted method to report and evaluate the gender and sex related evidence deriving from research and how to apply this information into clinical practice. To accomplish this paradigm shift, it is important that clinical researchers have useful instruments to standardize and elucidate the role of sex and gender on health care. This might be accomplished through several steps. First, the importance of using the right terminology in medicine literature. Misuse of the terms sex and gender cannot be tolerated in scientific literature: the term sex should be used when reporting biological factors while the term gender when gender identity, psychosocial and cultural factors are described [58]. Second, design of clinical trials should allow researchers to disaggregate demographics and outcome data by sex and gender [58]. Third, it is important to obtain a good representation of the women in clinical trials, trying to enroll samples of patients that might mirror the prevalence of the sex-distribution on each disease. This could modify the unacceptable pitfalls involving cardiovascular diseases: even if they are the first cause of mortality and disability in women, most studies have been conducted in only in men. Risk factors for cardiovascular diseases influence men and women in a different way; clinical manifestations of diseases and drug influences display several sex and gender differences too [63,66].

Another aspect to consider it that biological and sociocultural factors differ substantially among individuals within each sex over their respective lives [72]. Profound changes associated for example with reproductive biology (such as occur at puberty and, in women, throughout the menstrual cycle, during pregnancy, and at menopause) and with aging are of the utmost importance in the expression of disease [60,63]. Women/female and men/males may present with different age, socioeconomic status, lifestyle (*e.g.* physical activity, diet, alcohol, use of tobacco, *etc.*), and other gendered behaviors and variables [63].

Conclusions and future perspectives

Table 1 presents a summary of the available differences in sex/gender in HF. Indeed, remarkable differences exist with regard to epidemiology, etiology, pathophysiology, presentations, phenotypes, response to treatment and prognosis. Several issues are still outstanding. First, women are still underrepresented in clinical trial, and this might lead to a lack of knowledge and gaps in treatment and management. Second, we still do not precisely know how to assess gender (more than easily sex assessment) and how much it impacts on clinical outcomes. Finally, a raise in the awareness of the sex/gender issue is warranted. Future studies and research should focus on solving these relevant issues (as a prototype the ICD or CRT use in females and males with HF). Physicians should be more aware of these differences in order to get a tailored therapy of this clinical condition.

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