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Gender differences in heart failure

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Summary. Heart failure is a growing health problem in the western world. Over the age of 40, the prevalence of heart failure is higher in men than in women, but this ratio is reversed after the age of 80. The aetiology of heart failure is mainly arterial hypertension in women, although ischemic heart disease can be important as well. The genetic basis for differences in aetiology is the chromosomic XY configuration in men, because several genes on the Y chromosome are associated with many cardiovascular risk factors. The pathophysiology of heart failure in women is mainly heart failure with preserved ejection fraction phenotype, probably because hypertrophy can easily take place without stretching the sarcomere. Symptoms are generally more severe in women. In particular, acute ischemic disease is often accompanied by left ventricular failure. Management should be similar to men, although in randomized studies women are poorly represented. It is said that ACE-inhibitors are less effective in women, but beta-blockers are more effective. Cardiac resynchronization therapy is certainly more effective in women than in men while implantable cardioverter-defibrillators (ICD) are not, probably because sudden death is more uncommon in elderly women with heart failure of non-ischemic aetiology.

Key words. Heart failure, arterial hypertension, ischemic heart disease, ACE-inhibitors, beta-blockers.

Le differenze di genere nello scompenso cardiaco

Riassunto. Lo scompenso cardiaco è un problema crescente nel mondo occidentale. Dopo i 40 anni di età la prevalenza di scompenso è maggiore negli uomini che nelle donne, ma il rapporto si inverte dopo gli 80 anni, e così la prevalenza di scompenso negli anziani è maggiore tra le donne. L'eziologia prevalente nel genere femminile è l'ipertensione arteriosa, benché anche la cardiopatia ischemica giochi un ruolo significativo. Il fondamento genetico delle peculiarità genere-specifiche sta ovviamente nella configurazione XY dell'uomo e XX della donna. Il cromosoma Y contiene, infatti, molti geni che codificano i più comuni fattori di rischio. Una differenza fisiopatologica fondamentale nello scompenso della donna è che avviene più frequentemente con normale frazione di eiezione, realizzando quindi lo scompenso cardiaco con frazione di eiezione preservata (HFpEF), indicato spesso anche come "scompenso diastolico". Questo probabilmente perché l'ipertrofia può instaurarsi anche senza stiramento del sarcomero, e quindi senza rimodellamento ventricolare con aumento del volume telediastolico. I sintomi in generale sono più accentuati nelle donne che nell'uomo a parità di disfunzione. In particolare, nella cardiopatia ischemica acuta spesso si verifica scompenso acuto, con aggravamento della prognosi. Il trattamento in generale deve seguire le linee-guida, però va detto che queste sono basate su studi randomizzati in cui la rappresentanza femminile era squilibrata. Si dice che gli ACE-inibitori siano meno efficaci nella donna, probabilmente per la relativa prevalenza di HFpEF, mentre i betabloccanti lo sono di più. La terapia di resincronizzazione è molto efficace nelle donne, mentre i defibrillatori cardiaci impiantabili (ICD) lo sono meno, probabilmente perché la morte improvvisa non è un esito frequente nello scompenso delle donne anziane.

Parole chiave. Scompenso cardiaco, ipertensione arteriosa, cardiopatia ischemica, ACE-inibitori, betabloccanti.

Introduction

Heart failure is a growing health problem in the population of western world. This is the result of an increasing number of elderly individuals and their consequent long-term exposure to risk factors. Since life expectancy is approximately 5 years longer for women than for men, the prevalence of heart failure tends to be slightly higher in women. In this review we will briefly revise the gender-related features of heart failure, regarding epidemiology, pathophysiology, clinical presentation, treatment and prognosis.

Epidemiology

The prevalence of heart failure is shown in Table 1[1]. After the age of 40, the prevalence of heart failure is higher among men at a ratio of (approximately) 2:1.

Table 1. Prevalence (%) of heart failure by gender and age (years). Modified from Taylor AL, 2015[1].

Age	20-39	40-59	60-79	80+
Men	0.2	1.5	7.8	8.6
Women	0.4	0.7	4.5	11.5

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This condition is reverted after the age of 80. Since women outnumber men over the age of 80, the overall ratio of M:F in a given heart failure population is approximately 1:1.

The incidence of heart failure reduces over time in both sexes, but especially in women. The rate of hospital discharge is now convergent for men and women. This probably means that the rate of hospitalization is now the same for both sexes; previously this was not the case[2-6].

Genetic and physiological basis for gender difference

The basic genetics of gender difference is the chromosome XY configuration for males and XX for females. Several genes on the Y chromosome are associated with many cardiovascular risk factors, namely increased blood pressure, increased low density lipoprotein cholesterol, and – in European males – the propensity to myocardial infarction.

In all ethnic groups, young men tend to have a higher mean systolic and diastolic pressure than young women. However, with advancing age the prevalence of hypertension is greater in women, meaning that the male:female ratio is reversed.

Chronic hypertension activates neurohormonal axis. Peripheral resistances are directly proportional to sympathetic drive in young men, but not in young women. In post-menopausal women, however, peripheral resistances increase with sympathetic drive, probably because oestrogen levels have declined. In actual fact, baroreflex sensitivity is modulated by oestrogen hormones. Hypertensive disorders of pregnancy increase the life-long risk for the development of hypertension or other cardiovascular pathologies later in life[7-21].

Risk factors and aetiology

Clearly the risk factors facilitating heart failure are the same in both sexes: specifically, hypertension, ischemic heart disease, valvular heart disease, diabetes and obesity are important risk factors for both men and women. However, there are important differences in their relative distribution between genders. Hypertension is indisputably the most significant risk factor in women. Ischemic heart disease is less prevalent, but not less important. Curiously, in acute coronary syndromes with a given coronary involvement, women are more prone to develop acute heart failure than men.

Diabetes is very important. The risk of developing diabetes-related heart failure is approximately twice as high in women than in men.

Valvular heart disease is a more important cause of heart failure in women than in men. In particular, obstructive lesions (aortic stenosis and mitral stenosis) can induce heart failure during the reproductive lifespan, especially during pregnancy and in elderly women.

Another specific cause of heart failure in women is pericardial constriction following radiotherapy for breast cancer, which can occur up to ten or twenty years after index treatment.

It should be noted that excess alcohol intake is a cause of heart failure and a worsening factor in both genders, but in women 10 times more so than in men[22-27].

Pathophysiology

The most important pathophysiological feature of heart failure in women is that left ventricular remodelling is oriented toward concentric hypertrophy. As a result, heart failure occurs in most cases with preserved ejection fraction (HFpEF). This is in contrast with heart failure in men, where the prevailing phenotype is heart failure with reduced ejection fraction (HFrEF).

The renin-angiotensin system would appear to be less activated. Consequently, fibrosis is less important at a myocardial level, although there is a general stiffening of the circulatory system with an increase in the effective afterload.

The reason for the preferential concentric hypertrophy and HFpEF instead of left ventricular dilation and HFrEF is unknown. Some authors suggest that in normal conditions, myocyte diameter is reduced with respect to men, and it may therefore be possible to increase the amount of contractile proteins without stretching the sarcomere.

Response to acute ischemia is different, probably because of the presence of endogenous oestrogens. In short, ischemic damage is delayed, myocyte necrosis and even rupture are more difficult "in vitro", and late remodelling occurs less frequently. It should be noted that some of these experimental findings are inconsistent with well-known clinical knowledge. It is a well-known fact, for instance, that cardiac rupture after myocardial infarction occurs more frequently in women than in men, and that heart failure in acute coronary syndromes sets in commonly and early in women[28-43].

Clinical presentation

As a rule of thumb, symptoms are worse in women than in men at a given ejection fraction and/or isch-

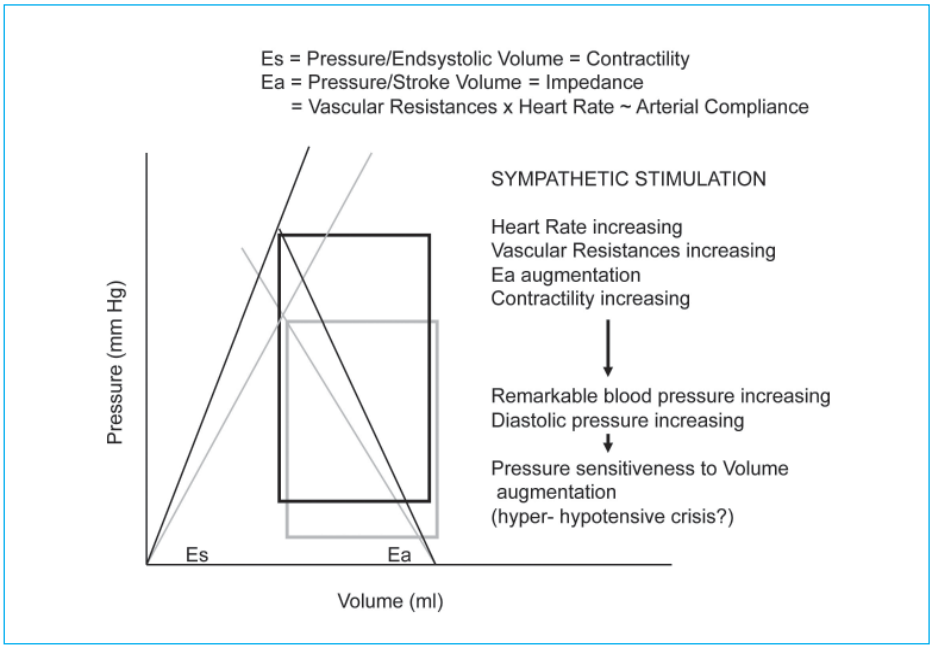

Figure 1. An example of ventriculo-arterial coupling in elderly women is represented. Pressure-volume loops in baseline (gray) and during hypertensive crisis are depicted. Volumes and pressures are governed by the interplay of contractility (Es) and effective afterload (impedance) (Ea). During hypertensive crisis both Ea and Es increase, and the whole pressure-volume loop is pulled up (black). Consequently, end diastolic pressure increases while end diastolic volume remains unchanged. Pulmonary flash oedema may ensue, with preserved ejection fraction.

emic burden. As far as ejection fraction is concerned, this is easily explained: reduced ejection fraction is not the main cause of heart failure in women. On the contrary, the main causes are increased left ventricular diastolic dysfunction and ventriculo-arterial coupling, due to increased systolic and arterial elastance (Figure 1). Therefore, a similarly increased left ventricular end diastolic pressure – the direct cause of respiratory symptoms in heart failure – is reached with a more depressed ejection fraction in men respect to women.

The increased incidence of heart failure early in acute coronary syndromes may have the same explanation. Failure by the myofiber to relax is an early mechanical manifestation of acute ischemia. Clearly, if a diastolic dysfunction is already present, symptoms appear earlier.

Although women suffer more severe symptoms, they tend to have a longer survival, which is not uniformly acknowledged. However, morbidity is much higher in women, who therefore experience a generally worse quality of life. It is unclear whether more severe symptoms entail an increased rate of hospitalization. Indeed, this may not be the case, because most symptoms are non-specific and are often – at least partly – overlooked[44].

One interesting feature is that depressive symptoms often accompany heart failure in women. In a community sample of 338 non-institutionalized adults aged 45 years old, depressive symptoms were measured using the Beck depression inventory. Women scored significantly higher than men. Adjusted score increased linearly with heart failure stages A to C in women, while in men only stage C was associated with a significantly higher score. It should be noted that depression worsens prognosis[45].

Treatment

Treatment of heart failure is not gender-specific. Therefore, as a general rule in selecting therapeutic strategies current guidelines should be followed. That said, one cannot help noting that in clinical trials less than 30% of participants are female. Considerations about gender-related activity of some drugs or drug classes derive from post-hoc analyses.

General consideration

The percentage of lean mass is lower in females; therefore, volume distribution of liposoluble drugs is greater, whereas volume distribution of hydrosoluble substances is smaller.

Cytochrome P_{450} isoenzyme activity differs in men and women (Table 2). The consequences are particularly important for beta-blockers and calcium blocking agents, whose action is respectively increased and decreased in females[46].

Table 2. Gender differences in cytochrome P450 isoenzyme activity. Modified from Regitz-Zagrosek V et al, 2008[47].

Isoenzyme	Gender difference	Cardiovascular relevant substrate
CYP1A2	Lower in women, hormone-sensitive	Caffeine Paracetamol
CYP2C9	No gender difference	Warfarin
CYP2C19	Controversial	Omeprazol Diazepam
CYP2D6	Higher activity in males	Propanolol Metoprolol
CYP2E1	Higher activity in males	Halotan Isofluoran
CYP3A4	Higher activity in females	Tacrolimus Diltiazem Nifedipin Triazelam Cyclosporin Verapamil

Drug classes

Ace-inhibitors

Although there is no substantial data, current opinion favours the idea that ACE-inhibitors are less effective in women than in men. In Consensus-1 and SOLVD-treatment trials, mortality reduction was 5% in women as compared with 30-40% in men. A cough is certainly a more frequent, disturbing side effect in women. One reason for the diminished efficacy of ACE-inhibitors could be the prevalence of HFpEF in females, where RAAS blockage is less useful. It is interesting to note that this gender-related difference does not appear to be present in angiotensin-II receptor blockers. In short, ACE-inhibitors would appear to be partially effective in the general female population with heart failure, and particularly effective in symptomatic women with reduced ejection fraction.

Beta blockers

Beta blockers are certainly useful in women, with some slight differences seen between the various molecules. In some cases, their effectiveness would appear to be higher than in men, but this may be a false impression, because natural history of heart failure is more favourable in women. The relative efficacy is the same. The most probable explanation is that the cytochrome P_{450} isoenzyme involved in metabolism of betablockers has an enhanced action in men, so that drug activity in women is enhanced[47-51].

Device therapy

Device treatment has significantly improved the outlook of heart failure patients. Indeed, ICD treatment, both in primary and secondary prevention, avoiding sudden death, has dramatically improved their survival. Once again, gender-specific data is lacking, but the impression is that ICD is not as useful in women as it is in men, probably because sudden death is less frequent in women with heart failure. A possible exception exists in the form of ischemic heart disease, where incidence of sudden death is appreciable.

By contrast, cardiac resynchronization therapy (CRT) is particularly effective in women. Reverse remodelling is easily induced, measurable as reduced left ventricular end systolic volume, and a survival advantage therefore ensues. A recent meta-analysis considers that the relative probability to reduce left ventricular end systolic volume ≥15% is 1.12 (0.99-1.26) in women with respect to men. One possible explanation is that normal QRS duration is slightly shorter in females than in men, and therefore, at a given QRS lengthening, the mechanical damage may be more severe[52].

Conclusions

There are certainly differences in pathophysiology, aetiology and clinical presentation of heart failure in men and women. These differences should probably prompt different treatment strategies. However, we do not presently have sufficient data to suggest gender-specific therapies. General guidelines should be followed, whilst awaiting gender-targeted studies on heart failure.

Key messages

- Later-in-life heart failure is more prevalent in women than in men.
- Aetiology is especially hypertension, although ischemic heart disease and diabetes play an important role.
- The most common phenotype is heart failure with preserved ejection fraction.
- Treatment should follow general guidelines, although in randomized studies the female gender is poorly represented.
- Cardiac resynchronization therapy is particularly efficient.

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