Lack of clinical usefulness of interleukin-6 in long-term follow-up of acutely decompensated heart failure

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ABSTRACT

Introduction: Interleukin-6 (IL-6) has been identified as a predictor of death, new heart failure (HF) episodes and need for heart transplantation in patients with advanced HF. The aim of this study was to examine the relationship between plasma IL-6 levels in patients with decompensated HF and either survival or new admissions due to HF.

Methods: We studied 111 patients admitted due to decompensated HF. Long-term survival was assessed from the day of admission to the hospital to the day of death or new admissions due to HF.

Results: The mean IL-6 concentration was 90 +/- 115 pg/ml (range 1.5-743 pg/ml). There were no differences in IL-6 concentration with regard to age, gender and cause of HF. At the end of follow-up period, 22 patients (20 percent) had died due to causes related to HF and 54 patients (48 percent) had been readmitted to the hospital due to new HF episodes. Using regression analyses, serum IL-6 levels were not identified as a prognostic factor. Systolic dysfunction, previous diagnosis of HF and diabetes mellitus were independent predictors of death.

Conclusion: These findings suggest that a single measurement of serum IL-6 in patients with decompensated HF lacks clinical usefulness in long-term follow-up.

Keywords: cytokines, decompensated heart failure, heart failure prognosis, interleukin-6

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INTRODUCTION

Heart failure (HF) is a major health problem in developed countries and is responsible for a great number of hospitalisations and deaths.[1] This syndrome is the final clinical presentation of a variety of cardiovascular diseases, such as coronary artery disease, hypertension, valvular heart disease, myocarditis and diabetes mellitus. It has been suggested that HF should be viewed as a neurohormonal model, in which progression of HF is the result of the overexpression of biologically-active molecules capable of exerting toxic effects on the heart and circulation. Norepinephrine, angiotensin II, endothelin, aldosteron and cytokines, such as tumour necrosis factor (TNF) or some interleukins, have been implicated in disease progression. Whereas activation of these systems is adaptative over the short term in acute HF and hypovolaemic shock, persistent activation can be harmful in chronic HF.[2,3]

Interleukin-6 (IL-6) is a multifunctional cytokine which mediates both immune and inflammatory responses. It is produced by a variety of different cell types including mononuclear phagocytes, some activated T-cells, vascular endothelial cells, and fibroblasts.[4] Several studies suggest that IL-6 is capable of independently modulating myocardial function, producing a concentration-dependent decrease in contractility.[5,6] IL-6 has been identified, in some studies, as a predictor of death, new HF episodes and need for heart transplantation in patients with advanced HF.[7] IL-6 predicts mortality independently of age, gender, aetiology of HF, New York Heart Association (NYHA) class, ejection fraction (EF) and serum sodium.[8] In addition, IL-6 has been related with progression of subclinical left ventricular dysfunction to clinical HF.[9] The aim of the present study was to elucidate the prognostic value of a single measurement of IL-6 among patients with decompensated HF and its relationship with survival or new admission due to HF during follow-up.

METHODS

We studied 111 patients admitted in an Internal Medicine Unit due to decompensated HF between September 2000 and May 2003. HF was diagnosed on the basis of clinical criteria, according to Framingham and Boston criteria, and echocardiography. Acute left heart decompensation was based on increase of dyspnoea or orthopnoea,

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pulmonary rates and radiographical findings consistent with pulmonary oedema. We excluded patients with diseases which could modify IL-6 levels, such as acute and chronic infectious diseases, inflammatory diseases, cancer and severe renal failure. Those patients who died during the course of hospitalisation (considered as the admission index) were also excluded.

Serum samples were taken in the first 72 hours after clinical onset. Each blood sample was centrifuged at 3000 rpm for ten minutes at 4ºC, separated and stored at –40ºC until analysis. IL-6 was determined by immunoassay (IL-6 ELISA IM 1120, Immunotech, Marseille, France). This ELISA is a one immunological step sandwich type assay. Samples and standards are incubated in the microtitre plate coated with the first monoclonal antibody, anti-IL-6, in presence of the second anti-IL-6 monoclonal antibody linked to acetylcholinesterase. After incubation, the wells were washed and the bound enzymatic activity was detected by addition of a chromogenic substrate. The intensity of the colouration is proportional to the IL-6 concentration in the sample or standard. Standard laboratory equipment was required. The inter-assay and intra-assay variations for determining IL-6 were 11.25% and 4.2%, respectively. Echocardiography was obtained in each patient. They were divided in patients with systolic dysfunction (if EF was lower than 40%) and patients with HF with EF preserved (according to the Vasan and Levy criteria).[10]

Informed consent for the test, stored samples and the review of records were obtained from participants. Depending on the type of variable, the values are expressed as mean value ± standard deviation or percent. The Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) was used for data entry and processing. Student's t-test and ANOVA were used to test for differences in continuous variables once normality was demonstrated (Shapiro-Wilks test); otherwise, a non-parametric test (Mann-Whitney U test) was used. Categorical variables were analysed by the χ^2 test. Long-term survival was assessed from the day of admission at the hospital to the day of death, day of a new admission or March 1, 2004. Cumulative survival curves were constructed according to the Kaplan-Maier method and differences between curves were tested by log-rank test. Predictors of new HF episodes or death were analysed by Cox proportional hazards analysis. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

The baseline characteristics of the population are summarised in Table I. 87% of patients were older than 65 years. In 56 of the patients (50%), HF was not known previously. Hypertension (32 patients, 30%) and ischaemic heart disease (40 patients, 36%) were the more frequent aetiologies. Other aetiologies were: valvular heart disease (12 patients, 11%), non-ischaemic dilated myocardiopathy (five patients, 4.5%) and non-identified aetiology (22 patients, 20%). Aetiologies were attributed according to history of patients.

Table I. Clinical characteristics of the population.

Variable	
Age and SD (years)	73.45 ± 7.95
Male	59 (53.2%)
Prior heart failure	55 (49.5%)
Hypertension	32 (28.8%)
Ischaemic aetiology	40 (36%)
BMI and SD (kg/m^2)	28.12 ± 4.46
ACEI	51 (45.9%)
ß-blockers	12 (10.8%)
Ejection fraction and SD	49.78 ± 15
Total proteins and SD (g/dL)	6.44 ± 0.5
Albumin and SD (g/dL)	3.43 ± 0.46
Cholesterol and SD (mg/dL)	169.88 ± 43
Diabetes mellitus	34 (30.6%)
COPD	25 (22.5%)

NYHA: New York Heart Association; AHA: American Heart Association; BMI: body mass index; ACEI: angiotensin converting enzyme inhibitors; COPD: chronic obstructive pulmonary disease; SD: standard deviation.

The mean IL-6 concentration was 90 ± 115 pg/ml (range 1.5–743 pg/ml). There were no differences in IL-6 concentration with regard to age (65 years or younger: 63 ± 62 pg/ml; and older than 65 years: 93 ± 121 pg/ml; p = 0.36; correlation: r = 0.38, p = 0.68), gender (men: 91 ± 111 pg/ml and women: 87 ± 122 pg/ml; p = 0.85) and cause of HF (ischaemic: 92 ± 135 pg/ml, hypertension: 78 ± 10 pg/ml, and other aetiologies: 93 ± 105 pg/ml; p = 0.93). There was no correlation between serum IL-6 levels and EF (r = 0.041, p = 0.67). Patients in basal class III or IV (NYHA) and patients in C or D (American Heart Association [AHA] classification) stage had lower concentrations than those in basal class I or II (NYHA) and stage A or B (AHA), but these differences were not statistically significant. Predictors of elevated IL-6 levels were not found.

The average duration of follow-up was 21 ± 11 months (range 1–41.2 months). At the end of the follow-up period, 22 patients (20%) had died due to causes related to HF, three patients had died due to non-related causes and 86 patients (77%) remained alive. During follow-up, six patients were lost (5.4%). After one, eight, 12, 13, 17 and 53 months, respectively, we could not contact them again. 54 patients (48%) were readmitted to the hospital due to new HF episodes. During follow-up, 26 patients were readmitted once, 15 patients were readmitted twice, seven patients were readmitted three times, and six

Table II. Predictors of death or the need for new admission due to heart failure during follow-up.

Variable	Readmission			Mortality		
	OR	OR CI 95%	p-value	OR	OR CI 95%	p-value
IL-6 serum level	1.000	0.996–1.003	0.915	1.002	0.999–1.004	0.287
Age	0.987	0.916–1.063	0.725	1.031	0.971–1.096	0.316
Male	1.333	0.428–4.149	0.619	1.344	0.493–3.663	0.562
Atrial fibrillation	1.754	0.457–6.711	0.412	0.433	0.151–1.298	0.138
Systolic dysfunction	1.503	0.483–4.671	0.481	3.333	1.071–10.30	0.037
Hypertension	1.388	0.404–4.761	0.602	0.473	0.147–1.519	0.209
Diabetes mellitus	1.097	0.324–3.703	0.881	3.154	1.173–8.474	0.023
Ischemic cardiopathy	2.262	0.658–1.930	0.195	0.847	0.267–2.688	0.779
Previous diagnosis of HF	5.986	0.518–69.10	0.152	10.63	1.923–58.82	0.007

OR: odds ratio. CI: confidence interval.

patients were readmitted more than three times. Among 54 patients, some clinical event (new hospitalisation or death) occurred. However, no differences in IL-6 levels were found with the rest of the population. IL-6 levels did not differ between the 54 patients who suffered from some clinical event (new hospitalisation or death) and the rest of the group. In patients with new hospitalisations, IL-6 levels were 93 ± 129 pg/ml and in patients who were not readmitted, their levels were 71 ± 82 pg/ml (p = 0.17). In patients who died, Il-6 levels were 126 ± 162 pg/ml, and in live patients, IL-6 levels were 78 ± 94 pg/ml (p = 0.15). There was no correlation between serum IL-6 levels and number of new episodes.

21-month mortality due to HF was higher among patients with elevated IL-6 levels (IL-6 > 50 pg/ml), compared to patients with IL-6 levels less than 50 pg/ml (63% versus 36%), but the difference did not reach statistical significance (p = 0.059). There were no differences in readmissions due to HF according to IL-6 levels. End-point analysis was performed isolated and combined, but differences were not found. The Kaplan-Maier survival and readmission curves for patients with different peak plasma concentration less than or greater than the sample median were not shown to have differences (Figs. 1 and 2). Using Cox proportional hazards regression analyses (Table II), serum IL-6 levels were not a prognostic factor in these patients. In a multivariate analysis systolic dysfunction, previous diagnosis of HF and diabetes mellitus were identified as independent predictors of death. None of the analysed variables were identified as predictors of new episodes and readmission due to HF. We considered a composite end point (readmission or death) but predictors were not found either.

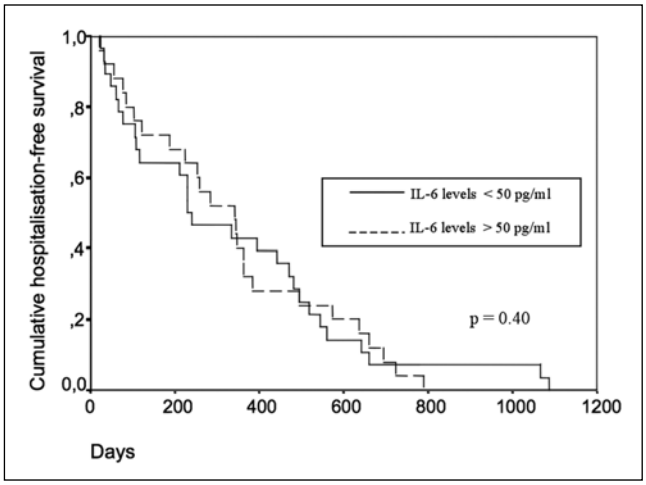

Fig.1 Curves illustrating patients who were readmitted due to new heart failure episodes. Broken line shows patients with serum IL-6 levels higher than 50 pg/ml.

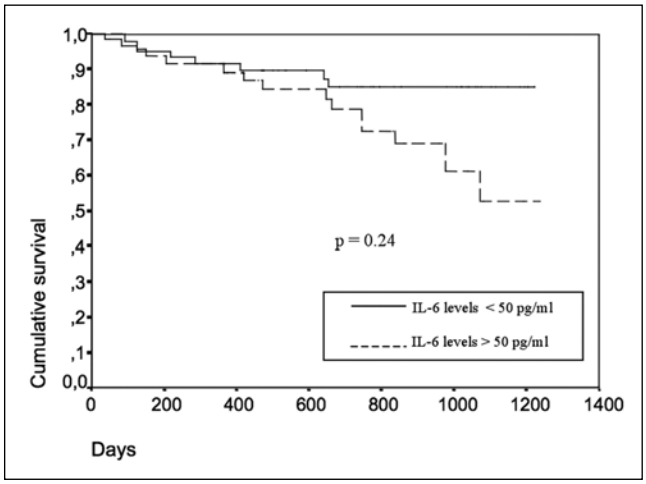

Fig. 2 Mortality curves illustrating deaths due to heart failure. Broken line shows patients with serum IL-6 levels higher than 50 pg/ml.

DISCUSSION

Since HF is a leading source of morbidity and mortality among the elderly, and lifespan is steadily increasing in

western countries, identifying markers of prognosis is becoming a key point in HF management. Furthermore, the use of a multibiomarker scoring in HF assessment has recently been suggested.[11] During the last few years, interest in the involvement of inflammatory factors in HF has emerged. The role of inflammation in the pathogenesis of HF has been strengthened further, with the implication of several cytokines (such as IL-6), in the disease process in experimental studies, and the demonstration that inflammatory markers are elevated in patients with milder degrees of HF, including those with asymptomatic left ventricular dysfunction and in patients at risk to develop HF.[9,12,13]

In our study, serum IL-6 was not associated with an increased risk of mortality or new admissions due to HF. In spite of these patients showing elevated concentrations of IL-6, these levels were not associated with a poorer prognosis. Perhaps a longer follow-up or a more defined population would have shown significant differences. These results may be explained by different reasons. Firstly, we studied patients during acute decompensation. Sato et al described an increase of IL-6 levels and other cytokines in a small group of patients with acute left heart decompensation that returned toward normal levels as the patients improved.[14] In patients with acutely decompensated HF, Suzuki et al, in a sample of 73 patients with different aetiologies, described a peak IL-6 level at admission. This peak was significantly correlated with pulmonary wedge pressure. In successive measurements, the percentage change of the IL-6 level was significantly correlated with the percentage of pulmonary wedge pressure. However, the prognostic value of the changes was not addressed.[15]

Secondly, mean age in our study was 73 ± 8 years. Harris et al found higher IL-6 levels associated with older age among healthy elderly subjects. Higher levels of IL-6 were associated with all-cause mortality in these patients.[16] Others studies have described an increased inflammatory response in elderly patients with high levels of IL-6 and other cytokines and acute phase proteins.[17,18] Hence, in our survey, where 87% of patients were older than 65 years, the inflammatory response could have been biased by age itself. Thirdly, cytokine concentrations in peripheral blood are unstable and modifiable by different factors, either clinical or pharmacological, present in patients with HF. In addition, cytokines operate both as a cascade and as a network. They regulate the production of other cytokines and cytokine receptors, and are components of a complex signalling network. Effects of cytokines on target cells may be modulated by other cytokines, hormones and cytokine-receptor antagonists. As a consequence, their serum levels may not reflect the actual complexity of cytokine action in tissues.[19]

Some limitations of the study should be acknowledged. The use of aspirin or drugs which could have affected IL-6 levels were not analysed. However, there were no differences between groups where aspirin is commonly prescribed (ischaemic aetiology group) and other aetiology groups. Hence, differences following the use of aspirin were not expected. Mean concentrations and standard deviation of IL-6 are widely dispersed. Therefore, as with other biological markers, a single value of IL-6 from individual patients must be interpreted with caution. We did not perform serial measurements of serum IL-6 levels. As a consequence, we did not address the influence of changes in IL-6 concentration and its relation to prognosis. We did not evaluate other cytokines and acute phase proteins implicated in HF physiopathology, such as C-reactive protein or TNF-alpha (TNF-α), which could have helped interpretation of IL-6 behaviour.[8,12,20,21] In our series, a number of patients had either obesity, atrial fibrillation or pulmonary emphysema, which precluded a reliable assessment of diastolic function by echocardiography. As a consequence, according to the Vasan and Levy definition, for statistical analysis, we assumed that patients with EF above 40% had HF with preserved EF.[10]

Strictly speaking, the classification of aetiologies was not very rigorous. However, we believe that in a high percentage of cases (in this study and in real clinical practice), clinical history is sufficient for adequately classifying HF aetiology. We included a heterogeneous group of patients. Given that these were representative of daily clinical practice, and that all of them had a long history of HF, we relied on clinical criteria to make inferences about their aetiologies. It is possible that inflammatory factors are implicated in different degrees among patients with distinct types of HF. In this setting, such a heterogeneous group, as our series represents, may have biased the role of IL-6. It is then possible that a study of a more specific group of patients can contribute to elucidating the role of IL-6 more accurately. In conclusion, according to our results, a single measurement of serum IL-6 in patients with decompensated HF seems to lack clinical usefulness in long-term follow-up.

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