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Serial Circulating Concentrations of C-Reactive Protein, Interleukin (IL)-4, and IL-6 in Patients with Acute Left Heart Decompensation

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Summary

Background: Interleukin (IL)-6 has recently been shown to have negative inotropic effects, and several studies have reported increases in circulating concentrations of this cytokine in patients with depressed left ventricular ejection fraction and chronic left heart failure. However, most previous clinical studies have measured cytokines in compensated chronic heart failure.

Hypothesis: The purpose of this study was to examine the temporal evolution of circulating concentrations of C-reactive protein (CRP) and cytokines in patients with cardiomyopathy and acute cardiac decompensation, free of infection and unstable angina.

Methods: The time course of circulating concentrations of CRP, an anti-inflammatory cytokine interleukin (IL)-4, and a proinflammatory cytokine IL-6 were studied in eight patients with cardiomyopathy and acute cardiac decompensation in the absence of infection or unstable angina. Control samples were obtained from eight age-matched asymptomatic subjects.

Results: Increased circulating concentrations of CRP (2.6 ± 0.8 mg/dl), IL-4 (164.6 ± 36.5 pg/ml), and IL-6 (17.1 ± 5.1 pg/ml) were found in all eight patients during acute cardiac decompensation; these values decreased significantly with the resolution of symptoms of cardiac decompensation (0.5 ± 0.1 mg/dl, 77.8 ± 23.6 pg/ml, 2.3 ± 0.1 pg/ml, respectively, $p < 0.05$ for both). There was a significant correlation between peak CRP and peak IL-6 ($p < 0.05$).

Conclusions: In patients with acute left heart decompensation in the absence of infection or coronary events, CRP, IL-4, and IL-6 increased and returned toward normal levels as the symptoms of heart failure resolved. Since the changes in concentrations of CRP, IL-4, and IL-6 in patients with heart failure are dynamic, the distinction between compensated and decompensated state is important when discussing the significance of acute reactive proteins or cytokines in the pathogenesis of heart failure.

Key words: C-reactive protein, cytokine, heart failure, cardiomyopathy

Introduction

Chronic left heart failure is the final common pathway of a variety of cardiac disorders, including ischemic heart disease, idiopathic dilated cardiomyopathy (IDC), and valvular disease, and is usually progressive. Some cytokines have recently been shown to have negative inotropic effects,[1] and several studies have reported increases in circulating concentrations of these cytokines in patients with depressed left ventricular ejection fraction (LVEF) and chronic left heart failure.[2–5] However, most previous clinical studies have measured cytokines in compensated chronic heart failure.

C-reactive protein (CRP), an acute phase reactive protein, is synthesized in the liver, and its serum concentration is a reliable index of overall inflammatory activity. Respiratory tract infections may precipitate the decompensation of chronic heart failure and are associated with increased serum concentrations of CRP. Likewise, patients with unstable angina, an inflammatory form of atherosclerotic disease, have increased

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serum levels of CRP.[6] The purpose of this study was to examine the temporal evolution of circulating concentrations of CRP and cytokines in patients with cardiomyopathy and acute cardiac decompensation, free of infection and unstable angina.

Study Populations and Methods

Patients

Five patients with IDC and three patients with ischemic cardiomyopathy (ICM) (seven men and one woman, mean age 70.6 years, range 50–83 years), admitted to the Hyogo Prefectural Amagasaki Hospital for treatment of acute left heart failure between August and October 1997, were studied. The underlying cardiomyopathy was diagnosed on the basis of cardiac catheterization, and the diagnosis of IDC versus ICM was made according to the criteria defined by the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) task force.[7] The diagnosis of acute left heart decompensation was based on all of the following findings: (1) complaint of dyspnea or presence of orthopnea, (2) moist rales audible in both lungs, (3) radiographic findings consistent with pulmonary edema, and (4) depressed LVEF on echocardiography. Heart failure was defined as acute when the onset of decompensation had occurred within 2 weeks. Although all patients had low LVEFs, they had been clinically stable, without signs or symptoms of pulmonary congestion for at least 2 months before the onset of acute decompensation.

Patients with a history of myocardial infarction or angina pectoris within 1 year were excluded, and serial creatine kinase enzyme measurements and electrocardiograms (ECGs) were obtained. Patients with infectious diseases, renal failure, cancer, or autoimmune diseases were also excluded. To avoid the nonspecific immunoreactive induction of CRP and inflammatory cytokines, cardiac catheterization procedures, including Swan-Ganz catheters, were withheld for the first 7 days.

Controls

Control blood samples were obtained from eight age-matched asymptomatic subjects, five men and three women, (average age 70.0 years, range 58–83 years), whose echocardiographic left ventricular systolic function was normal.

Blood Samples

Blood was collected daily for 5 to 7 days after admission of the patient to the hospital. Plasma concentrations of interleukin (IL)-4 and IL-6 were measured with commercially available enzyme-linked immunosorbent assay kits. Serum concentrations of CRP were assayed by automated enzyme immunoassays.

Statistical Analysis

Circulating concentrations of cytokines and CRP were expressed as mean value ± standard error. Paired *t*-test was used to test the significance of changes in variables over time during treatment of acute heart failure. Correlation between CRP and IL-6 was analyzed by Peason's correlation coefficient test. A p value < 0.05 was considered significant.

Results

Patients Characteristics

The mean LVEF on echocardiography was 29.5 ± 3.6%. No patient had abnormal serum concentrations of creatine kinase or evolving ECG abnormalities (data not shown) and three patients with ICM had serum concentrations of cardiac troponin T < 0.02 ng/ml. Absence of infection was verified by the collection of blood, sputum, urine, and stool cultures from each patient upon admission to the intensive care unit, and all remained afebrile throughout the study. All patients were treated with intravenous furosemide, six patients received an infusion of the phosphodiesterase inhibitor olprinone (Eisai, Japan), and one patient was placed on an infusion of dopamine. No patient received antibiotics. The symptoms and radiographic signs of pulmonary congestion resolved within 10 days in all patients.

C-Reactive Protein and Cytokines

Increased circulating concentrations of CRP (2.6 ± 0.8 mg/dl), IL-4 (164.6 ± 36.5 pg/ml), and IL-6 (17.1 ± 5.1 pg/ml) were found in all eight patients during acute cardiac decompensation; these values decreased significantly with the resolution of symptoms of acute left heart failure (0.5 ± 0.1 mg/dl, 77.8 ± 23.6 pg/ml, 2.3 ± 0.1 pg/ml, respectively, $p < 0.05$ for both) (Fig. 1). There was a significant correlation between peak CRP and peak IL-6 ($p < 0.05$). The peak concentration of CRP, IL-4, and IL-6 did not correlate with the left ventricular

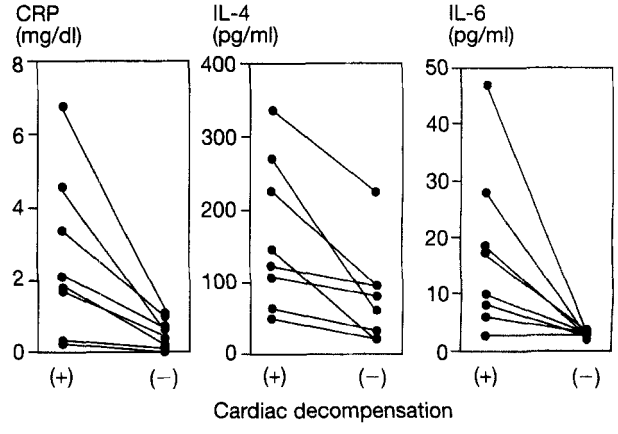

FIG. 1 Circulating concentrations of C-reactive protein (CRP), IL-4, and IL-6. All patients with acute cardiac decompensation had increased serum concentrations of CRP, interleukin (IL)-4, and IL-6, which decreased significantly with the resolution of symptoms ($p < 0.05$).

echocardiographic ejection fraction measured on admission (data not shown).

Corresponding concentrations in control subjects were 0.15 ± 0.01 mg/dl (CRP), < 20 pg/ml (IL-4), and 1.3 ± 0.1 pg/ml (IL-6).

Discussion

Our data indicate that CRP, IL-4, and IL-6 were elevated in all patients during the acute phase and decreased as the signs and symptoms of acute heart decompensation resolved. Since the acute phase response is a nonspecific phenomenon induced by nearly all forms of tissue injury and inflammation, concurrent disorders must be excluded when examining the specific association between concentrations of circulating acute-phase proteins and acute heart failure. In this study, patients with recent myocardial infarction, angina pectoris, and infections were systematically excluded.

Interleukin-6 is a proinflammatory cytokine that induces a wide variety of functional responses. It is a major inducer of CRP, and our data confirmed a significant correlation between CRP and IL-6 in patients with decompensated heart failure. Although the origin of the increase in IL-6 in patients with heart failure remains unknown, it is produced in monocytes/macrophages, endothelial cells, vascular smooth muscle cells, and fibroblasts; it has also been recently reported that hypoxic stress induces cardiac myocyte-derived IL-6.[8] Cardiac decompensation itself, and other organ injuries induced by low cardiac output, hypoperfusion, hypoxia, and venous congestion may each be sources of IL-6 which, in turn, may induce the production of CRP in patients with acute cardiac decompensation.

Interleukin-4 inhibits the ability of monocytes to produce IL-1β and TNF-α and is considered an anti-inflammatory cytokine. We found high circulating concentrations of IL-4 in all patients with acute cardiac decompensation and it seems to be an acutely induced cytokine in this clinical setting. The pathologic significance of IL-4 in patients with heart failure has not been described at the present time.

The imprecise onset of acute cardiac decompensation among individual patients is a limitation of this study. In addition, we have recently reported that several drugs used in the treatment of heart failure, including phosphodiesterase inhibitors, decrease the production of cytokine.[9] Since six of our patients received a phosphodiesterase inhibitor, it may have had an effect on the measured concentrations of cytokines.

Conclusion

Our findings indicate that patients with acute cardiac decompensation in absence of infection or myocardial ischemia have increased circulating concentrations of CRP, IL-4, and IL-6. Since the changes in these parameters in patients with chronic left heart failure are dynamic, the distinction between compensated and decompensated state is important when discussing the significance of acute reactive proteins or cytokines in the pathogenesis of heart failure.

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