C-Reactive Protein: an Inflammatory Marker with Prognostic Value in Patients with Decompensated Heart Failure

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Summary

Background: Inflammation has been implicated in the pathophysiology of a series of cardiovascular diseases. C-reactive protein (CRP) is a marker of inflammation easily obtained in the emergency room.

Objectives: To study the prognostic value of CRP in patients admitted for acute decompensated heart failure (ADHF).

Methods: A prospective cohort of 119 patients with ADHF treated in the emergency room. Mean age was 74±11 years and 76 (64%) of patients were male. All were New York Heart Association Functional Class III or IV. CRP was measured by nephelometry at admission. Patients were followed after hospital discharge for an average of 12±9.7 months and cardiovascular mortality was the outcome analyzed.

Results: There were 44 (36.9%) deaths, all from cardiovascular causes. Individuals with CRP > 3 mg/dl had higher mortality than those below this level (p=0.018). In the multivariate analysis using Cox proportional model, CRP proved to be the most important independent prognostic factor (odds ratio 0.0916 [95% CI = 0.0341 - 0.1490] for each one-unit increment in CRP).

Conclusion: CRP is an independent cardiovascular mortality predictor in patients with ADHF, indicating that inflammation represents an important component in the pathophysiology of the disease.

Key words: C-reactive protein; inflammation; cytokines; heart failure; cardiac output, low.

Introduction

Acute heart failure (HF) can appear as a decompensation in patients who are already in heart failure or occur in patients with no prior heart failure history. Besides the underlying disease, some factors can influence a decompensation episode and are identified as precipitating factors. Among these we underscore non-compliance with diet or medication, uncontrolled arterial hypertension, acute coronary syndromes, cardiac arrhythmias, and infections[1].

It has been known for some time that inflammation plays a vital role in the pathophysiology of some cardiovascular diseases, such as acute coronary syndromes, where it has prognostic value[2]. More recently, its participation in acute HF has been evident since it may be a precipitating factor in a decompensation[3-5]. Its role in the long-term progression of a disease after hospitalization, however, is poorly understood.

Initially described in 1930, C-reactive protein (CRP) is an acute phase protein and an unspecific marker of systemic inflammation[6]. Its prognostic value is well established in patients with coronary artery disease[7-9]. The objective of this article was to analyze the long-term prognostic value of CRP measured in patients admitted to an emergency unit with acute decompensated heart failure (ADHF).

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Methods

From March 1997 to December 1999, 170 consecutive patients were seen with ADHF at the emergency unit of a tertiary hospital in Rio de Janeiro (108 were male, age range of 17 to 99 years). Patients were excluded from the study if they showed signs of infection, acute coronary syndrome, acute myocardial infarct, neoplastic diseases, and other inflammatory illnesses such as pericarditis and rheumatoid arthritis. After exclusions, 119 patients were included, 76 (64%) men and 43 (36%) women, with a mean age of 74±11 years. Etiologies for HF were ischemic in 73 (61.5%) cases, hypertensive in 21 (18%), valvar in 9 (7.7%), and 'other' in 16 patients (12.8%). All were NYHA functional class III or IV. All patients had a troponin I levels lower than 1.0 ng/l and CK-MB lower than 10 UI/l. Patients with LV shortening fractions $\leq$ 25% were considered as having systolic dysfunction and 82 (68.9%) of them were in this group.

The diagnosis of HF was based on Boston criteria, and only patients with more than 8 points were included[10]. Variables studied were age, sex, etiology, New York Heart Association (NYHA) functional class, mean blood pressure, left ventricle shortening fraction, creatinine, and serum sodium levels. CRP plasma levels were determined upon admission

by nephalometry (Array 360 System Beckman, Abbott Laboratories, North Chicago, IL). Values under 0.8 mg/dl are considered normal (variation coefficient under 5%)[11].

Follow-up - Clinical progression and events from 119 patients were obtained by telephone contact with the patients or their relatives and referring physicians every six months for three years (mean 12.4±9.7 months). Deaths were classified according to the criterion established by Narang et al[12], considering activity, cause, mode, and event related to the death. The primary outcome analyzed was cardiovascular mortality.

Statistical analysis - The data collected were analyzed using SPSS statistical package, version 6.0. The univariate comparisons with categorical variables were performed using the chi-square test - ε^2, and continuous variables were analyzed by Student's t test or the Mann-Whitney test for non-normal distributions. Survival probability was estimated using the Kaplan-Meier method and comparisons were made by the log-rank test. Multivariate comparisons of the factors that influenced survival were done using the Cox poportional method. Values for $p<0.05$ were considered significant.

The study was approved by the institutional ethics committee, and is compliant with Helsinki criteria. Informed consent was obtained from all patients.

Results

There were no differences among the baseline characteristics of patients stratified according to CRP terciles, with the exception of a greater number of coronary patients in the group with CRP>4.3 mg/dl when compared to the group with CRP<1.3 mg/dl (p=0.04), as shown in Table 1. Of the 119 patients, 44 (36%) died during follow-up, 26 of them men (21.8%) and 18 women (15.2%). Thirty patients (68.2%) died from circulatory failure due to HF progression, 9 patients (20.5%) from sudden death, 2 patients (4.5%) from stroke, 2 patients (4.5%) during cardiac surgery, and 1 patient (2.3%) from pulmonary thromboembolism. The accumulated probability of survival for all patients was 73.6% in six months (87 alive), 66% in 12 months (78 alive), and 52% in 24 months (61 alive). CRP levels among systolic dysfunction patients and those with preserved systolic function were, respectively, 3.8±4.3 and 3.5±3.6 mg/dl (p=0.79). There was a tendency toward a higher CRP value in coronary patients than in non-coronary patients (4.4±4.9 *vs* 3.03±3 mg/dl, p=0.08).

CRP concentrations and mortality - In 87 patients (73.2%), CRP concentrations were above normal values. The group mean was 3.8±4.2 mg/dl. The mean CRP of patients who died at hospital was 5.4±4.8 mg/dl, and 3.9±4.7 in the survivors (p=0.21).

During follow-up, the mean CRP for patients who died was 5.1±5.0 mg/dl, while among survivors it was 3.02±3.4 mg/dl (p=0.02), as shown in Figure 1.

Patients were subdivided by serum CRP levels above and below or equal to 3 mg/dl, the median of CRP values. Twelve-month survival probability among those with levels over 3 mg/

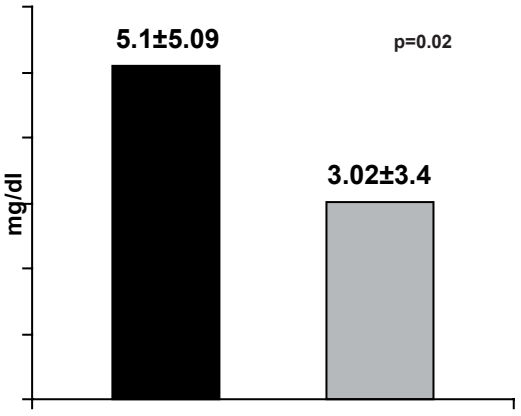

Fig. 1 - *Mean CRP values in survivors (gray) and non-survivors (black) during follow-up.*

Table 1 - Baseline characteristics according to C-reactive protein terciles

Variables	CRP<1.3 n=41	CRP 1.3-4.3 n=41	CRP>4.3 n=37	p value
Male	26 (63.4%)	25 (61%)	25 (67.5%)	0.43
Age (years)	73.3+13.5	74.7+11.9	75.7+11.9	0.41
Ischemic etiology	21 (51%)	25 (61%)	27 (73%)	0.04*
Systolic blood pressure	142.8+40	140.6+39.9	143+38.8	0.52
Mean blood pressure	104+26.7	101.8+25.5	102.8+23.5	0.47
Serum sodium (mEq/l)	137.5+3.8	135.6+5.3	136.6+4.9	0.42
Shortening fraction (%)	20.9+11	22.7+9.7	20.2+6.6	0.63
Urea (mg/dl)	67.4+42	66.3+53	69+52	0.64
Creatinine (mg/dl)	1.21+0.4	1.3+0.6	1.25+0.5	0.38
C-reactive protein (mg/dl)	0.51+0.36	2.56+0.9	8.83+4.3	NA

*NA - not applicable; data presented as mean and standard-deviation or n and percentage; *Statistically significant to compare with group CRP>4.3 vs CRP <1.3.*

dl was 52%, and 77% for patients with levels below this value (p=0.018). The survival curve is illustrated in Figure 2.

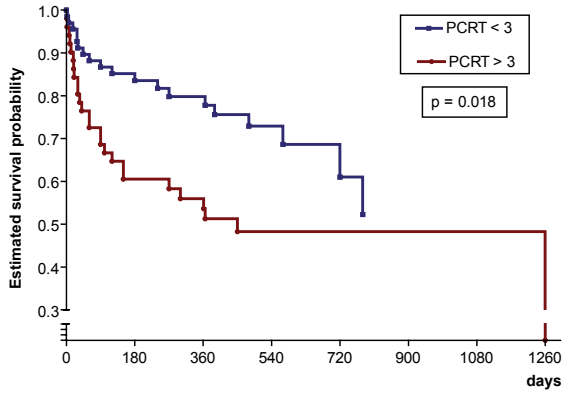

Fig. 2 - *Kaplan-Meyer curves according to C-reactive protein.*

Variables related to survival - The log-rank test analysis demonstrated that CRP (p=0.02), age (p=0.037), and mean blood pressure (inverse relation, p=0.041) were the variables related to 12-month survival. The mean blood pressure in patients who died and survivors was, respectively, 96±28 and 106±22 (p=0.041). The shortening fraction (p=0.152), serum creatinine (p=0.156), ischemic etiology (p=0.200), and serum sodium (p=0.788) did not correlate with survival.

Cox proportional hazards analysis - The variables independently associated with survival were CRP (odds ratio [OR] = 0.0916, 95% confidence interval [95% CI]: 0.0341 - 0.1490, for each one-unit increment in CRP), and age (OR = 0.0304, 95% CI: 0.0274 - 0.0333, for each one-unit increase in age). Mean blood pressure (OR= -0.0128, 95% CI: -0.0263 - 0.0007) was not an independent predictor for survival (Table 2). CRP was the independent factor with the greatest prognostic value.

Discussion

This study adds new information on the role of inflammation in ADHF. We demonstrated that CRP measurement, a test easily carried out in the emergency room, is capable of predicting long-term events after a hospital stay.

In the 1990s, it was shown that CRP is elevated in patients with chronic HF[13,14]. Shortly after that, its elevation in patients with ADHF was observed[3-5]. More recently, its prognostic value was established in patients with chronic HF[15,16]. A retrospective analysis of the Val-HeFT study showed that, regarding the lowest CRP quartile, patients in the highest quartile had a higher risk of death or of a morbid event[16]. CRP values have not changed over time for patients in the placebo group, but they did change in the group receiving valsartan without angiotensin conversion enzyme inhibitors, suggesting a modulation of inflammation with the medication.

The prognostic role of CRP in patients with ADHF was recently demonstrated in a study similar to ours. Mueller et al[17] retrospectively studied 214 ADHF patients treated at the emergency unit who were followed up for 24 months. Mortality rates from the first to the third tercile in CRP values were, respectively, 33.5%, 42.2%, and 53.6%. After multivariate adjustment, CRP remained as an independent predictor of death or death combined with hospitalizations. Our study confirms these findings and presents some particularities relative to the study done by Mueller et al. First of all, ours is the only study that we are aware of in which this issue was prospectively evaluated. Second, we excluded patients who had infections or inflammatory diseases. Therefore, data from our study suggest that inflammation was related to HF and not to external factors. On the other hand, Müeller suggests that, even when inflammation is associated to an infection, there is an impact on the short-term and long-term prognosis in the ADHF patient.

The mechanisms by which inflammation is set off are not yet well defined. Different theories besides that of infection include an autoimmune mechanism, hemodynamic overload, tissue hypoxia, and LDL oxidation[18]. Another increasingly accepted theory is that of endotoxins[4,19]. According to this assumption, intestinal edema and hypoperfusion would cause an increased capillary permeability, allowing the translocation of bacteria and endotoxins to circulation and leading to the activation of the inflammatory processes seen in heart failure. Peschel et al[4] demonstrated the presence of high concentrations of endotoxins in hepatic veins compared to the left ventricle in patients with ADHF, supporting this premise. It has also been shown that with treatment for the edema using diuretics, serum levels of endotoxins are reduced[20]. Reinforcing this hypothesis even further, Conraads demonstrated that selective intestinal decontamination with antibiotics in patients with serious chronic HF reduces plasma inflammatory endotoxins and cytokines with an improvement in endothelial function[21].

Some clinical implications merit emphasis. This study suggests that immune modifications are not an epiphenomenon in decompensated HF patients, but play an important role in

Table 2 - Analysis by Cox proportional model

Variables	Odds ratio (OR)	Variance	Exponential	95% confidence interval
C-reactive protein	0.0916*	0.0293	1.096	0.0341 to 0.1490
Age	0.0304*	0.0153	1.031	0.0274 to 0.0333
Mean blood pressure	-0.0128*	0.0069	0.987	-0.0263 to 0.0007

** For one-unit increments in values.*

the pathophysiology of the illness. This affords a therapeutic opportunity, since procedures that reduce inflammation could lead to an improved prognosis. This could explain the good response with statins in acute HF patients[22,23]. Our group is in an initial phase of a project of intestinal decontamination with neomycin in patients with serious and decompensated HF, which will evaluate clinical outcomes, cardiac remodeling, and inflammatory cytokine quantification.

Some limitations need to be mentioned. Serum CRP concentration may be influenced by other factors, such as hormone replacement and smoking. Our data were not adjusted for these factors. Another limitation refers to infectious causes. Despite our great care in excluding patients with pneumonia, this diagnosis is not always easy to make in elderly patients with associated ADHF, and some cases may have not been caught at admission. Lastly, we measured CRP at admission. Although the value of this measurement is evident, successive measurements would be even more important, since peak levels of CRP usually take place 48 hours after admission[5].

Concluding, we demonstrated that CRP quantification at admission in patients with ADHF has an important long-term prognostic value.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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