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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.

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

and subsequently stimulates lymphocyte adhesion and transendothelial migration.[37] Thus, SDF-1 participates in adaptive cellular immunity. Levels of SDF-1, and its receptor, CXCR4, are elevated in patients with CHF and have been found to attenuate cardiac myocyte contractility.[27] SDF-1 strongly attracts B cells, but also attracts monocytes.[38] CXCR4 receptors are also present on T cells.[39] Chemokines were used at optimal doses that were determined from prior studies;[40,41] the following chemokine concentrations were used: fMLP (10 nM) (Sigma) and SDF-1 (100 ng/mL) (Biosource, Camarillo, CA). After the pipetting of chemokines, the membrane was snapped on top of the plate and 20 uL of cell suspension was added to the top of each well. Cells were incubated for 2 hours at 37°C and then the top of the membrane was gently rinsed with phosphate-buffered saline and nonmigrated cells were scraped away using phosphate-buffered saline dampened cotton swabs. The membrane was removed from the plate and briefly submerged in phosphate-buffered saline. Once dry, the membrane was read by a fluorescence plate reader (CytoFluor) at an excitation of 485 nm and emission of 530 nm.

Exercise Testing

The exercise testing sessions commenced at approximately 11:30 AM and lasted for 1.5 hours. Participants abstained from food and drink (other than water) for 2 hours before the experiment, and from physical exercise, alcohol, and caffeinated beverages starting the evening before the test day.

Subjects performed a mild graded exercise task on a stationary bicycle (Viasprint 150p, Viasys, Yorba Linda, CA). After a 5 to 10-minute quiet rest, blood pressure was measured using an automated blood pressure monitor (Dinamap Compact BP monitor, Critikon, Tampa, FL) and venous blood was taken via an intravenous catheter that was placed in the antecubital vein 3 hours prior. Subjects began peddling on the bicycle and continued at the pace of their choice (eg, 60 rpm). The bicycle protocol consisted of 5 minute warm-up, 10-minute steady state, and 2-minute cool-down periods. To apply the similar exercise intensity in relative to existing fitness levels for all participants, Borg's ratings of perceived exertion scale[42] was used; the resistance (watts) of the bicycle was gradually increased during the warm-up period to reach the rating of 12 to 13 (''somewhat hard''), and the subjects continued to exercise at this level for 10 minutes through adjusting the resistance and speed of cycling. Based on our previous experience,[43,44] ratings of perceived exertion of 12 to 13 consistently corresponds to 65% to 70% of VO_{2peak} regardless of fitness levels. Blood pressure, heart rate, and oxygen saturation levels (via a finger probe) were monitored throughout the bicycle exercise every 2 minutes. Blood samples were obtained before, immediately after, and 10 minutes post-exercise. Exercise was terminated if a subject expressed discomfort, excessive muscle fatigue, chest pain, shortness of breath, or if blood pressure exceeded 220/100 mm Hg or dropped below resting levels.

Depressive Symptom Severity

On the morning of testing, depressive symptom severity was assessed with the 21-item Beck Depression Inventory (BDI) where scores ≥10 indicate possible clinical depression.[45] The BDI was developed for the assessment of depressive symptoms that correspond to the Diagnostic and Statistical Manual of Mental Disorders−IV criteria for major depressive disorder and measures somatic and a cognitive-affective dimensions of depression.[46] The BDI assesses symptoms related to sadness, feelings of guilt, perceptions of self-worth, suicidal ideation, and changes in appetite and body weight, among other characteristics. Subjects with scores ≥10 on the BDI were administered a modified Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV[47] to evaluate for possible major depressive disorder. If suspected of having major depressive disorder, potential participants were presented with a list of options and referred to their physician, but were allowed to remain in the study.

Statistical Analyses

All calculations were performed using SPSS (v11.0.1) software packages (SPSS, Chicago, IL). Results were considered statistically significant at the $P \leq .05$ level and all tests were 2-tailed. In case of missing data, cases were excluded listwise. Body mass index was calculated by the formula: weight in kg/(height in m)^2.

To test for group differences in sociodemographic and medical characteristics we computed univariate analyses of covariance (Table 1). To determine correlations between CHF severity and chemotaxis measures, Pearson correlations were performed between ejection fraction and BNP and chemotaxis to SDF-1 and fMLP. Also, Pearson correlations were performed to determine the associations between actual exercise workload (resistance or watts) and perceived workload and chemotaxis markers. To address resting associations of chemotaxis activity and depressive symptoms, we performed linear regression analyses with prestress measures of chemotaxis as a dependent variable while controlling for the group variable (CHF status) in a first step, age, gender, and physical function (meters walked in the 6-minute walk test) in the second step, and depressive symptoms was entered in the third step as a *continuous* independent variable. Next, to address associations between depressive symptoms and chemotaxis changes in response to acute exercise, we again performed linear regression analyses with chemotaxis change in response to exercise as the dependent variable. Chemotaxis change was calculated as chemotaxis post-exercise level minus pre-exercise level. We entered the BDI depression symptom scores as an independent continuous variable while controlling for subject group in a first step. In a second step, we additionally controlled for age, gender, and physical function. To address the potential influence depression symptoms had on group differences in chemotaxis, we calculated moderator analyses as described by Baron and Kenny[48] both for resting chemotaxis and for chemotaxis changes in response to exercise. We performed regression analyses with chemotaxis changes in response to exercise as the dependent variable and we entered the depression score, the group variable, and their interaction as independent variables. We centered the group variable to the mean to allow calculation of interaction terms. To graphically illustrate our continuously calculated regression results we split BDI scores into ≥10, and <10 in each subject group rendering 4 subgroups of subjects of depressive symptoms (ie, CHF patients high or low BDI scores and controls with either high or low BDI scores; Fig. 1).

Results

Sociodemographic and medical characteristics are presented in Table 1. CHF patients were older ($F(1,107) = 13.05, P < .01$) and had higher mean BDI scores ($F(1,107) = 17.9, P < .01$), but no differences in incidence of major depression disorder.

Table 1. Sociodemographic and Medical Characteristics According to Group

Demographics	CHF patients (Mean ± SD; Min.-Max.)	Non-CHF controls (Mean ±SD; Min.-Max.)	*P* Value
Beck Depression Inventory score	12.0 (7.8); 1−34	6.0 (8.2); 0−44	<.01
Major depressive disorder	1.5%	4.4%	.29
Age (y)	59.8 (14.5); 30−81	52.1 (11.6); 34−84	<.01
Body mass index (kg/m^2)	28.7 (5.9); 20.2−54.4	31.9 (8.8); 20.1−59.0	.07
Male	89%	59%	<.01
Current smokers	13%	17%	.83
% Monocytes	8.9 (2.4); 4−15	8.7 (2.4); 5−14	.80
% Lymphocytes	23.6 (8.4); 4−49	33.7 (9.9); 10−57	<.01
CHF severity			
Ejection fraction (%)	32.0 ± 9.0; (14−58)		
NYHA Class II	89.7%		
NYHA Class III	10.3%		
Resting BNP	224.4 (228.0); 6−889	13.2 (9.7); 2−38	<.01
Medication			
Antidepressants	24%	2%	<.01
Angiotensin-converting enzyme inhibitors	82%	0%	
β-blockers	95%	0%	
Statins	67%	0%	
Aspirin	51%	5%	<.01
Diuretics	90%	0%	
Antiarrhythmics	15%	0%	
Digoxin	61%	0%	
Warfarin	38%	0%	

CHF, congestive heart failure; NYHA, New York Heart Association.

As expected, the absolute workload during the exercise challenge (average resistance or watts) was significantly greater in the non-CHF (38.1, SEM = 3.1) versus CHF (25.6, SEM = 1.9) group, F(1,107) = 6.9, $P = .01$. However, in accordance with the study design the average *perceived* workload during exercise determined using the Borg Scale did not differ between groups, with non-CHF = 13.49 (SEM = 0.13) and CHF = 13.5 (SEM = 0.13), F(1,107) <.001, $P = .990$. Neither the absolute or perceived workloads were significantly correlated with changes in chemotaxis in response to exercise. BNP and ejection fraction percentage were not significantly correlated with chemotaxis to SDF-1 or fMLP either at rest or in response to exercise.

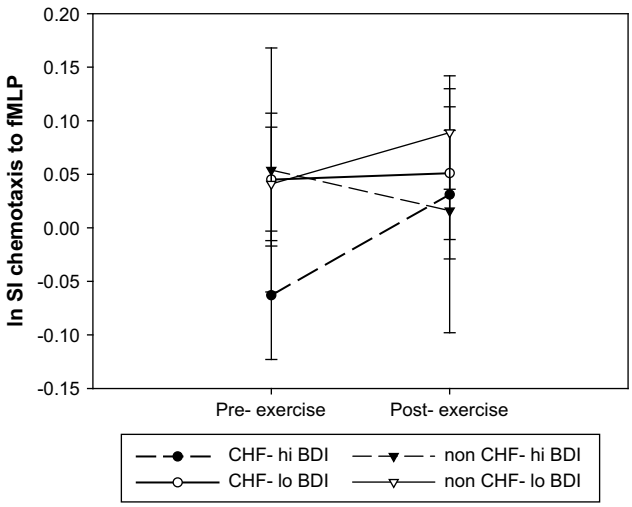

Fig. 1. Values are means ± SEM. Changes in a logarithmic transformed stimulation index (SI) of chemotaxis to *f-met leu phe* (fMLP) in congestive heart failure (CHF) patients and non-CHF controls with high (≥10) and low (<10) Beck Depression Inventory (BDI) scores in response to exercise.

Chemotaxis in CHF Patients versus Controls

After controlling for age and gender, a univariate analysis of variance revealed there were no baseline differences between CHF and non-CHF subjects for chemotaxis to fMLP; however, there was for chemotaxis to SDF-1 (F(3, 103) = 4.99, $P = .025$), which was lower in CHF patients. Although there were group differences in percentages of lymphocytes between CHF and non-CHF patients at baseline (Table 1), when entered into the univariate analyses of covariance as a covariate percentages of lymphocytes did not contribute to baseline group differences for chemotaxis to SDF-1.

Depression Symptom Severity and Chemotaxis

At Rest. Linear regression analyses revealed that BDI scores were not significantly associated with chemotaxis to fMLP although they were for chemotaxis to SDF-1 ($t = -2.7$, $p < .01$, *beta* = −.323, $\Delta R^2 = .10$) after controlling for CHF status, age, gender, and physical function, where chemotaxis was lower in the more depressed subjects in both groups. However, there were no CHF status by BDI score interactions, suggesting that CHF status and BDI scores were independently associated with chemotaxis responses when subjects were at rest (Tables 2, 3) (Fig. 1, 2). When analyses were performed only on CHF patients controlling for age, gender, and NYHA Class, BDI scores were negatively associated with chemotaxis at rest to both fMLP (t = −2.4, $P = .02$, *beta* = −0.329, $\Delta R^2 = .10$)

Table 2. Peripheral Blood Mononuclear Cell Chemotaxis Stimulation Index (Chemotaxis to Chemokine Divided by Random Chemotaxis) to fMLP and SDF-1 in CHF Patients and Controls according to BDI Scores

Chemotaxis (Mean ± SD)				
			BDI < 10	BDI ≥ 10
fMLP	Pre-exercise	CHF	1.11 (0.39)	.96 (0.20)
		Non-CHF	1.18 (1.07)	1.10 (0.40)
	Post-exercise	CHF	1.11 (0.34)	1.05 (0.22)
		Non-CHF	1.19 (0.75)	1.06 (0.37)
SDF-1	Pre-exercise	CHF	1.01 (.30)	0.88 (0.17)
		Non-CHF	1.08 (0.42)	0.95 (0.19)
	Post-exercise	CHF	0.98 (0.22)	1.00 (0.24)
		Non-CHF	1.11 (0.42)	0.92 (0.19)

fMLP, *f-met leu phe*; SDF-1, stromal cell derived factor-1; CHF, congestive heart failure.

and SDF-1 (t = −2.03, P = .048, *beta* = −0.288, ΔR^2 = 0.077).

Reactivity to Exercise

Linear regression analyses revealed that after controlling for CHF status, age, gender, and physical function, BDI scores did not significantly contribute to exercise-related chemotaxis to fMLP or SDF-1. However, there was CHF status by BDI score interactions such that higher BDI scores were associated with an increase in chemotaxis to fMLP (t = 2.1, P = .046, *beta* = 1.28, ΔR^2 = .064) and to SDF-1 (t = 2.49, P = .018, *beta* = 1.51, ΔR^2 = .088) in response to exercise in the CHF patients and little change in non-CHF individuals. Neither changes in monocyte or lymphocyte percentages appeared to account for the CHF status by BDI score interactions, determined by entering pre- to post-exercise changes in monocyte or lymphocyte percentages into the regression equation (Tables 2, 3; Fig. 1, 2). When analyses were performed only on CHF patients controlling for age, gender, and NYHA Class, BDI scores were significantly associated with the chemotaxis response to exercise to SDF-1 (t = 2.03, P = .049, *beta* = 0.289, ΔR^2 = .076) and a trend to fMLP (t = 1.94, *beta* = 0.278, P = .059, ΔR^2 = 0.07).

Table 3. Hierarchical Regression Analyses Examining Associations between Depression (BDI scores) and Chemotaxis of Peripheral Blood Mononuclear Cells to fMLP and SDF-1 in CHF Patients and Controls after Controlling for Age, Gender, and Physical Function

Regression						
			Standardized β-coefficient	t	P	ΔR^2 Change
Baseline	fMLP	CHF	−0.436	−2.65	.013	0.18
	SDF-1	CHF	−0.387	−2.27	.031	0.14
	fMLP	Non-CHF	−0.072	−.0391	.70	0.072
	SDF-1	Non-CHF	−0.193	−1.11	.28	0.037
Response to exercise	fMLP	CHF	0.348	2.16	.04	0.11
	SDF-1	CHF	0.410	2.63	.014	0.16
	fMLP	Non-CHF	.04	0.22	.83	0.002
	SDF-1	Non-CHF	−0.049	−0.26	.79	0.002

fMLP, *f-met leu phe*; SDF, stromal cell derived factor-1; CHF, congestive heart failure.

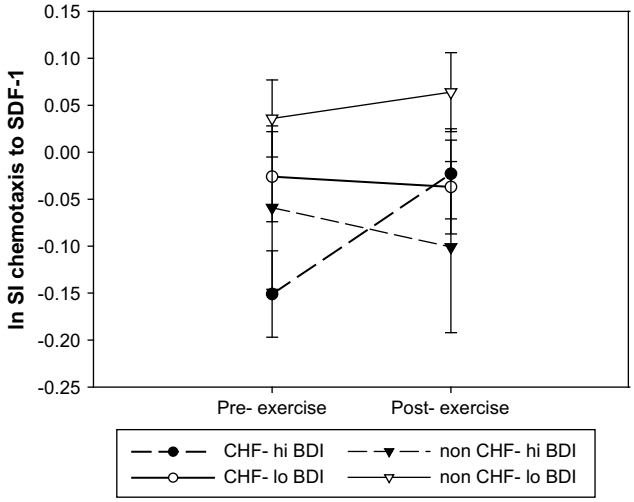

Fig. 2. Values are means ± SEM. Changes in a logarithmic transformed stimulation index (SI) of chemotaxis to SDF-1 in congestive heart failure (CHF) patients and non-CHF controls with high (≥10) and low (<10) Beck Depression Inventory (BDI) scores in response to exercise.

Subscales of Depression (Cognitive and Somatic Symptoms) and Chemotaxis

Regression analyses revealed that cognitive depressive symptoms but not somatic depressive symptoms were negatively associated with baseline chemotaxis to fMLP (t = −2.4, P = .01, *beta* = −0.308, ΔR^2 = 0.081) and SDF-1 (t = −2.88, P = .006, *beta* = −0.362, ΔR^2 = 0.11, respectively) in both CHF patients and controls (after controlling for CHF status, age, physical function and gender). To determine if this was still significant in only CHF patients (because CHF patients likely have more somatic symptoms), subanalyses were conducted on data solely from CHF patients controlling for age, gender, and NYHA class. Cognitive but not somatic depressive symptoms were again associated with chemotaxis to fMLP (t = −2.46, P = .018, *beta* = −0.337, ΔR^2 = 0.19) and SDF-1 (t = −2.02, P = .049, *beta* = −0.285, ΔR^2 = 0.12, respectively) at rest. However, neither cognitive nor somatic symptoms individually predicted changes in chemotaxis from pre- to post-exercise task for either chemokine, in both groups.

Discussion

Results from the present study suggest that in CHF patients with elevated depression symptoms, there may be an immune shift away from specific cellular immune activity and toward a more generalized nonspecific immune

activation in response to a physical challenge. This shift in immune activity may be a sign of immune dysregulation in CHF patients with increased depressive symptoms. The present study found less PBMC chemotaxis to SDF-1 in CHF patients at rest (baseline) compared with controls, which is in agreement with studies,[23,49] suggesting that CHF patients are more prone to infection and reduced wound healing because of reduced functional immune activity. Additionally, higher depression symptoms were associated with reduced chemotaxis to SDF-1 in both CHF patients and non-CHF controls. This is also in agreement with a number of early studies that suggest reduced cellular immune activity is associated with increased depression symptoms.[6,18,19] However, we did not find an interaction between CHF status and depression symptoms at rest, with further decreases in chemotaxis to SDF-1. This suggests that CHF status and depressive symptom levels are independently associated and likely additive for reductions in chemotaxis. This finding may be important for CHF morbidity and mortality because reduced immune migration can attenuate cardiac tissue repair and increase risk of infection.[50]

In response to moderate exercise the present study found as expected that CHF patients with elevated depressive symptoms had increased chemotaxis to the bacterial peptide fMLP, which suggests increased nonspecific natural immune cell mobility. However, unexpectedly there was also an increase in chemotaxis to chemokine SDF-1, which may indicate mobility of immune cells to a chemokine considered to generate a specific adaptive immune response. This apparent increase in adaptive and natural immune cell chemotaxis may reflect general immune activation. These findings extend prior research in physically healthy individuals, that depression symptoms are linked with acute stress associated increases in pro-inflammatory cytokine interleukin (IL)-6, and activation of nuclear factor-kB, a transcription factor that signals the inflammatory cascade,[32] which may in turn mediate leukocyte recruitment.

To examine immune responsiveness in CHF patients with a continuum of depressive symptoms, chemoattractants fMLP and SDF-1 were intentionally chosen for the present study to measure natural and adaptive immune responsiveness. The bacterial peptide fMLP stimulates nonspecific natural immune responses; recently recruited interstitial monocytes respond against bacterial-related peptides, providing a role in the protection against invading pathogens.[51] However, overactivation may lead to nonspecific immune induced remodeling. On the other hand, for adaptive immune responses it is suggested that phenotype, the expression of a specific receptor is a critical factor influencing the lymphocyte's trajectory to its final destination.[52] Chemokines exert their functions by binding specific G protein−coupled chemokine receptors on the lymphocyte surface.[53] Regulation of chemokine receptor responsiveness by expression level modulation appears to be important for interstitial lymphocyte mobility and placement.[531] SDF-1 is a potent chemotactic factor for a variety of cell, including lymphocytes and monocytes. SDF-1, binding to its specific receptor CXCR4, can activate integrins and initiate firm adhesion of rolling leukocytes.[37] CXCR4 plays a pivotal role in lymphocyte homing and recruitment into inflammatory sites.[37] SDF-1 is also secreted by immune cells in response to tissue damage and is suggested to be instrumental in chemoattracting CXCR4(+) cells involved with cardiac tissue repair.[54,55]

Although we found a reduction in baseline chemotaxis to SDF-1 in CHF, other studies determined circulating SDF-1 levels[56] and cardiac tissue levels of SDF-1 and its receptor, CXCR4 are increased, which are subsequently associated with reduced cardiac contractility.[27] It is not clear whether the findings in our study of reduced chemotaxis to SDF-1 are contrary to the increases in SDF-1 levels and receptors in CHF found in other studies. However, theoretically, these seemingly contradictory findings may be explainable. There may be a decrease in immune sensitivity to SDF-1 in CHF and therefore reduced chemotaxis due to chronic elevated levels of SDF-1. However, SDF-1 levels were not measured in the present study and therefore circulating levels versus sensitivity to SDF-1 could not be evaluated. Future studies are needed to further understand the relationship between chemokine levels, PBMC sensitivity to chemokines, depression symptoms, and cardiac tissue infiltration in CHF.

One of the most important insights from the large body of work that has emerged over the past 2 decades is that patients with CHF experience progressive changes in cardiac structure and function that are caused by activation of pathways that increase systemic and local cardiac immune activation that promote maladaptive cardiac growth.[17] Elevated inflammatory cytokine levels, including tumor necrosis factor (TNF)-α, IL-1 beta, and IL-6, which are involved in immune cell recruitment are linked with ischemia/reperfusion injury, and abnormal myocardial remodeling of CHF.[57] In CHF, increased depression symptoms are associated with increased inflammatory mediators, soluble TNF-a receptor1 (sTNFr1)[7] and TNF-α[11] and exercise-induced sP-selectin.[58] A limitation of the present study is the lack of available peripheral blood pro-inflammatory biomarker data such as cytokines to determine whether alterations in chemotaxis during exercise are associated with other proinflammatory activities in CHF patients with increased depressive symptoms. Depressive symptoms and associated upregulation of inflammatory mediators can play a role in cardiovascular pathology.[15] Chemokines and their receptors are inflammatory constituents that factor into modulating myocardial dysfunction in CHF. Chemotaxis increased in response to exercise in CHF patients with higher depression symptoms, which could subsequently result in greater leukocyte migration into cardiac tissue.

Although CHF is associated with many somatic symptoms, it is of interest to note that the composition of the elevated depression symptom scores from the BDI that were related to less chemotaxis to SDF-1 in both groups was predominately cognitive depressive symptoms versus somatic. This was true even when CHF patients were examined alone, suggesting that the non-CHF patients did not carry

these findings. Meanwhile, depression score−associated increased chemotaxis responsiveness to exercise did not differ in composition of cognitive versus somatic depression symptoms suggesting that both types of depression symptoms may contribute to immune responsiveness to physical exertion.

The mechanisms associated with these findings as yet remain to be determined; however, alterations in chemotaxis are likely the result of immune regulatory alterations. Patterns of migration of lymphocytes change depend on regulatory peptides such as cytokines and chemokines. For example, the numbers of migrating T cells toward SDF-1 markedly increased after preincubating the cells with transforming growth factor via upregulation of the expression of the SDF-1 receptor CXCR4 and occurs through integrin-mediated lymphocyte migration.[59] Furthermore, IL-4− and interferon (IFN)-g−producing CD4+ T cell subsets are differentially attracted by chemokines, which could lead to Th1- or Th2-dominated tissue infiltrates.[60] Lower measurements of IL-2 and IFN-g (Th1) cytokines were observed in depression groups,[61,62] suggesting reduced presence of Th1 cells available for migration. Similarly, CHF patients with lesser IFN-gamma/IL-10 expressing CD4+ T cell ratios were also related to higher depressive symptom scores at baseline and a prospective increased incidence of cardiac-related hospitalization or death over a 2-year period.[63] This also suggests a shift from cellular states in CHF patients with higher depression symptoms. However, the specific mechanisms linking depression symptoms with a shift in immune activity in CHF are still unclear. The clinical implications of these findings may be important, as these immune factors are relevant to cardiac tissue repair, remodeling, and protection against pathogens in this vulnerable population.

Endocrine factors such as glucocorticoids and catecholamines are also likely to alter immune cell function in CHF patients with elevated depression symptoms. In a study by Miller et al,[64] at rest in vitro IL-6 and TNF-α production was reduced in the presence of glucocorticoids to a greater extent in depressed subjects than control subjects, suggesting greater sensitivity to the antiinflammatory properties of glucocorticoids. However, after exposure to a stressor protocol glucocorticoid sensitivity apparently decreased among depressed subjects and increased among controls. These findings suggest that under acute challenges, depression may be associated with greater resistance to hormones that normally attenuate the inflammatory cascade. Impaired inflammatory regulation could be the cause of some of the depression-associated increases in morbidity and mortality. It is not known whether immune cell motility is directly affected by glucocorticoid regulation; however, these findings suggest that cytokines associated with immune cell regulation may be.

In addition, the neurohormone norepinephrine may be involved in migration of macrophages and monocytes. Norepinephrine stimulates the chemotaxis of macrophages and monocytes mainly mediated by α-adrenergic receptors.[65,66] Furthermore, neurotransmitters released at peripheral sympathetic nerve endings attract monocyte migration similarly to fMLP, as both are dependent on intracellular cAMP concentration.[65] These findings may have implications for immune responses to the physical challenge in CHF patients with increased depression symptoms. However, this needs to be further elucidated.

In summary, results from this study suggest that depression symptoms are associated with reduced adaptive immune cell motility in CHF patients. Cognitive as opposed to somatic depression symptoms had a greater relationship with the reduced adaptive response of chemotaxis to chemokine SDF-1. This may be important for CHF morbidity and mortality due to attenuated cardiac tissue repair and increased risk of infection. Meanwhile, CHF patients with greater depression symptom levels had augmented both natural and adaptive chemotaxis activity to a physical challenge, which suggests a generalized immune activation. This extends findings of elevated inflammatory activity in response to acute psychologic stress in persons with greater levels of depression symptoms. Increased immune activation, in turn, may play a role in cardiovascular pathology. Altered motility responses may represent immune dysregulation resulting from both immune regulatory and neuroendocrine changes. However, the specific mechanisms associated with the immune changes are unclear and warrant further research.

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