Basic Science and Experimental Studies

A Potential Shift From Adaptive Immune Activity to Nonspecific Inflammatory Activation Associated With Higher Depression Symptoms in Chronic Heart Failure Patients

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ABSTRACT

Background: Chronic heart failure (CHF) patients with elevated depression symptoms are at greater risk of morbidity and mortality. The mechanisms linking symptoms of depression with disease progression in CHF are unclear. However, research studies have found evidence of alterations in immune activity associated with depression symptoms that may influence heart function. The present study sought to determine the relationship between depression symptoms and chemotaxis of peripheral blood mononuclear cells (PBMCs) in CHF patients, both at rest and in response to moderate exercise.

Methods and Results: Sixty-five patients diagnosed with CHF (mean age, 59.8 ± 14.5 years) and 45 non-CHF control subjects (mean age, 52.1 ± 11.6) completed the Beck Depression Inventory (BDI) before undergoing a moderate 20-minute bicycle exercise task. Chemotaxis of PBMCs was examined in vitro to a bacterial peptide *f-met leu phe* (fMLP) and a physiologic chemokine, stromal cell derived factor-1 (SDF-1) immediately before and after exercise. CHF patients had reduced chemotaxis to SDF-1 ($P = .025$) compared with non-CHF subjects. Higher BDI scores were associated with reduced baseline chemotaxis to SDF-1 in both CHF and non-CHF subjects ($P = .027$). In contrast, higher BDI scores were associated with *increased* chemotaxis to fMLP ($P = .049$) and SDF-1 ($P = .018$) in response to exercise in the CHF patients.

Conclusion: The present study suggests a shift in immune cell mobility in CHF patients with greater depression symptom severity, with reduced chemotaxis to a physiologically specific chemokine at rest but increased chemotaxis to both nonspecific and specific chemical attractants in response to physical activity. This could have implications for cardiac repair and remodeling in CHF patients and therefore may affect disease progression. (*J Cardiac Fail 2009;15:607–615*)

Key Words: Immune, dysregulation, heart failure, depression.

Nearly 5 million people in the United States alone are affected by congestive heart failure (CHF). Mounting literature suggests worse clinical outcomes for CHF patients portraying symptoms of depression.[1–5] However, mechanisms linking depressive symptoms and CHF progression are unclear. Investigation into the influence of depressive symptoms on immune alterations and consequent cardiac remodeling may help to clarify this link.

Depression in physically healthy persons is associated with complicated patterns of immune changes whereby disproportionate inflammatory activity is coupled with an attenuation of specific cellular immune responses.[6] However, the relationship between depression symptoms and inflammation markers among patients with cardiovascular diseases have been inconsistent.[7–12] Overproduction of proinflammatory factors are suggested to lead to excessive infiltration of leukocytes into cardiovascular tissue,[13–15] which greatly affects the myocardial interstitium and can cause myocardial remodeling in CHF.[16,17]

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Meanwhile, there is a concomitant reduction of various cellular immune activities associated with depressive symptoms such as T lymphocyte cytotoxicity and lymphocyte proliferation.[6,18,19] An apparent shift from adaptive immunity to a nonspecific pro-inflammatory profile is associated with dilated cardiomyopathy and CHF[20] and ensuing cardiac disease progression.[9,11,21,22] Moreover, dysregulation of immune activity is reflected by increased infections and reduced wound healing in CHF patients.[23] However, immune cell migration, particularly chemotaxis has been largely ignored in respect to depression symptoms, although chemotaxis is important for both natural and adaptive cellular immunity. Chemokines are essential for providing signaling to leukocytes for extravasation from the blood and directed locomotion.[24,25] When overexpressed, recruitment and migration factors are injurious to the cardiovascular system[26] and can generate angiogenesis and fibrous tissue deposition, which can lead to myocardial dysfunction in CHF.[27,28]

Studying acute physiologic responses to controlled challenges serve as a window into the complex physiologic processes involved in cardiac diseases.[29] Treadmill exercise, for example, elicits greater increases in immune cell recruitment and migration factors such as cytokines and cellular adhesion molecules in coronary artery disease (CAD) and CHF patients.[30,31] In response to acute psychologic stress, depression symptom severity is positively associated with increased cytokines and percentages of subpopulations of lymphocytes in physically healthy subjects.[32] However, exercise has not to our knowledge been used to unmask effects of depression symptoms on immune changes in CHF patients.

To further elucidate depression symptom-associated immune alterations that may influence CHF disease progression, we measured peripheral blood mononuclear cells (PBMC) chemotaxis to a bacterial peptide and a physiologic chemokine in response to acute exercise in CHF patients and non-CHF controls. It was hypothesized that although depression symptoms would be negatively associated with chemotaxis at baseline for cellular/adaptive activity, exercise would generate increases in natural (chemotaxis to *f-met leu phe* [fMLP]) but not adaptive (chemotaxis to stromal-cell derived factor-1 [SDF-1]) chemotaxis responsiveness in CHF patients with elevated depression levels. If confirmed, these findings may indicate an immune shift away from an adaptive cellular and toward an increased nonspecific inflammatory state associated with depressive symptoms in CHF patients.

Methods

Study Participants

The study sample consisted of 65 patients diagnosed with CHF and 45 individuals with no cardiovascular pathology except for elevated blood pressure as a control group. Patients were recruited from the San Diego Veterans Affairs Medical Center and the University of California, San Diego Medical Center Heart Failure Program, as part of a larger study on Neuroimmune Characteristics of CHF and Depression. We recruited the control non-CHF individuals from the local community via various advertisements (eg, newspaper, flyers, brochures, and websites) and word of mouth referrals.

Inclusion criteria for all study participants included age between 30 and 85 years, blood pressure <180/110 mm Hg, and men and women of all ethnicities and races. Inclusion criteria for CHF patients included New York Heart Association (NYHA) Classes II through IV, symptoms of CHF for at least 3 months that have been optimally treated with β-blockers, diuretics, and angiotensin-converting enzyme inhibitors, and an ejection fraction ≤45% or CHF with preserved ejection fraction with diastolic dysfunction. We assessed left ventricular ejection fraction by echocardiography as part of the patient's routine medical evaluation. To assess physical function capacity in all subjects, we used the 6-minute walk test.[33] Exclusion criteria included recent myocardial infarction (1 month), recent stroke or significant cerebral neurologic impairment, severe chronic obstructive pulmonary disease, and psychiatric illnesses other than major depression.

The protocol was approved by the UCSD Institutional Review Board, and participants gave written informed consent. The study was carried out in accordance with the Declaration of Helsinki principles.

Biochemical Analyses

For measurement of B-type natriuretic peptide (BNP), blood was drawn into EDTA-coated Vacutainer tubes (BD Biosciences, San Jose, CA). Blood samples were centrifuged for 10 minutes at 3000 rpm and 4°C and plasma was stored at −80°C until analysis. Plasma BNP levels were determined by the Bayer/Centaur BNP Assay (Bayer Diagnostics). The Bayer BNP assay is an enzyme-linked immunosorbent assay measuring BNP concentrations up to 2500 pg/mL with a minimum detectable concentration of <1.0 pg/mL. The interassay coefficient of variation was 1.8 % and the intra-assay coefficient of variance was 2.2 %. To minimize intra-assay error variance, all samples from an individual subject were analyzed in the same run.

Chemotaxis of PBMC Assay

Ten milliliters of blood was collected into heparinized tubes pre- and post-exercise task and processed within 3 hours. PBMCs were separated from whole blood using Ficoll-Hypaque sedimentation and resuspended in RPMI 1640 with 20 mmol/L HEPES (serum-free media). Cells were incubated for 45 minutes at room temperature in the dark, shaking lightly with 0.1 uM calcein-AM (acetomethyl ester).[34] Cells were then washed and resuspended to 3×10^6 cell/mL RPMI 1640 with 20 mmol/L HEPES, L-glutamine, and 0.1% bovine serum albumin (chemotaxis buffer). In a modified Boyden chamber (Neuroprobe, Gaithersburg, MD), 29.5 uL of chemokines or chemotaxis buffer were pipetted into each well at the bottom of the chamber.

SDF-1 and FMLP were used as chemoattractants in this study. Chemotaxis responsiveness in vitro of PBMCs to bacterial peptide fMLP is commonly used to measure nonspecific natural immune activity. CHF patient responses to fMLP are greater than in non-CHF controls, suggesting increased sensitivity to antigenic stimuli and exaggerated nonspecific inflammatory responsiveness.[35] Increased rates of spontaneous monocyte migration are also found in patients with various cardiac abnormalities in comparison to healthy controls.[36] SDF-1 binds to its specific receptor CXCR4