Heart Failure in Women: A Disease with Peculiar Pathophysiological Mechanisms and Clinical Presentation

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Abstract  Heart Failure (HF) is a disease whose prevalence is increasing in developed countries, involving up to 10% of the older population; the increase is due both to better therapy and to the aging population. Fifty percent (50%) of these patients are women, most of them presenting with preserved systolic function and diastolic dysfunction. Female patients show different etiology to males; they present several comorbidities and at an older age. Despite this, women appear to have a lower mortality risk, and female gender is an independent prognostic factor for better survival. An explanation for this different presentation and prognosis may be different ventricular remodeling in response to pressure burden on the left ventricle, leading to completely different left ventricular geometry and compliance mechanisms. These differences are not only detectable at macroscopic examinations but also appear in microscopic gene and molecular expression, with a reduction in apoptosis during lifetime and a lower myocyte volume. Although all these mechanisms have a protective role in chronic HF, different remodeling in women leads to a weak balance in the acute setting, with an imbalance between compensatory mechanisms and higher cardiac output requirements. This impairment goes along with the loss of “female gender advantage” after hospitalization. Despite the peculiar presentation of HF in women, there is little evidence about therapy in this setting, due to under-representation of women in clinical trials and the absence of sex-specific, prospective randomized trials.

Keywords: heart failure, gender

1. Introduction

Heart failure (HF) affects 1-2% of the adult population in developed countries [1], approximately 5.3 million people in the USA [2], with prevalence rising to 10% among the population aged 70 years or older [1], and an incidence of 10/1000/year in people over 65. In 2004, 1 in 8 death certificates in the US mentioned HF [2]. Nearly 50% of patients with HF are women [3] and HF accounts for 35% of female CVD mortality [2]; the estimated percentage increase of HF incidence in women over next years is 8%, while in men it is only 3% [4]. At 40 years of age, the lifetime risk of HF occurring without a prior MI is 1/6 in women and 1/9 in men. This difference may be explained by the greater prevalence of hypertension among women (the lifetime risk of developing HF in people with BP>160/90mmHg is double that in people with BP<140/90 mmHg). Despite this greater prevalence, women are often under-represented in clinical trials [5].

2. Methods

This review will focus on gender differences in presentation, physiopathology and current therapy of Heart Failure, in consideration of studies published in major journals.

3. Differences in Presentation

3.1. Clinical Differences

Observational clinical studies have recognized an important sexual dimorphism in cardiovascular structure, function, disease and clinical outcomes [6,7]. For instance, women have better age-adjusted survival than men in the same condition and with the same etiology [4,8]. Women (59%) are more likely than men to have a history of hypertension (39%) [9]; they have more severe signs and symptoms (despite similar NYHA) of HF, a higher heart rate and higher percentage of diabetes, while they are less commonly ischemic than men [10]. Furthermore, women have HF with preserved EF twice as often as men, and those with impaired left ventricular EF have higher mean EF compared with men [3]. One cause of the greater frequency of symptoms among female patients may be increased diastolic pressure leading to lower stroke volume, and the need for a higher heart rate to maintain the required cardiac output. This may lead to a more marked perception of heart rate by the patient herself and to more dyspnea and fatigue than men experience, even during lower physical exertion [11].
While in men ischemic etiology is the first cause of HF, in women the main risk factors for HF are hypertension, valve disease and atrial fibrillation [12]. One possible explanation could be the older age of women with HF, resulting in the accumulation of more risk factors [13]. Another reason could be the higher prevalence of obesity among women, since both obesity [14] and diabetes are independent risk factors for HF. Moreover, diabetes in women leads to a risk of developing HF twice as high as in diabetic men and 4-5 times as high as in non diabetic women [15]. Women with HF have greater arterial stiffness [16], which is an independent risk factor for developing HFpEF. Diabetes mellitus is associated with higher pulse pressure and stiffer vasculature, and the high prevalence of this comorbidity among women may contribute to the higher prevalence of diastolic dysfunction. While women appear to be protected from hypertension by estrogens, the increase in presentation of isolated systolic hypertension after menopause may explain their development of HF at an older age than men.

In addition, women are more susceptible to cardiomyopathies [17] and thyroid dysfunction [18] during the whole of life.

While men are more likely to have ischaemic cause, atrial fibrillation, chronic obstructive disease and anemia, women are more likely to be obese and to have a history of hypertension and renal impairment [19]. Obesity is an independent predictor of LV diastolic dysfunction, along with age, hypertension, and diabetes mellitus [20]. The higher percentage of obesity in women may explain the higher prevalence of HFpEF in this sex. Moreover, women appear to have a higher probability of developing diabetes and renal impairment [21]. Diabetes mellitus itself is an independent risk factor for HFpEF [22]. Furthermore women have a higher risk of stroke, which leads to higher rates of hospitalization [23].

Women with advanced HF appear to have better survival rates than men, and this finding is strongest among patients with a nonischemic etiology of heart failure [24]. Regardless of β-blocker treatment and baseline clinical profile, female sex is a significant independent predictor of better survival in patients with CHF [25]. While diabetes and renal impairment are independent prognostic factors of mortality in HF, the higher prevalence of these comorbidities in women doesn’t appear to affect the death rate among women with HF.

3.2. Differences in LV Geometry

Women’s better prognosis can be only partially explained by different presentation and etiology: in the CHARM study, female gender was an independent risk factor predicting better prognosis in both the ischemic and non ischemic groups [8]. Many studies have demonstrated sex related differences in remodeling after cardiovascular burden [26,27]. In women there is a greater degree of Left Ventricular Hypertrophy (LVH) and changes in LV geometry, but also preserved LV function in response to pressure overload, as demonstrated in patients with aortic valve stenosis [28] and in patients with isolated systolic hypertension [27]. It is not known whether there is an intrinsic molecular adaptation in women or if it is a hormone dependent mechanism, but it has been demonstrated in mice that males present earlier dilatation of LV and loss of LV function compared with females (with similar pressure overload) [29]. Adult females have lower gene expression of β-myosin heavy chain and mRNA for ANF in the early stages of pressure overload and hypertrophic development, while this difference was not found in neonatal rats [30]. That female hormones influence myocardial function and gene expression is suggested by the fact that gonadectomy in mice decreases heart function, while hormone replacement therapy prevents the molecular changes observed in gonadectomized mice [31].

3.3. Differences in Molecular Expression

Many studies have investigated the different gene and molecular expression which may explain the difference in cardiac remodeling between males and females. The complete pathway of gene expression and molecular proteins involved is not yet known, but different signaling cascades involved in this pathway have been studied and recognized as protective [32]. Estrogen is produced by both gonads and myocardium, promoting two different signaling pathways. This difference may explain the protective effect of estrogen against MI during the premenopausal period and the lifetime protective role of female gender in HF. Estrogen receptor (ER) signaling has been discovered to be protective against ischemic-reperfusion injury [33], to directly relax coronary arteries and to improve endothelial function both in normotensive and hypertensive post menopausal women [34,35], contributing to the reduction of left ventricular hypertrophy by paracrine-autocrine estrogen-mediated ANF induction by myocyte cells. Moreover, ER activation in cardiac myocytes and cardiac fibroblasts targets genes that are involved in LVH, myocyte survival and apoptosis [36]. Concerning apoptosis and myocyte survival - and therefore the total number of myocytes - estrogen activates the Akt gene [37] which has several functions, promoting antiapoptotic genes [38,39], inhibiting caspases [40,41], and promoting glycogen synthesis (thus providing a reserve for anaerobic glycolysis and inducing cardioprotection from ischemia reperfusion injury) [42]. Another important estrogen signaling cascade involves the insulin-like growth factor-1 (IGF-1) receptor on myocytes; it improves cell survival [43] both by enhancing expression of antiapoptotic gene products and decreasing production of proapoptotic proteins [44]. Furthermore, estrogen and IGF-1 stimulate nitric oxide, promoting vasodilatation and anti-thrombogenic and anti-inflammatory responses, increasing cell resistance to citotoxic stimuli [45].

Differences in apoptosis may lead to a difference in aging cardiomyopathy: women with HF are on average older than men [8]. This could be explained by a difference in myocyte number and volume loss with age: as observed by Olivetti et al. [46], women have preserved myocyte number and volume, while in men there is a loss of 1g/year of myocardium with an increase in myocyte volume of 158µm3/year in the left ventricle and 167µm3/year in the right ventricle. Furthermore, women maintain a stable number of mononucleated and binucleated myocytes with aging, while men have a reduction of 0.3%/year in myocardial monocytes with a
symmetrical increase of 0.3%/year in biventricular myocardial cells in the left ventricle. Moreover, sex appears to be a determinant for apoptosis, as found by Mallat; indeed, the apoptotic index in men is 3 times greater than in women [47]. Differences in apoptosis and response to ischemic injury may explain the dissimilar remodeling mechanisms after myocardial injury: males have a 10 times higher apoptotic rate than females in the perifuct region [48], suggesting that lower apoptosis protects against HF and cardiac decompensation, as demonstrated by the association between the lower rate of cell death in women and longer duration of cardiomyopathy [49]. One more explanation of better prognosis after MI is the delayed myocardial healing observed in female patients, which leads both to a worse prognosis in the acute setting (higher risk of cardiac rupture) and to better cardiac function and better remodeling in the chronic setting; in fact, males appear to have faster degradation of matrix and delayed removal of necrotic tissue and scar formation, due to a greater number of neutrophils and a lower concentration of macrophages in the perifuct region [50].

3.4. Differences in Ischemic and Acute Response

Reduced ventricular dilatation, although it is protective for CHF outcome, may act as an unfavorable factor in an acute HF setting. In fact, concentric hypertrophy and lower left ventricular end-diastolic volume lead to lower stroke volume. Accordingly, a higher heart rate is required to maintain the same cardiac output. As shown in several studies, heart rate is higher in women than in men. This compensatory mechanism is useful during normal life, but may act as an unfavorable process when additional cardiac output is required, for example in case of infection. For instance, during myocardial infarction stroke volume cannot be sustained by increasing systolic function (because of myocardial damage and in some cases because of mechanical factors like ischemic mitral regurgitation), and must be supported by an increase in diastolic filling. Because women have mostly diastolic dysfunction and higher diastolic filling pressures, they cannot compensate as much as men, which leads to a higher probability of developing cardiogenic shock in the acute setting [51].

This reduction in compensatory mechanisms may explain a similar risk of morbidity and mortality in women and men after hospitalization for HF [52]. In fact, sex exerts an independent effect on long term survival, but not on short term survival after hospitalization [53]. As observed by Jong, age, sex and comorbidities show a strong interaction and affect both short and long term survival: the “survival advantage” possessed by women decreases along with an increase in comorbidities, and this difference is far more evident in the long term. Thus, while women with few comorbidities have a better long term prognosis than men, this advantage disappears when they have more than 3 points on Carlson’s score [54]. The same is true of the association of age and sex: women’s advantage disappears with sex. This data may be explained by the lower compensatory efficiency of women’s hearts and their lower cardiac output.

In addition to all these mechanisms, women more frequently have impaired renal function. It has already been widely demonstrated that impaired renal function is an independent risk factor for mortality due to HF [55] and that baseline renal insufficiency impacts outcome more than worsening of renal function alone during decompensated HF [56]. This could be another explanation for the similarity between gender survival curves after hospitalization.

4. Current Evidence in Therapy

Despite all these sex related differences and the greater prevalence of HF among women, in most clinical trials the female population is under represented (Table 1). This may be due to the age limits used in many studies and to the type of HF (most studies have LVEF<40% as an inclusion criterion). Moreover, there is a lack of sub analysis involving gender differences. Therefore current HF guidelines are not sex specific due to under-representation of females and the lack of sex specific, prospective randomized trials [57].

<table>
<thead>
<tr>
<th>Table 1. Percentage of women’s population in HF trials</th>
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<tr>
<td><strong>Trial</strong></td>
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<tr>
<td>CONSENSUS [58] (Enalapril)</td>
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<tr>
<td>SOLVD [59] (Ramipril)</td>
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<tr>
<td>ATLAS [60] (Lisinopril)</td>
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<tr>
<td>COPERNICUS [61] (Carvedilol)</td>
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<td>MERIT HF [62] (Metoprolol)</td>
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<td>CIBIS II [63] (Bisoprolol)</td>
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<tr>
<td>SENIORS [64] (Nebivolol)</td>
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<tr>
<td>BEST [65] (Bucindolol)</td>
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<tr>
<td>COMET [66] (Carvedilol vs Metoprolol)</td>
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<tr>
<td>EMPHASIS [67] (Eplerenone)</td>
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<tr>
<td>RALES [68] (Aldactone)</td>
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<tr>
<td>EPHESUS [69] (Eplerenone)</td>
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<tr>
<td>VAL-HeFT [70] (Valsartan)</td>
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<tr>
<td>CHARM Added [71] (Valsartan vs Candesartan vs placebo)</td>
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<tr>
<td>ELITE II [72] (Losartan vs Captopril)</td>
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<tr>
<td>HEEAL [73] (Losartan vs Lisinopril)</td>
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<tr>
<td>VALIANT [74] (Valsartan)</td>
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<tr>
<td>OPTIMAAL [75] (Losartan vs Captopril)</td>
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<td>SHIFT [76] (Ivabradine)</td>
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<td>BEAUTIFUL [77] (Ivabradine)</td>
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<td>MADIT II [78] (ICD)</td>
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<td>SCD-HeFT [79] (ICD)</td>
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<td>COMPANION [80] (CRT)</td>
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<td>CARE-HF [81] (CRT)</td>
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Hsich’s review of published studies suggests sex differences in the degree of benefit from current therapeutic guidelines. For instance, morbidity and mortality benefit have been demonstrated in HF women treated with β-blockers, aldosterone antagonists and cardiac resynchronization therapy, but the same benefit has not been shown with ACE抑制剂 and ICD [57].
Furthermore, sex differences in gene and molecular expression in myocytes are not completely understood yet, but may represent an important target for therapy in the future. Although nowadays most molecular and pathophysiological studies do not examine gender differences in depth, further studies may analyze those molecular and cellular mechanisms that could lead to earlier recognition and better treatment of a disease which appears increasingly to be systemic the more thoroughly it is investigated.

5. Conclusions

Given that more women die every year of CVD than of breast or uterine cancer, and that 50% of HF patients are women, HF in women should reach public awareness and receive as much public recognition as ischemic disease or breast cancer, and clinical trials should enroll a representative female sample, as the NIH has been requesting since 1986 [82].

References

[1] McMurray JI, Adamopoulos S, Anker SD, et al. ESC Committee for Practice Guidelines, “ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC” EHJ, 33. 1787-1847. 2012.


[63] Dickstein K, Kjekshus J, OPTIMAAL Trial Steering Committee and Investigators, “Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan. Comparison of baseline data, initial course, and management: losartan versus captopril following acute myocardial infarction (The OPTIMAAL Trial),” *OPTIMAAL Trial Steering Committee and Investigators, Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan,* *Am J Cardiol.* 87. 766-71. 2001.


