Major Depressive Disorder and Inflammatory Markers in Elderly Patients With Heart Failure

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The authors evaluated levels of inflammatory markers in 34 chronic heart failure (CHF) outpatients age 65 years and over, with (N = 18) and without (N = 16) major depressive disorder (MDD), and healthy-control subjects (N = 13). Patients with CHF had left-ventricular ejection fractions <0.40 and were in the New York Heart Association functional class II or III. The authors used the SCID DSM–IV to diagnosis MDD. High-sensitivity C-reactive protein levels were significantly higher in patients with CHF and MDD as compared with healthy-control subjects. No differences regarding tumor necrosis factor$_\alpha$ or interleukin$_6$ were found among the three groups.
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Heart failure is the main cause of hospital admission in patients older than 65 years.[1] Independently, depression leads to a disability equal to or greater than that of chronic diseases such as diabetes or arthritis,[2] and it has been associated with increased morbidity or mortality in subjects with and without cardiac disease.[3,4] Among chronic heart failure (CHF) patients, depression has been associated with increased rehospitalization and mortality,[5] and depressive symptoms were reported to be the strongest predictor of health status decline.[6] Reported prevalence rates of current depression in patients with CHF have ranged from 11% to 48% for outpatients[7–11] and from 35% to 51% for inpatients.[5,12–14] Although with some disagreement,[15,16] it has been proposed that increased levels of inflammatory factors may play a role in the relationship between depression and cardiac disease.[7,17]

Both depression and heart failure have independently been associated with increased levels of C-reactive protein (CRP)[18–22] and circulating proinflammatory cytokines, including tumor necrosis factor$_\alpha$ (TNF$_\alpha$)[23,24] and interleukin$_6$ (IL$_6$).[9–12,25–28]

Inflammatory cytokines may have profound effects on myocyte phenotype[29,30] and may stimulate myocyte apoptosis[31,32] and depress myocardial functioning.[33] TNF$_\alpha$ may be produced as a response to pressure overload or myocardial infarction by activated macrophages, cardiac cells, and even systemic tissues with underperfusion.[34] It has been suggested that TNF$_\alpha$ regulates nitric oxide metabolism in macrophages, vascular endothelial cells, and vascular smooth-muscle cells.[35,36] Up-regulation in the production of IL$_6$ may be involved in the pathophysiology of major depressive disorder (MDD),[27] possibly via hyperactivity of the hypothalamic–pituitary–adrenal axis (HPA).[37] Also, TNF$_\alpha$ has been reported to produce flu-like

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symptoms, such as increased sleep, decreased appetite, and general malaise.[38]

CRP can activate vascular endothelium and accumulate in atherosclerotic plaque, probably playing a relevant role in plaque inflammation.[39,40] Increased levels of CRP in patients with a history of depression have been proposed to be a possible pathway by which depression could increased cardiovascular risk, both directly[17,41] or moderated by body mass index (BMI).[41,42] Among inflammatory markers, CRP has been considered the strongest predictor of cardiovascular events; CRP levels can predict treatment response to statins and significantly improve the cardiovascular risk-prediction of cholesterol level.[43] Although some studies have previously focused on inflammatory markers as a possible underlying factor linking depression and cardiac disease,[44–46] to our knowledge, only one study specifically addressed the relationship between depression and proinflammatory cytokines in patients with CHF,[7] and no study has investigated CRP levels in this comorbid population. Thus, this study aimed to investigate levels of inflammatory cytokines and CRP in elderly outpatients with compensated CHF and MDD.

METHOD

Study Population

Between January 2000 and January 2003, 586 patients over age 65 were being followed up for heart failure at the Geriatric Cardiology Outpatient Clinic of the Heart Institute of the University of São Paulo. Patients with a diagnosis of compensated heart failure due to ischemic, hypertensive, or idiopathic cardiomyopathy, who were in the New York Heart Association functional class (NYHA) II or III and had a left-ventricular ejection fraction (LVEF) $\leq$0.40 were recruited to participate in the study.

The exclusion criteria were patients with hemodynamically significant valve disease, myocardial infarction, or coronary-artery bypass graft surgery within the past 3 months, or hospital admission for heart failure within the past 30 days. We also excluded patients with diabetes; hypothyroidism; active smoking; infectious, inflammatory, neoplastic, or chronic disease; organic cerebral disease, and other psychiatric diseases. Patients using drugs (e.g., corticosteroids, nonsteroidal anti-inflammatory or immunosuppressive medications, beta-blockers, and psychotropic medications) that could interfere with inflammatory activity[47,48] in the last 30 days were also excluded.

According to the established criteria, 182 patients were referred by their assistant cardiologist for this study. Thirty-six patients refused to participate. A psychiatrist interviewed the remaining 146 patients. Major depressive disorder (MDD) was diagnosed in 42 patients (28%), and 18 classified as having MDD formed the CHF–MDD group. Among the 104 nondepressed patients, 16 fit the inclusion and exclusion criteria and constituted the non-MDD–CHF group.

A control group of 13 healthy individuals over age 65 was recruited from a program at the Geriatric Division of the University of São Paulo Clinics Hospital. Individuals in this group had no evidence of any significant disease and were taking no medications.

All participating individuals provided written informed consent, and the study was approved by the Ethics Committee for Medical Research of the Hospital das Clínicas of the University of São Paulo School of Medicine.

Depression Evaluation

Major depressive disorder was diagnosed by one of two psychiatrists using the Brazilian Version[49] of the Structured Clinical Interview for DSM-IV, Patient Version (SCID–P).[50]

Blood-Drawing and Plasma Storage

Plasma levels of high-sensitivity CRP (hs-CRP), TNF_{α}, and IL_6 were measured in the three groups. Two samples of blood were drawn from each individual into heparinized tubes over an interval of at least 3 weeks. After centrifugation at 2,800 rpm for 12 minutes at -4°C, plasma samples were stored at -80°C. The period between blood-drawing and plasma storage was less than 30 minutes.

Measurement of Plasma Levels of Inflammatory Markers

The IMMULITE™ system (Euro/DPC, Llanberis, UK), an automated immunometric assay with a chemiluminescent substrate, was used to measure TNF_{α} and IL_6. High-sensitivity-CRP was assessed by an immuno-turbidimetric assay using monoclonal anti-CRP antibodies (Roche). A second measurement of hs-CRP plasma levels was obtained at least 3 weeks later if the initial value was $>$5 mg/liter, and the lower of these values was used.

Statistical Analysis

We performed a normality test for all three variables. For hs-CRP, log-transformation passed the normality test, and ANOVA analysis was applied. The other two variables did not pass the normality test, even with log-transformation, and therefore a nonparametric analysis (Kruskal-Wallis test) was performed. The chi-square test or Fisher's ex-

act test was used to assess differences in the frequency distribution among the groups. Data are expressed as means (standard deviation [SD]) or as percentages, where appropriate. Statistical significance was set at the 0.05 level, two-tailed.

RESULTS

The three groups were comparable with respect to clinical and demographic characteristics (Table 1). The LVEF, CHF etiology, NYHA functional class, and currently used medications were similar between the groups with CHF (Table 2).

High-sensitivity CRP levels in patients with CHF and depression were significantly higher than those of healthy volunteers (log hs-CRP in the non-MDD–CHF group was 1.086 (SD: 1.115) versus 1.567 (SD: 1.372) in the CHF–MDD group, versus 0.545 (SD: 0.658) in the healthy-control subjects; $p = 0.049$). There were no other significant differences in inflammatory markers (TNF_α and IL_6) among the three groups. In 23% of the obtained samples, cytokine levels were below the limit of detection. Values for all three variables in the three groups are shown in Table 3.

DISCUSSION

We found significantly higher mean levels of hs-CRP in patients with CHF and depression, but not in those with CHF without MDD, as compared with normal-control subjects. To our knowledge, this is the first study to report increased circulating hs-CRP levels as one of the possible inflammatory factors that may play a role in the increased association between CHF and MDD. Although hs-CRP levels in our patients with CHF and MDD were numerically higher than in subjects with CHF without MDD (12.3 [SD: 18.4] versus 5.3 [SD: 6.9]), this difference did not achieve statistical significance, probably because of the small number of subjects in our study and low statistical power. The lack of statistical difference between the two groups may also be related to a reduction in CRP levels by statins in patients with MDD;[51] depression has been associated with increased levels of CRP in patients not taking statins but not in patients taking statins.[45]

Our results are in line with previous evidence suggesting that activation of the inflammatory cascade could be a possible link between CHF and depressive symptoms, and between CHF and Type D personality. Increased levels of

TABLE 1. Characteristics of Patients With Heart Failure With and Without Major Depressive Disorder (MDD) and Healthy-Control Subjects

	Healthy Controls	Heart Failure Without MDD	Heart Failure With MDD	p
Age, years	71.7 (4.8)	76.3 (5.4)	75.1 (4.9)	0.053
Men, N (%)	6 (46.1%)	10 (62.5%)	11 (61.1%)	0.624
Weight, kg	63.5 (10.9)	63.6 (10.5)	59.1 (12.4)	0.432
Height, m	1.59 (0.1)	1.61 (0.1)	1.60 (0.1)	0.773
BMI, kg/m^2	25.0 (3.1)	24.4 (3.2)	23.0 (3.9)	0.264

Values are mean (standard deviation). BMI: body mass index.
Statistical significance was set at $p<0.05$.

TABLE 2. Clinical Characteristics of Patients With Heart Failure With and Without Major Depressive Disorder (MDD)

	Without MDD N (%)	With MDD N (%)	p
Medicines used			
Digoxin	7 (43.75)	12 (66.67)	0.179
Diuretics	14 (87.50)	12 (66.67)	0.233
Spironolactone	5 (31.25)	7 (43.75)	0.642
Nitrates	6 (37.50)	6 (33.33)	0.800
Acetylsalicylic acid	8 (50.00)	8 (44.44)	0.746
Statins	2 (12.50)	2 (11.11)	1.000
Ischemic etiology of CHF	8 (50%)	8 (44.4%)	0.746
Functional Class II (NYHA)	9 (56.3%)	12 (66.7%)	0.533
Left-ventricular ejection fraction, mean (SD)	0.34 (0.04)	0.32 (0.07)	0.285

SD: standard deviation; CHF: chronic heart failure; NYHA: New York Heart Association.
Statistical significance was set at $p<0.05$.

TNF_α (a pro-inflammatory cytokine) and lower levels of $interleukin_{10}$ (an anti-inflammatory cytokine) have previously been reported in 20 patients with CHF and depressive symptoms, as compared with 15 patients with CHF without depressive symptoms.[7] Type D personality, characterized by the combination of a tendency to experience negative emotions (i.e., tension, anxiety, worry, anger, and sadness), and to inhibit the expression of emotions in social interaction, has been associated with increased circulating levels of TNF_α[52] in patients with CHF. The Prospective Epidemiological Study of Myocardial Infarction (PRIME) found that depressive symptoms prospectively predicted cardiovascular events independently of inflammatory factors.[15] However, that does not preclude the idea that the inflammatory factors may mediate the relationship between more severe clinical presentations of depression and cardiac disease.

We found no differences in plasma levels of TNF_α and IL_6 among the three groups. These results contrast with previous studies that have shown elevated levels of these pro-inflammatory cytokines in patients with heart failure.[23,26,53] Some methodological factors may have contributed to this discrepancy. First, we included only patients with compensated CHF, and it has been reported that inflammatory factors tend to increase in the acute phase of decompensation and to decrease during compensation in heart failure.[54] Also, 22% of our cytokine measurements yielded undetectable values; although this limitation has also been previously reported by others,[55] it may have contributed to the absence of detectable difference of TNF_α and IL_6 among our groups.

Several limitations of our study should be considered. First, the study is cross-sectional, and the direction of the relationship between CHF, depression, and inflammatory factors cannot be determined. To our knowledge, studies that have reported increased levels of CRP in depressed patients were also cross-sectional.[19,24,41,56] With respect to the cardiovascular system, the relationship seems to be reciprocal. Increased levels of CRP have been reported prospectively to predict cardiac disease,[57] cardiac events,[58,59] and sudden[60] or early death;[61] and CHF may lead to hepatic cell damage, CRP release,[20] and increased CRP levels. Our sample of 18 patients with CHF and MDD, 16 patients with CHF without MDD, and 13 comparable healthy-control subjects is small, and the results should be considered as preliminary. The small sample is in part the consequence of the rigorous criteria used to exclude patients with confounding conditions (e.g., smoking, hypothyroidism, diabetes).[62,63] A further limitation is that patients in this study had to be off medications such as beta-blockers and aspirin, which are routinely used in CHF, for at least 30 days. Although the CHF patients tended to be older than the healthy-controls, the difference was not statistically significant. Moreover, the oldest patients were in the non-MDD–CHF group, where mean CRP values were not different from those of the normal-controls. Nevertheless, our sense is that adjusting for age should be considered in future studies, with a significantly greater number of subjects, which could allow for performing an analysis of covariance.

We only measured three cytokines. Although all three have been previously correlated with cardiac disease, other cytokines, not measured in our study, may be important for the relationship between MDD and CHF.

In this cross-sectional study of elderly CHF patients, subjects with MDD had higher hs-CRP plasma levels than did healthy-control subjects, thus reinforcing the role of inflammatory processes in the relationship between CHF and depression. Additional prospective studies are needed to confirm this important relationship.

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TABLE 3. Inflammatory Markers in Patients With Heart Failure With and Without Major Depressive Disorder (MDD)

	Healthy-Control Subjects	Heart Failure No MDD	Heart Failure With MDD	Value	p
hs-CRP (mg/L)	2.1 (1.3)	5.3 (6.9)	12.3 (18.4)	2.33[a]	**0.049***
TNF_α (pg/mL)	8.10 (8.13)	10.13 (10.31)	9.67 (12.81)	0.48[b]	0.787
IL_6 (pg/mL)	1.12 (1.96)	3.91 (5.84)	2.95 (5.34)	1.05[b]	0.592

Values are mean (standard deviation).
hs-CRP: high-sensitivity C-reactive protein; TNF: tumor necrosis factor; IL: interleukin.
[a] z value.
[b] Chi-square value.
*Significance was set at $p<0.05$.

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