Point of view

Sex, lies and heart failure. Conceptual mistakes in classification and epidemiology

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Heart failure (HF) is the common final pathway of many cardiac diseases, being the only cardiovascular syndrome with an increasing incidence, prevalence and total mortality in western societies[1]. However, and although our knowledge about this condition is rapidly increasing, ancient conceptual mistakes still persist in many clinicians' minds, resulting in a misunderstanding of HF (Table I). In the present article we will describe some of these "lies".

Sex

Lies. *Heart failure is less frequent and has a better prognosis in women than in men. Systolic dysfunction is a prognostic factor in both genders.* A higher prevalence of HF in women than in men is an ever-increasing finding in non-selected populations[2-8]. Probably, both genders have a similar prevalence, slightly higher in women. However, in younger individuals a male predominance is found, just the opposite of what happens in the elderly, in relation with the prevalence of ischemic heart disease. In spite of this fact, females are clearly underrepresented in HF trials, in part due to exclusion of older patients[9]. In recent trials only 20% of patients are women[8,10] and this is the main reason for the misperception of a lower prevalence of HF in females.

Two important epidemiological studies – the Framingham and the National Health and Nutrition Examination Survey (NHANES-I) – both not including left ventricular ejection fraction (LVEF), have suggested that, in patients with HF, female gender is an independent predictor of survival[11,12]. However, the results of studies including selected patients with left ventricular systolic dysfunction are inconsistent[13-16]. There is a paucity of data regarding non-selected patients, including elderly subjects with and without systolic dysfunction. Two small studies[2,17] found that female gender was an independent predictor of survival. However, Vaccarino et al.[18], studying a larger sample of 2445 patients > 65 years, 76% with LVEF assessment, found that gender was not an independent predictor of mortality. On the other hand, the longer life expectancy found in the general population for women (82.7 vs 75.3 years for males in Madrid[19]) clouds the interpretation of gender-related differences in mortality.

Although LVEF has a prognostic value in women with advanced HF and severe left ventricular systolic dysfunction[20], when we study a non-selected HF population, systolic dysfunction has no prognostic value in women. In the Heart failure Observation of Local Admissions (HOLA) study[19], with a total of 1065 hospital inpatients with confirmed HF, we found a similar survival in women irrespective of LVEF and in men with a LVEF > 0.30, while men with a severely depressed LVEF had a worse prognosis (Fig. 1). Although the reasons for this better prognosis in women remain unknown, we have recently shown that females with a severely depressed LVEF less frequently have right ventricular dysfunction than men[21]. Another finding that supports our theory of a different prognostic relevance of systolic dysfunction in each gender is the fact that female sex is related with a better prognosis only in the studies performed in patients with HF and systolic dysfunction[13-16], being the survival similar in both genders when LVEF is normal[22].

Table I. The ten most frequent mistakes in the classification and epidemiology of heart failure.

1. Heart failure is less frequent and has a better prognosis in women than in men.
2. Systolic dysfunction is a prognostic factor in both genders.
3. Heart failure has a clear and sole etiology in most patients.
4. Patients who receive heart failure treatment have heart failure and vice versa.
5. Heart failure patients have a correct knowledge about the medication they receive.
6. The number of readmissions is useful to compare different therapies.
7. Heart failure with a normal ejection fraction is rare and is due to diastolic dysfunction.
8. Effective treatment is available for heart failure with a normal ejection fraction.
9. Heart failure gradation is objective and has a good correlation with the prognosis and degree of systolic dysfunction.
10. B-type natriuretic peptide levels differentiate patients with heart failure from those who do not have the syndrome.

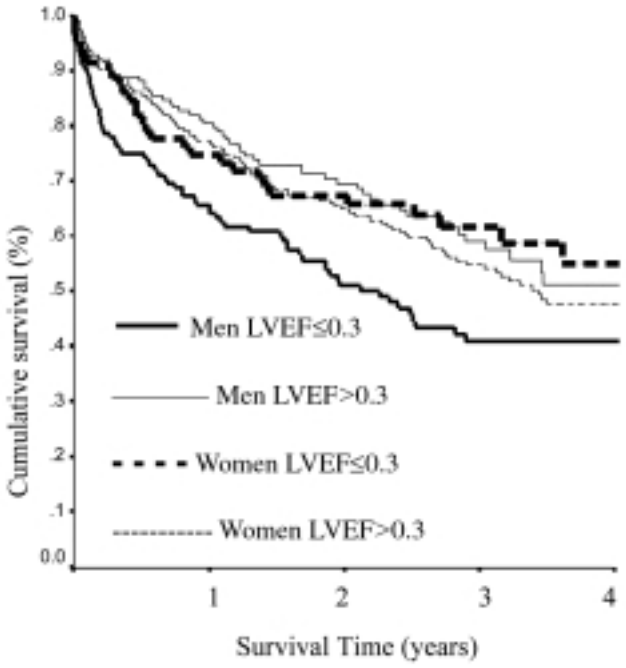

Figure 1. *Survival curves in the HOLA (Heart failure Observation of Local Admissions) registry[19] according to gender and left ventricular ejection fraction (LVEF).*

Etiology

Lie. *Heart failure has a clear and sole etiology in most patients.* HF is the common result of many disorders that produce cardiac dysfunction, it being a multifactorial syndrome related to many predisposing factors. HF risk factors include age, hypertension/left ventricular hypertrophy, ischemic heart/vascular disease, diabetes, obesity, renal disease, atrial fibrillation, valvular heart disease, alcoholism, etc.[23]. For this reason, it would be a mistake to consider any of these factors as the only cause of HF. However, both in everyday clinical practice as in the medical literature we find patients with HF or cardiomyopathy classified as ischemic, hypertensive, alcoholic, etc. Many studies perform this classification in a stepwise manner. If a patient has coronary heart disease it is assumed that this is the "cause" of his HF. Even if he is alcoholic, the inclusion will be in the ischemic HF group, only assigning an alcoholic "cause" to patients with no other "cause" of previous steps. When the patient has no history of alcohol abuse, we go to the next step, perhaps hypertension, and the process continues until a "cause" is found. However, there are no pathophysiological bases for this ranking of etiologies. Moreover, this artificial ranking has many problems: i) assigning a single factor is difficult as many patients have more than one. For example, a typical HF patient could be elderly, with hypertension, diabetes, atrial fibrillation, and a previous myocardial infarction; ii) there is a great variability in the prevalence of ischemic HF. This is due not only to the different study populations, but mainly to the different criteria used in making the diagnosis of ischemic HF. Many studies assign an ischemic etiology to patients with coronary artery disease of a single vessel or an etiology based solely on symptoms; iii) in about one third of the patients there is no clear "etiology" of HF and these are classified as having idiopathic HF/cardiomyopathy[24]; iv) this diagnosis is changed to hypertensive cardiomyopathy if an elevated systemic pressure is present. However, 20-25% of the adult population has hypertension, and in people > 65 years this percentage reaches 41%[23]. As the mean age of HF patients is 75 years[7], the limitations of this methodology are evident. Moreover, patients with a history of hypertension could have a normal blood pressure when they develop HF[25], rendering this etiologic classification even more difficult; v) whereas some conditions such as atrial fibrillation may be a cause of HF (tachycardia-induced cardiomyopathy), they may also be a consequence of a ventricular dysfunction; vi) diabetes mellitus is not included as a cause in the majority of HF studies. However, diabetes increases the risk of developing HF, not only by means of an indirect mechanism – through its association with ischemic heart disease, hypertension and dyslipidemia – but also directly by producing diabetic cardiomyopathy consequent to cardiac microangiopathy[26]. In the Framingham study, diabetes increased the risk of HF 2- to 7-fold, suggesting an effect independent of coronary artery disease[27].

Treatment

Lie. *Patients who receive heart failure treatment have heart failure and have a correct knowledge about the treatment they are receiving. Cardiologists rarely treat patients admitted for heart failure and the number of readmissions is useful to compare different therapies.* Although nowadays therapeutic regimens with a clear

survival benefit in patients with HF and left ventricular systolic dysfunction are available, there still are many HF patients who do not receive adequate treatment. Moreover, many patients are treated for HF despite the fact that they do not have this syndrome. According to Sharpe[28], among all patients receiving HF treatment, half did not present with HF, a quarter had HF but did not receive a correct treatment, and only a quarter had HF and received adequate therapy. In the HOLA registry, including patients hospitalized at our institution, 23% with a HF diagnosis and receiving treatment for HF had no objective data in support of this diagnosis[7].

Evidence-based treatment of HF, at least HF due to systolic dysfunction, implies an increasing number of drugs: angiotensin-converting enzyme inhibitors, beta-blockers and, frequently, spironolactone, diuretics, angiotensin receptor blockers and, in some cases, digoxin or the combination of isosorbide dinitrate and hydralazine. If coronary artery disease is present, aspirin and statins are frequently used. This results in three quarters of the patients receiving six or more pills daily and one third eleven or more pills daily[29]. However, HF affects mainly the elderly and the use of so many drugs could result in non-compliance. As non-compliance is a common cause of HF decompensation and as new, additional drugs, are currently being developed as "add-on" therapies alongside current treatments, this problem will probably increase in the future. Moreover, HF patients already have a poor knowledge about the medication they are receiving[29]: only half of them know that hypotensive drugs decrease blood pressure and less than 42% of patients treated with acenocoumarol and one third of those treated with aspirin know that they have been prescribed these drugs for anticoagulation purposes. Finally, only 14% of patients are aware of the possible initial deleterious effect of beta-blockers on symptoms.

Although it is true that the majority of patients hospitalized for HF are not admitted in cardiology departments, a good 20% of them are admitted to such wards[7]. Moreover, many data suggest that cardiologists more frequently follow the recommended management as their treatment choices more frequently conform to published guidelines and the results of clinical trials[30]. For example, cardiologists prescribe angiotensin-converting enzyme inhibitors to patients with systolic dysfunction more frequently than non-cardiologists and the opposite holds true for patients with a normal LVEF[31]. In addition, cardiologists submit their patients to echocardiography more frequently[32]. Previous studies suggest that patients gain more benefit from cardiologic care in that their quality of life is better and they are less frequently hospitalized for HF-related reasons than patients cared for by internists; however, definitive demonstration of the prognostic advantage of cardiologic care is still lacking[32-34]. Moreover, and although HF is a cardiovascular disorder, it is not possible for all HF patients to receive specialist care. A multidisciplinary approach is probably the best option as many patients have coexisting disorders such as diabetes mellitus, chronic lung disease, renal dysfunction or peripheral vascular disease, and internists, geriatricians or other physicians are often responsible for these patients when they are hospitalized.

The all-cause mortality is undoubtedly the most unbiased endpoint in HF trials, has the advantage of being a "hard" endpoint, easy to measure, not readily subject to observer bias, and it clearly represents an important event[35]. However, as mortality studies usually require a large sample size, mainly in patients with initial HF, and as patients with HF have an impaired quality of life requiring frequent hospitalizations, more and more studies rely on the number of readmissions avoided with a new therapy and the rate of hospitalization is becoming a frequent endpoint in clinical trials.

The event of hospitalization apparently represents an objective endpoint but the truth is that this is not the case. One should take into account the definition of hospitalization (either a short ward stay or a real admission), the varying thresholds for hospitalization in different centers, the different regional policies for hospitalization, and the different ways of defining decreased requirements for hospitalization (either in the length of stay or in readmissions, or a combination of these two factors)[35,36]. Some study protocols have attempted to define hospitalization for HF in a way that minimizes the inclusion of hospitalizations of minor significance. Specifically, to be counted as an endpoint, some protocols have required hospitalizations for HF to have a minimum duration (e.g., 24 hours) and to be accompanied by an aggressive intervention specific for HF (e.g., the use of intravenous medications)[37].

In addition to the issue of subjectivity the main problems with the use of readmission as an endpoint are: i) the fact that it is difficult to define the main cause for hospitalization, especially in patients with several concomitant diseases, where one may speculate whether the patient was hospitalized with HF, or because of HF[35]; ii) the fact that the patient who is hospitalized for HF is considered as being in a worse shape shortly after the initiation of treatment even if he presents with a marked (but delayed) clinical response to the drug[34]; iii) the fact that mortality is often not taken into account; since patients who die are obviously no longer rehospitalized, these comparisons should always be performed using the combination death or rehospitalization but not the rate of rehospitalization alone, a caution that is also necessary when the rate of treatment compliance is measured[38].

Systolic/diastolic heart failure

Lie. *Heart failure without left ventricular systolic dysfunction is rare, is due to left ventricular diastolic dysfunction and has an effective treatment.* About 50% of

patients with HF have a normal LVEF[2,39-41]. This percentage is even higher in the elderly and in women[19,42-44] (Fig. 2). Moreover, previous studies clearly show the entity of HF with a preserved LVEF[45] as having a natural history and treatment that could be different from those of HF with systolic dysfunction[43-47]. In spite of these evidences, some experts still doubt that the majority of patients diagnosed with HF and a normal LVEF do indeed have HF. There are even authors who suggest that isolated left ventricular diastolic dysfunction is rare[48] and that patients with the diagnosis of HF and a normal LVEF have other illnesses such as pulmonary diseases and obesity[49].

Although HF with a normal LVEF and diastolic HF are frequently used indistinctly, there is no evidence that the majority of HF patients with a normal LVEF do actually have diastolic dysfunction[50,51]. The reasons for HF with a normal LVEF and a normal diastolic function are unknown but include a combination of vascular stiffness[51] and transitory ischemia.

Finally, and although the therapeutic arsenal for the treatment of HF with left ventricular systolic dysfunction has notably increased in the last years, we do not yet have a single drug with a demonstrated survival benefit in patients with HF and a normal left ventricular systolic function. This is due, at least in part, to the, until recently, systematic exclusion of patients with a normal LVEF from HF trials.

Heart failure onset and functional class

Lie. *Heart failure has a clear beginning and its time of onset may be easily determined. The gradation of heart failure is objective and is well correlated with the prognosis and degree of systolic dysfunction.* Some diseases have an abrupt beginning, for example myocardial infarction, with a clear time of onset, and investigators can report the incidence of those conditions using phrases such as "2% of the studied population presented with a myocardial infarction during the follow-up period". Although similar sentences are used for HF, this syndrome has, in most cases, an insidious beginning with frequent outbreaks alternating with long-lasting periods free of signs and symptoms. For this reason, pretending that we can precisely define the onset of HF is misleading. Moreover, if the aim is to detect HF as early as possible, then the diagnostic criteria by which to define the initial stages of this syndrome should be modified. As this condition may progress slowly for many years, and the most specific definitions of HF are those pertaining to the end phases of the disease, it clearly follows that although a few cases are misclassified, only manifest cases can be detected[52].

In daily clinical practice, the gradation of HF is an extremely important concept that is used to establish the prognosis and to evaluate different therapeutic alternatives. The most frequently used classification is that of the New York Heart Association (NYHA)[53] which is based on the correlation between the intensity of exercise performed and the appearance of dyspnea or fatigue. In spite of it being a conceptually simple classification, it has a low interobserver concordance[54], the assessment of dyspnea remains subjective, and it lacks sufficient sensitivity for the detection of small but important changes in clinical status[37].

A patient with moderate exercise dyspnea and occasional episodes of paroxysmal nocturnal dyspnea may be classified in functional class IV; however, his symptoms, prognosis and quality of life will be very different from the moment he develops permanent rest dyspnea. The classification of highly variable functional statuses in the same functional class is difficult to resolve. Some useful alternatives are the 6-min walking test, with a good prognostic value[55], and the Minnesota auto-evaluation questionnaire[56]. Moreover, HF symptoms are poorly correlated both with the prognosis as well as with the degree of left ventricular systolic dysfunction[57]. Besides, even the NYHA classification is poorly correlated with the peak oxygen consumption and with the prognosis in patients with mild to moderate HF[58]. Because of difficulties in standardization, the evaluation of symptoms has been characterized by marked intraobserver and interobserver variability that have im-

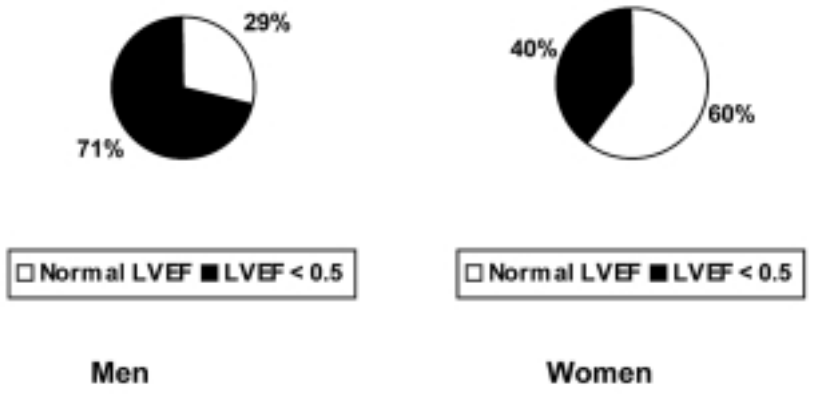

Figure 2. *Left ventricular ejection fraction (LVEF) in the HOLA (Heart failure Observation of Local Admissions) registry[19] according to gender.*

paired the usefulness of this measure in discerning changes in clinical conditions or in the effects of treatment[37]. Even the interobserver agreement on the presence or absence of symptoms of HF may be low, as the characteristic symptoms of HF (breathlessness, ankle swelling, and fatigue) may be difficult to interpret, particularly among elderly patients, the obese and in women[57]. Finally, and although the term "symptomatic HF" is frequently found in the literature[13], the correct denomination is symptomatic left ventricular dysfunction, as HF is, by definition, symptomatic; patients in NYHA class I would have to have a past history of HF symptoms and be receiving treatment for HF in order to fulfill the definition of HF[57].

Diagnosis

Lie. *B-type natriuretic peptide levels differentiate patients with heart failure from those who do not have the syndrome.* Although B-type natriuretic peptide is useful in the diagnosis of patients with dyspnea and in the follow-up of patients with HF it has important limitations when trying to determine whether a patient actually has HF, as almost one third of HF patients may present with normal B-type natriuretic peptide levels. These limitations are particularly important in patients with HF and a preserved left ventricular systolic function, with considerable overlap between B-type natriuretic peptide levels in patients who have HF with a preserved systolic function and in those without HF[59]. Moreover, B-type natriuretic peptide levels are also elevated in patients with dyspnea due to other causes, as in case of acute pulmonary embolism[60]. For all these reasons the diagnostic role of B-type natriuretic peptide levels in HF is limited, and it is not clear whether B-type natriuretic peptide determination improves the evaluation of patients with a preserved left ventricular systolic function[61]. This marker should not substitute an integrated and accurate clinical approach. As Rodeheffer[62] points out in a recent revision, the introduction of the natriuretic peptides as diagnostic tools in ventricular dysfunction has given rise to high expectations as to their accuracy and clinical value but the diagnostic utility of B-type natriuretic peptide is still a work in progress. At present, it is reasonable to adopt plasma B-type natriuretic peptide levels as an aid in the diagnosis of dyspneic patients in whom the cause is uncertain. However, it must be borne in mind that the value of B-type natriuretic peptide in the screening of asymptomatic patients and in monitoring therapy is an area still under investigation[62].

Conclusion

We are in the midst of an increasing epidemic of HF, a multifactorial syndrome with numerous etiologies in most patients and a similar prevalence in both genders. Left ventricular systolic dysfunction is present in about 50% of patients, is more frequent in males and is related to mortality only in men and not in women with HF. Although drugs that are clearly beneficial in HF with a depressed LVEF are available, many patients do not receive it, and compliance with evidence-based treatment is difficult in a condition which manifests at a mean age of 75 years. Finally, in spite of the enormous prevalence of HF with a normal LVEF, we have no treatment with a demonstrated survival benefit to offer to such patients.

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