Prognosis assessment in patients with decompensated heart failure. Simple clinical parameters or neurohormonal factors

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In the United States, heart failure has emerged as the leading first-listed diagnosis among hospitalized older adults[1,2], and the number of hospitalizations with a principle diagnosis of heart failure has increased for the past two decades[1,3,4]. Despite the large number of hospital admissions for decompensated heart failure, little data are available on factors that affect outcome of such patients after discharge to the outpatient setting[4]. This situation contrasts sharply with that of chronic heart failure or acute coronary syndromes, in which numerous studies describe predictors of short- and long-term prognosis[4].

Hospitalization for acutely decompensated congestive heart failure is associated with a high mortality after discharge[5,6]. In addition, readmission is very common, estimated at 44% at 6 months[7]. As medical therapies, devices, and surgical therapies advance, it becomes important to identify high-risk patients who may benefit from new and aggressive therapies. Accurate prognostic modeling for patients admitted for decompensated heart failure can help in improving clinical care and is also important for the appropriate design of clinical trials and application of new treatment strategies[4]. Studies evaluating possible prognostic factors in patients admitted for decompensated heart failure have largely used simple and readily available clinical data or neurohormonal indices (Table I)[8-20].

Recent studies have shown that renal function is a powerful determinant of prognosis in patients with stable chronic heart failure[21]. We recently evaluated whether renal function in the decompensated state can predict survival after hospital discharge in 541 patients with a previous diagnosis of heart failure NYHA functional class III or IV, who were admitted for clinical decompensation and followed for a mean of 343 ± 185 days after discharge. In unadjusted analyses, all measures of renal function including baseline creatinine, calculated creatinine clearance, blood urea nitrogen (BUN) and BUN/creatinine ratio had a significant and strong association with all-cause mortality. After adjusting for other risk variables (including age, sex, diabetes status, primary etiology of heart failure, previous NYHA functional class, presence of atrial fibrillation, heart rate and systolic blood pressure on admission, serum sodium, presence of rales on physical examination, and use of medications), only BUN (relative risk [RR] 1.9, 95% confidence interval [CI] 1.2-3.1] for patients in the upper BUN quartile compared to the lower BUN quartile) and the BUN/creatinine ratio (RR 2.3, 95% CI 1.4-3.8) for patients in the upper BUN/creatinine quartile compared to the lower BUN/creatinine quartile) remained independent predictors of mortality. Other independent predictors of mortality were age (RR 1.2, 95% CI 1.0-1.4 per 10-year increase), lower systolic blood pressure (RR 0.9, 95% CI 0.8-1.0), hyponatremia (RR 1.5, 95% CI 1.1-2.3), and ischemic etiology of heart failure (RR 1.6, 95% CI 1.2-2.3)[10].

The prognostic value of BUN and systolic blood pressure has also been confirmed in the OPTIME-CHF trial, in which 949 patients with systolic dysfunction and exacerbated heart failure were randomized to receive intravenous milrinone or placebo[8]. In this study, hemoglobin on admis-

Table I. Prognostic markers in patients with decompensated chronic heart failure.

Anemia[8]
Pulse pressure[9]
Baseline renal function[10]
Worsening renal function[11]
Troponin[12-14]
Echocardiography
Ejection fraction
Diastolic function[15]
Neurohormonal factors
B-type natriuretic peptide[16-18]
Endothelin[19]
Heart rate variability[20]

sion was an independent predictor of death (odds ratio 0.89 per 1 g/dl increase, 95% CI 0.82-0.97)[8]. Pulse pressure may be a better predictor of outcome than systolic blood pressure[9]. Proportional blood pressure < 25% suggests a cardiac index < 2.2 l/mim/m^2 [22].

It is important to emphasize that association between these simple markers and adverse outcome behave as a linear function, in which they can be used as continuous variables. By contrast, the use of neurohormonal markers usually entails a dichotomous cut-off that separates patients at high and low risk (see below).

Small elevations of serum troponin have been observed in patients with heart failure, and are thought to represent leakage of the cytosolic pool of troponin due to myocyte injury and loss of cell membrane integrity. Because progressive myocyte loss is an important mechanism in the progression of left ventricular dysfunction, troponin elevations in patients with heart failure may serve as a marker of ongoing myocyte loss, and therefore, for poor prognosis. La Vecchia et al.[23] reported that elevated troponin I was present in 29% of hospitalized patients with heart failure, and was associated with death at 3 months. In another study of 98 patients hospitalized with class III or IV heart failure, Ishii et al.[16] found that elevated troponin T on admission was associated with increased risk of death. Similar results were reported in patients referred for cardiac transplantation[12].

Neurohormonal factors

Chronic heart failure is characterized by generalized neurohormonal activation that is thought to contribute to progressive circulatory failure and influence survival. Among the major manifestations of neuroendocrine activation are profound abnormalities in autonomic control, characterized by sympathetic overactivity and parasympathetic withdrawal. As patients progress from early asymptomatic or mildly symptomatic left ventricular dysfunction to overtly decompensated heart failure, additional progressive neuroendocrine activation and autonomic dysfunction occur.

The use of neurohormonal variables for the prediction of survival in heart failure has been investigated mainly in patients with stable heart failure. The rationale favoring neurohormonal evaluation in the chronic rather than decompensated phase is the assumption that neurohormonal parameters measured acutely might change dramatically within hours or days[24]. Consequently, little data exist on the prognostic value of neurohormones and measures of autonomic dysfunction in the setting of decompensated heart failure requiring hospitalization.

B-type natriuretic peptide (BNP) is elevated in patients with various forms of heart failure, and its plasma concentrations have closely correlated with several clinical and hemodynamic indicators of disease severity. BNP has been used for risk stratification in various heart failure settings. BNP levels can rapidly fall in response to in-hospital therapy in patients with decompensated heart failure[17,18,24]. Two studies have shown that elevated pre-discharge BNP levels may help to predict short-term death or readmission after acute hospital care for decompensated heart failure[17,18]. Cheng et al.[17] found that patients who were not readmitted in the 30 days after discharge could be characterized by falling BNP levels during hospitalization, whereas patients who were readmitted or died had no decrease in BNP levels. Thus, BNP levels may be used both to optimize therapy for heart failure[25] and to assess short-term outcome. It should be emphasized, however, that the optimal target discharge BNP levels have not been established.

We examined the relative ability of an array of neurohormonal (plasma renin activity, aldosterone, norepinephrine, endothelin-1) and cytokine (tumor necrosis factor-α and interleukin-6) variables obtained during hospital admission for decompensated heart failure to predict short-term survival[19]. Among these six neurohormonal factors, only plasma endothelin-1 levels above the group median remained an independent and significant predictor of death after hospital discharge (RR 3.9, 95% CI 1.2-12.6, p = 0.022)[19]. We also calculated a composite neurohormonal score that incorporated results of all neurohormones and cytokines. In a Cox multivariate analysis, the neurohormonal score was an independent and significant predictor of death after hospital discharge, giving somewhat higher RR than plasma endothelin-1 alone (RR 5.1, 95% CI 1.2 21.4, p = 0.024).

We have recently studied whether the severity of autonomic perturbations as assessed by heart rate variability in hospitalized patients with decompensated heart failure provides prognostic information on the outcome of these patients after discharge. Twenty-four hour Holter recordings were obtained on admission in 199 patients with a previous diagnosis of heart failure NYHA functional class III or IV, and measures of heart rate variability were calculated in the time and frequency domain[20]. In a multivariate Cox regression model, depressed indices of overall heart rate variability were

independently associated with increased mortality following hospital discharge. The relative risk associated with heart rate variability indices in the lower tertile was 2.2 for standard deviation of the RR intervals over a 24-hour period (RR 2.2, 95% CI 1.05-4.3, p = 0.036), 2.1 for standard deviation of all 5-min mean RR intervals (RR 2.1, 95% CI 1.05-4.2, p = 0.04), 2.2 for total power (95% CI 1.08-4.2, p = 0.03), 2.6 for ultra low frequency power (95% CI 1.3-5.3, p = 0.007)[20].

It has been suggested that neurohormonal markers have the strongest association with outcome[26]. However, there are several limitations to the clinical use of neurohormonal data. Cut-off values indicating high risk differ markedly between studies and are often chosen to maximize the RR for the endpoint. In addition, central to the implementation of neurohormonal data in clinical practice is the incremental value of such data over simple prognostic markers, which are readily available for the clinician. Because models based on simple clinical parameters are highly predictive, it would be difficult to prove that neurohormonal measurements (which are expensive and not available in many institutions) significantly increase the predictive accuracy of prognostic models based on clinical data alone and therefore to justify their clinical use. To date, no study addressed this issue. In fact, studies using neurohormonal measurements for prognostic modeling have largely ignored simple and powerful clinical indicators for high risk such as hyponatremia and kidney function[12,17,18].

Conclusion

Simple clinical parameters provide considerable prognostic information in patients with decompensated heart failure. Several neurohormonal factors appear to be helpful in risk stratification and are interesting from the pathophysiological standpoint. However, presently there is no proof that neurohormonal data provides incremental information over clinical parameters.

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