Prognostic Factors in Patients with Congestive Heart Failure

Humberto Villacorta, Evandro Tinoco Mesquita

Rio de Janeiro and Niterói, RJ - Brazil

The natural history of congestive heart failure (CHF) was initially described in the Framingham Heart Study, carried out in the US city of Framingham, Massachusetts, in which 5,209 individuals were randomly selected and followed for four decades (1949 to 1987) [1]. In 1971, the descendents of this initial population and their respective spouses (5,135 individuals) were also included in the study and, in 1993, the evolutional data of this cohort study of 10,344 participants were published [2]. The survival rate in five years was 25% for men and 38% for women; this survival rate is similar to that observed in patients with some types of cancer, such as lung cancer, for example [3].

It is estimated that in the US almost four million people have CHF and that 700,000 new cases occur every year [4]. In addition to the high prevalence, there is another factor of concern. There is evidence that the number of hospital admissions due to CHF has increased in the last two decades. According to North American statistics, the number of hospital admissions of individuals older than 65 years and whose main diagnosis was CHF increased from 7.5 per 1,000 in 1986 to 16.3 per 1,000 in 1989[2].

These data cause CHF to be regarded as a public health problem throughout the world. The high morbidity and mortality show that the current treatment is still unsatisfactory. On the other hand, economic resources are limited and every strategy should be well assessed to avoid wasting. Therefore it is very important to identify the individuals with poor prognosis who can eventually benefit from aggressive management.

This manuscript discusses prosent issues of the main prognostic factors used in the assessment of patients with CHF. Some have recognized value and are used frequently in the clinical practice. Others have a controversial or not well-established value, as we will see below.

The role of gender

CHF is more common in men than in women, but the role of sex as a prognostic factor is not clear. In the Framingham study [1,2], two years after the diagnosis of CHF, 37% of the men and 38% of the women were deceased. Six years thereafter, however, there was a clear difference favoring women, whose mortality rate was 67% compared to 82% in men. According to Hermann and Greenberg [5], however, it is not known if this reflects a difference in the natural history of the disease or if it results from the influence of the underlying etiology or from gender-dependent res-ponse to treatment. Schocken et al [6], in another population study, also found smaller mortality in women. In Chagas' disease, the male patients, who have greater impairment in ejection fraction (EF), also have the poorest prognosis compared to women [7,8].

In other studies, the opposite was observed. In the prevention substudy of the SOLVD investigators [9], women, who comprised 26% of the total patient population, had an annual mortality rate significantly higher than that of men (22% compared to 17%) and a higher rate of hospitalization due to CHF (33% compared to 25%). In the substudy that assessed the treatment with enalapril [10], in the same project, only 15% of the participants were women and there was no difference in mortality rate between the genders.

Adams et al [11] evaluated the prognostic value of gender in relation to etiology of CHF and reported a higher survival rate in women with CHF caused by nonischemic heart disease than in men with or without coronary artery disease (CAD). When CHF in women was caused by ischemic heart disease, however, there was no significant difference between genders.

In a multicenter Italian study [12] of idiopathic dilated cardiomyopathy, women showed more advanced disease than men, in regard to symptoms and left ventricle (LV) dimensions. There was, however, no statistically significant difference in regard to mortality, even though there was a tendency toward a poorer prognosis in females.

A limiting factor for establishing the role of gender in the prognosis of CHF is the small number of women usually included in the studies. Lindenfeld et al [13] suggest that this happens because of the higher proportion of diastolic CHF, in relation to systolic dysfunction, in women. In large clinical trials the selection of patients is usually based on EF, in an attempt to include those with severe systolic dysfunction. The number of women with severe systolic dysfunction is

Hospital Pró-Cardíaco, Rio de Janeiro and Universidade Federal Fluminense, Niterói
Mailing address: Humberto Villacorta - Rua Raimundo Correa, 23/601 - 22040-040 - Rio de Janeiro, RJ - Brazil

much smaller than that of men. According to these same authors, this would also explain the better prognosis for women observed in the Framingham study.

An ongoing study (BEST study) [5] that evaluates the effects of the beta-blocker bucindolol is the first study of CHF survival designed to include a great number of women, so that an accurate statistical analysis can be made of the relation between gender and prognosis and the therapeutical response [5].

Age

Advanced age, independent of gender and race, is related to a poorer prognosis. In the Framingham Study, there was an increase in mortality with the increase in age at the moment of diagnosis of CHF. The increase was 27% and 61% for each decade of life, in men and women, respectively [2].

In the SOLVD study [14], the annual mortality in individuals from 21 to 55 years of age was 16.6%, increasing to 38.4% in those older than 76 years. The second Veterans' study [15], however, did not show any relation between age and survival, but the subgroups may have been too small to detect it [5].

Presence of comorbidity

Many diseases can occur in association with CHF, worsening its prognosis. The most studied ones are hypertension and diabetes mellitus. Hypertension triples the risk of developing CHF [6]. In addition, persistent hypertension in a patient with CHF worsens the cardiac performance due to vasoconstriction and, therefore, should be aggressively treated [5].

Diabetic cardiomyopathy was described as an entity in the 70s [16], and there is evidence that its incidence has increased [2]. Independently from the risk of developing CAD, diabetes increases the risk of developing CHF, and this risk is at least double in women than in men [6,17]. The risk of CHF is increased five times when hypertension is associated with diabetes [5]. Data of mortality directly related to these entities are difficult to analyze because of the frequent association of other affections, such as atherosclerotic disease and stroke [5].

Both renal and hepatic failure can worsen the prognosis of CHF because they limit the use of some medications – angiotensin-converting enzyme inhibitor (ACEI), for example – and impair the therapeutic response [5]. In a metanalysis by Golper [18], involving more than 60 patients in peritoneal dialysis, the survival rate in one and two years was only 37% and 15%, respectively. In another study [19] carried out in 35 patients with CHF being treated with continuous hemofiltration, the mean survival rate was 10 months.

Other associated disorders, such as pulmonary hypertension of any etiology, tobacco use, alcohol consumption, and pulmonary diseases are related to a worse prognosis [5,20].

Etiology of congestive heart failure

The etiology of CHF can sometimes influence prognosis. The presence of CAD as a cause of CHF is questioned as a factor worsening the course of the disease. So far, there is no agreement in regard to this question. Studying individuals with CAD, Franciosa et al [21] found a mortality rate of 46% and 69%, for one and two years, respectively. For patients with idiopathic dilated cardiomyopathy, the rate was significantly smaller, 23% and 48%, respectively.

In a study carried out in Japan [22], patients with CAD had a worse survival rate in five years than those with idiopathic dilated cardiomyopathy (35% to 40%). Other authors [23-25]also found a worse prognosis in patients with ischemic cardiomyopathy. Bart et al [25], in a recent study on patients who underwent coronary angiography, not only demonstrated that the ischemic etiology was an independent predictor of mortality, but also observed that the extension of CAD was a stronger predictor than the presence or absence of ischemic heart disease.

In the Veterans' study [26] and in the studies of Cohn et al [27] and Parameshwar et al [28], the presence of CAD was not related to worse prognosis.

Some diseases, such as hypertrophic cardiomyopathy [29], hemochromatosis [5], endomyocardial fibrosis [30], Chagas' cardiomyopathy [31], and amyloidosis, [5] have a significantly poorer prognosis when they evolve with CHF. Amyloidosis has a mortality rate of 100% in two years, after the onset of symptoms [5,32], and the prognosis is worse in those with restrictive cardiomyopathy [33].

Functional class

The severity of the symptoms caused by CHF seems to be related to mortality [10,14,21,34,35]. The classification most used to quantify the symptoms is that of the New York Heart Association (NYHA). In the SOLVD study [10], patients in functional class (FC) IV had a mortality of 64% during a mean follow-up of 41.4 months compared to patients in FC III, II, and I, whose mortality rates were 51%, 35%, and 30%, respectively.

The NYHA classification, despite being practical and widely known and a determinant of prognosis, is criticized by some authors [5]. It not always correlates with the degree of ventricular dysfunction or with objective measures of exercise capacity [26,36,37]. Therefore, we can find patients with preserved systolic function and with significant diastolic alterations that, despite severe symptoms of CHF, have a long-term prognosis better than those with systolic dysfunction [22,38,39]. It is not uncommon to find patients with severe systolic dysfunction of the LV and mild symptoms.

Another less known but more reproducible classification is the Specific Activity Scale [40]. Its advantages are smaller subjectivity in the assessment of the symptoms and better correlation with the functional capacity. It lacks, however, data about mortality.

Cardiothoracic ratio

This is an easily obtainable parameter, and its increase has been associated with worse prognosis. In the Veterans' studies, the cardiothoracic ratio was an independent predictor of mortality, surpassed only by EF and peak exercise oxygen consumption [36]. Nicklas et al [14] showed that a cardiothoracic ratio higher than 0.52 was related to higher mortality. In another study, where only noninvasive prognostic factors were evaluated, the cardiothoracic ratio was between the three strongest parameters independently associated with mortality [41].

The cardiothoracic ratio has limitations. As the cardiac silhouette in the anteroposterior projection is mainly formed by the right chambers, the cardiothoracic ratio changes only in the greatly dilated hearts, being, therefore, a specific index but one with little sensitivity [5].

Ejection fraction

The EF of the LV can be obtained, in a noninvasive way, using echocardiography or radionuclide ventriculography. In patients with systolic dysfunction of the LV, the EF is among the strongest predictors of mortality [10,15,36,42]. In the SOLVD study [10], patients with EF of 23% to 35%, with a mean follow-up of 41.4 months, had a mortality rate of 28%; for those with EF of 23% to 29%, this rate was 39%; and for those with EF of 6% to 22%, the mortality rate was 50%. Other studies showed similar results. In the study of Cohn et al [36], patients with EF smaller than 25% had a worse prognosis than those whose EF was greater than 35%. Serial studies of EF are also useful in the evaluation of prognosis. In a study [43], a reduction of the EF greater than 5% in one year was associated with a mortality almost two times higher.

The EF of the right ventricle (RV) has also shown to be a predictor of mortality. DiSalvo et al [44], through radionuclide ventriculography of the RV, showed that a EF higher than 35% was more strongly correlated with survival than the isolated oxygen consumption (VO_2). Another advantage of this parameter is that it correlates very well with the exercise capacity measured using VO_2, the opposite of what happens with the measurements of the LV function [5].

Exercise capacity

Decreased tolerance to exercise is a frequent symptom in CHF. This way, the degree of the patient's tolerance to effort provides significant information and can be measured in an objective way. A frequently used index to assess the exercise capacity is VO_2, which provides indirect information about the cardiovascular and pulmonary reserves and has been useful in the prognostic evaluation of the patients with CHF [28,45,46]. Maximum oxygen consumption would be the ideal index, but it is often impossible to be obtained because the patient usually interrupts the effort before that point, due to muscular fatigue and exhaustion. Therefore, peak exercise VO_2 is more usually cited [47].

Szlachcic et al [45] were the first to demonstrate the association of VO_2 with prognosis. In that study, the survival of individuals with VO_2 higher than 10mL/kg/min was 80% compared to only 20% for those with VO_2 smaller than that value. Mancini et al [46] showed similar results. To a similar degree of EF reduction, patients with a peak exercise VO_2 smaller than 14mL/kg/min had a higher mortality in one year (30% to 50%) than those with exercise capacity preserved, whose mortality was smaller than 10%. Maximum VO_2 is also useful in the indication for heart transplantation. Values smaller than 14 ml/kg/min indicate possible transplantation and when values are smaller than 10mL/kg/min the transplantation indication is definitive [48,49].

In Chagas' cardiomyopathy, VO_2 is a significant prognostic factor [31,50,51]. In the study by Mady et al [31], maximum VO_2, along with EF, was an independent predictor of mortality during an average 30-month follow-up.

On the other hand, VO_2 was not a good predictor of mortality in the studies by Wilson et al [52] and Franciosa et al [53]. Another important fact is that there may not be any correlation between VO_2 and EF [36,37], showing the independent prognostic value of these two variables.

Another test used to assess exercise capacity is the six-minute walking test [54,55,56], which correlates well with the patient's symptoms during daily activities [5]. In the studies by Sueta et al [57] and Bittner et al [58], there was a strong correlation between the distance walked and survival. Bittner et al [58] showed that when the distance walked was smaller than 305m, the annual mortality was 11% compared to only 4%, when the distance walked was higher than 443m. In this latter study, the six-minute walking test was also a predictor of future hospitalizations.

Hemodynamic variables

Several authors [59-62] found a worse prognosis for patients with hemodynamic variables severely altered. Creager et al [60] found a worse prognosis in patients with reduced cardiac output. Franciosa [62] found a higher mortality in patients with LV filling pressures higher than 27mmHg, systemic vascular resistance higher than 23 Wood units, and cardiac index smaller than 2.25L/min/m^2. Some authors, however, found no significant correlation between LV filling pressures, cardiac output and mortality, even though these variables were slightly altered in those who did not survive [52,63].

Right atrium (RA) pressure has also been correlated with survival. In the studies by Creager et al [60], Unverferth et al [61], and Lee and Packer [64], patients with a smaller RA pressure had a better prognosis than those with high pressures in this chamber. In another study [57], the mean pulmonary pressure was the only hemodynamic variable independently related with a worse prognosis in patients with CHF treated on an outpatient basis.

It is interesting to note that even though the hemodynamic variables, when significantly altered, indicate a

worse prognosis; no correlation between these variables and the symptoms or the exercise capacity was found [52,61,65]. Treatment with drugs that increase the cardiac index and reduce the filling pressures also did not increase survival [66]. It is important to note that the hemodynamic parameters are useful mainly when a population with varied severity of symptoms is assessed [62].

Neurohormonal system

In patients in advanced stages of CHF (FC III and IV and low EF), the hemodynamic and functional factors are no longer predictors of the disease course, and the factors related to the neurohormonal system are fundamental for determining prognosis [27,52,63,67]. Several systems are activated in CHF in order to compensate for the circu-latory disorder caused by reduction of the cardiac output. The sympathetic nervous and the renin-angiotensin-aldosterone (RAAS) systems cause vasoconstriction and water retention, in an attempt to compensate the low cardiac output and the poor tissular perfusion [68,69]. Excessive and prolonged activation of these systems, however, ends up being pernicious [67]. Vasodilating systems are also activated aiming to reduce the noxious effects of the vasoconstrictors [69]. The prognostic value of the main systems involved in the pathophysiology of CHF will be discussed below.

Sympathetic nervous system – The plasmatic level of norepinephrine reflects the activity of the sympathetic nervous system [67] and is substantially increased in patients with CHF, proportionally to the clinical severity of the disease [67,70-72]. This elevation precedes and predicts the development of CHF, even in patients with asymptomatic ventricular dysfunction [27,67,70].

Countless studies show the prognostic value of the plasmatic concentration of norepinephrine [27,36,60,67,70,72]. In the study by Cohn et al [27], values between 400 and 800ng/mL were related to high mortality. Patients with levels higher than 800ng/mL had a 24-month survival lower than 20%. In that study, the dosage of norepinephrine was also useful to determine the mode of death. Individuals who died because of the progression of the CHF had average levels of 1,014ng/mL compared to 619ng/mL in those who died suddenly. This difference is statistically significant. It is important to emphasize that the prognostic significance of norepinephrine depends on the population being studied and it is higher in patients in advanced stages of the disease [67,70].

Sympathetic hyperactivity is not only a prognostic determinant but it also seems to contribute directly to clinical and hemodynamic worsening of CHF. This conclusion can be drawn from the results of multicenter studies that showed an improvement of the hemodynamic parameters and reduction of mortality due to the use of drugs that block beta-adrenergic receptors [73-78]. Opposite results were obtained with agonists of these receptors [79-81].

Renin-angiotensin-aldosterone system – The plasmatic activity of renin reflects the degree of activation of the RAAS [63,82] and its levels are increased in CHF, in the same proportion of disease severity [63,67,83]. Activation of the RAAS contributes directly to the deterioration of CHF [84], as shown by clinical trials with ACEI [10,34,85,86], whose results show improvement of clinical findings and increase of survival with these drugs. As the sympathetic activity, the RAAS activation is more important as a prognostic factor in the more severe patients, in whom the hemodynamic variables are no longer able to predict the prognosis [67].

The renin activity has a linear inverse relation with the plasmatic concentration of sodium [63,67,87-89], so that the presence of hyponatremia identifies a group of individuals with great activation of the RAAS [67]. This relation is partially due to the fact that RAAS has a great importance in the pathogenesis of the hyponatremic CHF [90]. In fact, patients with hyponatremia have clinical characteristics similar to those with high levels of renin, i. e., they tend to be clinically decompensated, with high levels of circulating hormones and they frequently have prerenal uremia [67,83]. Tissular hypoperfusion that exists in CHF and the action of angiotensin II stimulate, in a nonosmotic way, the release of vasopressin [91], which through its antidiuretic action may contribute to hyponatremia [67,91,92].

In 1984, Cohn et al [27] were the first to show the prognostic importance of hyponatremia and the plasmatic renin. In their study on 106 patients with CHF, these two variables were associated with mortality through univariate analysis. In multivariate analysis, however, they lost their statistical value, being surpassed by plasmatic catecholamines. Two years later, Lee and Packer [63] showed in a definitive way the prognostic value of sodium and plasmatic renin. Patients with sodium higher than 137mEq/L had a greater survival than those with mild hyponatremia (133 to 137mEq/L) or moderate to severe hyponatremia (<133mEq/L) [63,67]. Those with sodium <130mEq/L had an one-year survival rate lower than 20% compared to those with serum sodium higher than that value, whose survival rate was almost 50%.

In a recent study [93] involving patients with decompensated CHF admitted to the emer-gency department, we observed that the presence of hyponatremia was the only factor independently related to hospital mortality and survival at 16-month follow-up, among routine clinical, laboratorial and echocardiographic variables. Global mortality was 52% for patients with serum sodium <135mEq/L compared to 16.6% for those with serum sodium >135mEq/L.

The SOLVD study [14] confirmed the prognostic value of the RAAS in CHF. The plasmatic activity of renin, as well as the plasmatic norepinephrine and the atrial natriuretic factor (ANF) were strong predictors of mortality in one year.

In the CONSENSUS I study [94], increased levels of angiotensin II and aldosterone, in addition to norepinephrine and ANF, had a significant correlation with mortality. Angiotensin II had a stronger correlation than norepinephrine, the opposite of what had been found in

previous studies. This fact can result from the type of population studied in CONSENSUS, where only patients in FC IV were included [5].

Aldosterone in animal models plays an important role in the proliferation of fibroblasts and in myocardial fibrosis [5]. In the SOLVD study [95], the ACEIs caused reduction of the myocardial mass measured by echocardiography and, in the CONSENSUS study [94], they reduced the aldosterone levels by almost 60%. These findings suggest that aldosterone has a deleterious effect on the failing myocardium. The RALES study [96] that assessed the effect of spironolactone, an inhibitor of aldosterone, in the mortality of patients with CHF was recently interrupted for evidencing the benefits of the drug (unpublished data).

Vasopressin – Arginine vasopressin is released in response to a reduction in intracellular volume (osmotic stimulus) or in response to a reduction in extracellular volume or in blood pressure (nonosmotic stimulus). It acts increasing the water reabsorption in the kidneys and causing systemic vasoconstriction [68].

Vasopressin plasmatic concentration is increased in patients with severe CHF [67,91,92,97]. Its exact role in the pathophysiology of CHF, however, is not clear. It is known that, in hyponatremic CHF, vasopressin is frequently increased, along with renin activity, and it has been implicated in the pathogenesis of the disturbance of water metabolism found in this condition. Goldsmith et al [97], however, did not find any correlation between vasopressin and serum sodium or osmolarity in patients with CHF, suggesting that hyponatremia is not a simple outcome of the release of vasopressin in this syndrome.

The value of vasopressin as an independent prognostic factor is not well defined, and there are no data suggesting that it has a direct deleterious effect on survival [67]. In the SOLVD study [14], the serum level of vasopressin was not a predictor of mortality.

Atrial natriuretic factor – In 1985, Lang et al [98] demonstrated the presence of this factor in humans, for the first time. The main stimulus for its release is atrial distension or stretch and not the increase of pressure [99]. It has a diuretic, natriuretic and vasodilating action, the opposite of the deleterious effects of the vasoconstrictive hormones [67,69].

Plasmatic levels of ANF are increased in CHF [67,100-102]. In the CONSENSUS [103] and SAVE [104] studies, these levels correlated with the symptoms, cardiac index, and LV filling pressure, but not with EF. Values superior to 125ng/mL were related to a greater mortality [104].

Brain natriuretic factor – This factor was discovered in 1988 [105]. It has a great chemical similarity to the ANF [106]. Patients with CHF have extremely elevated plasmatic levels of this peptide, and its release by the patient's ventricles is also quite increased [107,108]. As the ANF, the brain natriuretic factor seems to play a significant role in the pathophysiology of the CHF, acting as an endogenous vasodilator and diuretic. The clinical improvement observed when it is administered to patients with CHF confirms this hypothesis [109]. Its importance as a prognostic factor was recently demonstrated. McDonagh et al [110], in a population-based study carried out in Glasgow, Scotland, demonstrated that values of the brain natriuretic factor superior to 17.9 pg/mL were independently related to total and cardiovascular mortality. In addition to the prognostic value, it is worth emphasizing the great accuracy of this method in the diagnosis of the ventricular systolic dysfunction, where it is increased even in the asymptomatic phase, and can be used as a screening test for early identification of these individuals (Dargie, personal communication).

Prostaglandins – Prostaglandins are not true hormones, but autacoids, i. e., they are locally synthesized and activated [69]. Metabolites of prostaglandin, such as PGI_2 and PGE_2, however, are circulating substances and are increased in CHF [67,69,88,111,112]. This increase is partially due to a direct response to systemic hypoperfusion and also to stimulation of activated vasoconstrictive hormones, especially angiotensin II [67]. As observed with the vasoconstrictive hormones, the activity of prostaglandins increase with the aggravation of the disease [69].

Patients with advanced CHF are strongly dependent on prostaglandin to maintain an adequate renal function, with an appropriate excretion of sodium [69]. In hyponatremic patients, worsening of CHF was observed after utilization of drugs that inhibit the synthesis of prostaglandin, such as indomethacin [88]. There was a decrease in the cardiac index and an increase in systemic vascular resistance and pulmonary capillary pressure.

In patients with chronic CHF [67], the metabolites of prostaglandin are accurate – although not independent - prognostic markers because of their relation to hyponatremia.

Endothelins – A potent vasoconstrictor produced by the cells of the vascular endothelium, called endothelin, was described by Yanagisawa et al [113], in 1988. Today, at least four different isoforms (ET-1, ET-2, ET-3, and an intestinal vasoactive form) are known. Once released, they have a great variety of effects on the cardiovascular, renal, pulmonary, and neuroendocrine systems, acting in two distinct receptors (ET_A and ET_B) [69].

Endothelins levels are tripled in patients with CHF [114-116] and correlate with the FC [114,116] and the degree of pulmonary hypertension [117]. A precursor named big endothelin-1 was an important predictor of short-term mortality in patients with advanced CHF, surpassing hemodynamic variables and ANF [118]. Blockers of endothelin receptors and inhibitors of the endothelin-converting enzyme have been developed and should help to clarify the role endothelins play in the genesis and prognosis of CHF [69,119].

Cytokines – Some peptide mediators, such as growth factors and inflammatory cytokines, have important effects on the myocardium and blood vessels and seem to be

involved in the genesis of CHF [120]. Growth factors may cause hypertrophy associated with the expression of fetal genes [120]. Inflammatory cytokines, such as the alpha tumor necrosis factor, may cause immediate myocardial damage in vitro [120] and are increased in CHF [121]. Another inflammatory cytokine, beta interleukin-1, causes myocardial hypertrophy in vitro [122].

Cytokines may be involved, in the long run, in myocardial remodeling and alterations of the vascular tissue [120]. Their role in the pathophysiology and prognosis of CHF, however, is yet to be defined.

Thyroid function

Alterations in the metabolism of the thyroid hormones, such as hyper- or hypothyroidism, are known as cause or precipitating factors of CHF [123]. Lately, these hormones have been observed to also have prognostic value. In CHF, Hamilton et al [124] evaluated the situation called "state of euthyroid disease" characterized by low triiodothyronine (T_3) or T_3 index, increased reverse T_3, normal thyrotropin (TSH), and variable thyroxine (T_4). They studied 84 patients admitted to the coronary unit with severe CHF and reported that the decrease of the free T_3 index/reverse T_3 ratio was an important predictor of mortality in the short-term, surpassing variables such as EF, serum sodium and hemodynamic variables.

Cardiac arrhythmias

Patients with severe CHF have high incidence of ventricular arrhythmias when evaluated through dynamic electrocardiography [20,24,125,126]. Multifocal and paired ventricular extrasystoles are common and more complex arrhythmias, such as nonsustained ventricular tachycardias (NSVT), are found in 50% of the individuals [125].

It is known that the frequency and complexity of the ventricular ectopic beats are not directly responsible for higher mortality, but only reflect the hemodynamic and functional severity of the disease, being related to the degree of impairment of ventricular function [61,127]. In fact, the utilization of antiarrhythmic drugs of the group I-C in asymptomatic patients with frequent ventricular arrhy-thmias, previous myocardial infarction and low EF caused increase in mortality, despite suppressing the arrhythmias [128].

The presence of these arrhythmias, however, provide additional prognostic information, even in the thrombolytic era. Data from the GISSI study [129] show that, in postinfarction patients with EF <35%, the presence of 10 or more ectopic beats per hour or complex ventricular ectopia is associated with an increase of 2.1 to 2.4 times of the risk of sudden death.

The presence of NSVT increases the risk of death by three times [130] and has been described as an independent predictor of sudden death [131]. The annual mortality for patients with previous myocardial infarction, EF <30% and presence of NSVT reaches 40% compared to 20% for those without NSVT [126,130].

Sustained monomorphic ventricular tachycardia occurs in approximately 9% of the patients with severe CHF referred for cardiac transplantation [132]. Its presence identifies a group with high probability of recurrence of arrhythmia and sudden death [133,134]. Ventricular fibrillation usually occurs in the presence of acute myocardial ischemia or severe ventricular dysfunction. As sustained ventricular tachycardia, ventricular fibrillation has a high index of recurrence, therefore justifying aggressive therapeutics [134].

Atrial arrhythmias have also been associated with worse prognosis. The presence of atrial fibrillation has been related to a higher incidence of embolic phenomena and sudden death, in the majority of the studies of CHF [135]. An exception to this finding was the Veterans study [136], which, however, did not include patients in FC IV.

Left bundle branch blockade (LBBB) was described as an important prognostic factor in the study of Unverferth et al [61]. In a prospective study, Franciosa [62] observed a strong correlation between arrhythmic events and the presence of LBBB in the basal electrocardiogram (ECG). According to Hermann and Greenberg [5], however, the usefulness of these findings is limited by the high prevalence of electrocardiographic abnormalities in CHF.

Invasive electrophysiological study – This exam has been used in the attempt to identify patients at risk for sudden death. Its value in patients with cardiomyopathy is not clear yet. In a metanalysis performed by Kowey et al [137] of 12 studies including 926 patients with NSVT, one out of three patients had sustained arrhythmia induced in the invasive electrophysiological study (sustained monomorphic ventricular tachycardia). During follow-up, 7% of the noninducible patients had events (sustained ventricular tachycardia, ventricular fibrillation and sudden death) compared to 18% of the inducible ones. The use of antiarrhythmic drugs in inducible patients, however, impairs the interpretation of these data because of the possibility of pro-arrhythmia.

Signal-averaged ECG – In a patient with previous infarction, the presence of late potentials is associated with induction of tachycardia in the electrophysiological study and with the increased incidence of arrhythmic events (sudden death and sustained ventricular tachycardia) [138]. The limitation of this method is that despite presenting elevated negative predictive value [126], its positive predictive value is low [139]. Its accuracy can be enhanced when its results are combined with data of ventricular function, mainly the left ventricle ejection fraction (LVEF) [140,141].

In patients with nonischemic dilated cardiomyopathy and history of sustained ventricular tachycardia, the prevalence of late potentials is high, reaching 80% [142]. In patients with NSVT, the presence of late potentials varies and does not seem to predict the occurrence of sudden death [143]. Mancini et al [144] evaluated the prognostic value of the signal averaged ECG (SAE) in patients with nonis-

chemic dilated cardiomyopathy. Of 66 patients with normal exam, none had arrhythmic events during the follow-up. On the other hand, from the 20 patients with abnormal exams, four had ventricular tachycardia and five died suddenly. In multivariate analysis, SAE was an independent predictor of prognosis. It is interesting to notice that among the patients with abnormal exams, nine had a previous history of ventricular tachycardia or sudden death compared to only one among those with a normal exam.

Other authors obtained different results. Yi et al [145], studying patients with idiopathic dilated cardiomyopathy, showed that abnormal SAE identified patients who evolved with progression of the CHF, but did not identify the patients who died suddenly.

Dispersion of the Q-T interval – This method has been pointed out by some authors [146,147] as an important prognostic variable in CHF. Barr et al [146] showed that individuals who died suddenly had a higher dispersion of the Q-T interval (mean 98.6ms) than those who survived (mean 53.1ms) or those who died due to CHF progression (mean 66.7ms). Pinsky et al [147] observed, in patients awaiting heart transplantation, that dispersion of the Q-T interval higher than 140 ms was an important predictor of death, both sudden and due to CHF progression.

Autonomic dysfunction

The autonomic balance upon the heart has been consistently evaluated through the heart rate variability (HRV), using measures in the time and frequency domain (spectral analysis). In patients with CHF, the HRV is greatly reduced, reflecting sympathetic hyperactivity and reduction of vagal activity, correlating with the severity of the disease [148-150]. Several authors found correlation between HRV, LVEF [148,150], and also the plasmatic level of noradrenaline [149,151]. Kienzle et al [151] did not find correlation between HRV and EF or FC. They observed, however, a strong negative correlation with indicators of sympathetic excitation, sympathetic neuromuscular activity, and plasmatic level of noradrenaline.

In the last five years, HRV has been shown to of important prognostic value in CHF [149,152-154]. Despite the small number of patients in the series, the largest consisting of 102 patients [153], the results have been consistent. Binder et al [152], studying patients awaiting heart transplantation, observed that those with SDANN (an index of HRV in the time domain) of 55 ms had a 20-time increase in the risk of death. The authors suggest that HRV is superior to other prognostic factors, such as EF, pulmonary capillary pressure, cardiac index, and serum sodium. Mortara et al [149], studying patients before and just after heart transplantation, found similar results.

Recently, Ponikowski et al [153] showed that HRV is an independent prognostic factor in patients with CHF secondary to ischemic or idiopathic dilated cardiomyopathy. Patients with SDNN (another index of HRV in the time domain) inferior to 100 ms had a 3.8-time higher risk of death than those whose indices are higher than that value. In another recent study, Fauchier et al [154] observed that, in patients with idiopathic dilated cardiomyopathy, the analysis of the HRV can identify individuals at greater risk of death or evolution to heart transplantation. In this study, the HRV was reduced, even in patients without manifest heart failure. This reduction, however, was much more pronounced when there was deterioration of the hemodynamic state.

We emphasize that in the majority of these studies, the HRV was correlated with the degree of ventricular dysfunction and the presence of cardiac arrhythmias [148-150,154]. In fact, in the study by Fei et al [150], the measures of HRV were not predictors of sudden death in patients with ischemic or idiopathic dilated cardiomyopathy, in a one-year follow-up.

Final comments

CHF is a potentially lethal syndrome, whose prevalence is increasing throughout the world. The stratification of death risk is essential for the early identification of individuals with a higher chance of adverse events, so that a more aggressive therapy or even extreme interventions, such as the use of implantable defibrillators, heart transplantation or drugs under investigation, can be utilized.

The etiology of CHF, the demographic profile of the patient, and the presence of comorbidities influence the prognosis. An individualized and careful investigation is necessary to detect abnormalities that can be corrected. Patients who do not respond to the conventional therapy or whose etiology is not clear should be referred to specialized centers or to experts in the area of heart failure and cardiomyopathies.

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