Depression as a Potential Modulator of Beta-Adrenergic–Associated Leukocyte Mobilization in Heart Failure Patients

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Objectives The aim of this study was to determine whether depressive symptoms are related to alterations in the sensitivity of peripheral blood mononuclear cells to β-adrenergic agonists in patients with heart failure (HF) by measuring in vitro chemotaxis (CTX) to isoproterenol at rest and after acute exercise in patients with HF and controls.

Background Clinical outcomes are worse for patients with HF presenting with symptoms of depression. Sympathetically modulated immune dysregulation associated with depression may be one mechanism leading to worse prognosis.

Methods Seventy-seven patients with HF and 44 controls (mean age 56.4 ± 1.3 years) completed the Beck Depression Inventory and a 15-min mild-graded exercise task on a stationary bicycle. Exercise intensity was kept relative to fitness levels for all participants by gradually increasing resistance to reach a Borg scale subjective rating of 12 to 13, "somewhat hard." Plasma norepinephrine and epinephrine levels were measured before and after exercise. Chemotaxis to isoproterenol was determined by measuring in vitro peripheral blood mononuclear cell migration through a modified Boyden chamber.

Results In patients with HF, depressive symptom severity was associated with greater CTX after exercise ($p = 0.001$). Higher resting norepinephrine in patients with HF was also associated with increased CTX to exercise ($p = 0.03$).

Conclusions Patients with HF with higher depressive symptoms and norepinephrine exhibited increased peripheral blood mononuclear cell CTX to isoproterenol to mild exercise, suggesting greater β-adrenergic sensitivity. Increased immune migration in patients with HF who have elevated depressive symptoms could be associated with cardiac remodeling and HF disease progression. (J Am Coll Cardiol 2010;56:1720–7) © 2010 by the American College of Cardiology Foundation

The prevalence of depression ranges from 20% to 45% in patients with symptomatic heart failure (HF) and corresponds with significantly greater morbidity and mortality (1). However, the biobehavioral pathways linking depression with adverse outcomes in HF are unclear. One potential mechanism is depression-associated dysregulation of neuroendocrine modulation of immune responses to stress and exercise (2), which may be injurious to the cardiovascular system (3), leading to worse prognosis in HF (4,5).

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Autonomic innervation and regulation of the immune system are well recognized (6,7). Sympathetic activation during stress and exercise elicits the release of leukocytes from the spleen, lymph nodes, and blood vessel subendothelia into the bloodstream (8,9). These immune cells express greater surface β-adrenergic receptor density and sensitivity (9–11). The endogenous β-adrenergic neurohormones norepinephrine (NE) and epinephrine (EPI) can thereby regulate immune mobility, as powerful chemoattractants (6,12). Additional inflammatory markers also respond to exercise-related increases in catecholamines in patients with coronary artery disease patients compared with controls (13).

Depression is associated with modified sympathetic and neurohormonal activation to stress and exercise, including increased NE and EPI (14). Thus, depression may alter immune responses to stress and exercise through changes in neuroendocrine-immune interactions. Indeed, depression is

associated with increased leukocyte sensitivity to stress hormones (15) and greater pro-inflammatory responses to stress and physical exertion (2,3). Our research suggests that patients with HF with elevated depressive symptoms also exhibit augmented immune migration processes to exercise (16,17). Although the clinical relevance of these findings remains to be elucidated, excessive leukocyte mobilization can elicit leukocyte infiltration into myocardial interstitium, which can underlie injury to the cardiovascular system (4,5).

In light of prior research, the primary objective of the present study was to investigate the relationship between depressive symptoms in patients with HF and leukocyte mobility toward a β-adrenergic agonist in response to physical exertion, as a model to explore changes in immune cell sensitivity to neuroendocrine modulation in this group. This was done by assessing depression symptoms and in vitro chemotaxis (CTX) of peripheral blood mononuclear cells (PBMC) to isoproterenol (CTX-I) at rest and after acute exercise, comparing patients with HF and non-HF controls. Furthermore, the influence of endogenous sympathetic activity on these relationships was explored. The determination of a link between depression and neuroimmune dysregulation in patients with HF may suggest one mechanism that leads to worse HF outcomes.

Methods

Study participants. Included in the study were 124 subjects (80 patients with HF and 44 non-HF controls) assessed for in vitro CTX-I, depressive symptoms, physical function, and demographic variables from 2005 to 2009. Patients were recruited from the San Diego Veterans Affairs Medical Center and the University of California-San Diego, Medical Center as part of a larger study on the effects of depression on neuroimmunity in HF. Control subjects were recruited through advertisements and word-of-mouth referrals.

Inclusion criteria for all subjects were age 30 to 85 years, blood pressure <180/110 mm Hg, and men and women of all ethnicities and races. Patients with HF were in New York Heart Association functional classes II through IV; had symptoms of HF for at least 3 months optimally treated with β-blockers, diuretics, and angiotensin-converting enzyme inhibitors; and had systolic dysfunction, defined by an ejection fraction ≤45%, or diastolic dysfunction with preserved ejection fraction. Left ventricular ejection fraction was assessed by echocardiography. A 6-min walk test assessed physical function capacity (18). Exclusion criteria included recent myocardial infarction (1 month), recent stroke or significant cerebral neurological impairment, severe chronic obstructive pulmonary disease, major depression, and other psychiatric illnesses.

The protocol was approved by the University of California-San Diego, Institutional Review Board, and participants gave written informed consent. The study was performed in accordance with the principles of the Declaration of Helsinki.

Abbreviations and Acronyms

BDI = Beck Depression Inventory
CTX = chemotaxis
CTX-I = chemotaxis to isoproterenol
EPI = epinephrine
HF = heart failure
NE = norepinephrine
PBMC = peripheral blood mononuclear cell

Depressive symptom severity. Depressive symptoms were assessed with the 21-item Beck Depression Inventory (BDI), on which scores ≥10 indicate possible clinical depression (19). The BDI was developed to assess depressive symptoms that correspond to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, criteria for major depressive disorder (20). A modified Structured Clinical Interview for DSM-IV (21) was used to evaluate for major depressive disorder. Those diagnosed with major depressive disorder were referred to their treating physicians but allowed to remain in the study.

Exercise testing. Testing began at approximately 11 AM. Participants abstained from physical exercise, alcohol, aspirin, and caffeinated beverages the evening before testing and from food and drink (other than water) for 2 h before testing. An intravenous catheter was placed in the antecubital vein at least 1 h before testing, and blood samples were obtained before and immediately after exercise, all while the subject was in an upright, sitting posture. A blood pressure cuff was placed on the opposite arm of the intravenous catheter and was connected to a Dinamap machine (GE Healthcare, Milwaukee, Wisconsin) for automatic measurements of heart rate and systolic and diastolic blood pressure throughout the session. Subjects performed a mild graded stationary bicycle task (Viasprint 150p, Viasys, Yorba Linda, California) consisting of a 5-min warm-up, 10 min at steady state, and a 2-min cool-down. The Borg Rating of Perceived Exertion Scale (22) was used to obtain similar exercise intensity relative to existing fitness levels of all participants; the resistance (watts) was gradually increased during the warm-up period to reach a rating of 12 to 13 ("somewhat hard") which was maintained for the 10-min steady-state period by adjusting the resistance and speed of cycling. On the basis of our previous studies (23), a rate of perceived effort of 12 to 13 consistently corresponds to 65% to 70% of peak oxygen uptake regardless of fitness levels.

CTX of PBMC assay. Isoproterenol (1, 10, and 100 nmol/l) was used as a chemoattractant, as in previously reported methods (24). Briefly, at pre- and post-exercise time points, 10 ml of blood was collected into heparinized tubes and processed within 3 h. PBMCs were separated from whole blood with Ficoll-Hypaque and resuspended in serum-free media. Cells were incubated in the dark for 45 min at room temperature, shaking lightly with 0.1 μmol/l calcein acetoxymethyl ester at 2×10^6 cells/ml (25). Cells were washed and resuspended to 3×10^6 cells/ml in media

with 0.1% bovine serum albumin (CTX buffer). In a modified Boyden chamber (Neuro Probe, Inc., Gaithersburg, MD), 29.5 μl of isoproterenol or CTX buffer was pipetted to the bottom wells. Twenty microliters of cell suspension was pipetted on a membrane above the chemoattractants and incubated for 2 h at 37°C. The membrane was then submerged in phosphate-buffered saline, and non-migrated cells were scraped away with cotton swabs dampened with phosphate-buffered saline. Once dry, the membrane was read by a fluorescence plate reader (CytoFluor, MTX Lab Systems, Inc., Vienna, Virginia) at an excitation of 485 nm and emission of 530 nm.

NE and EPI measures. A subgroup of 80 patients with HF and control subjects also had blood drawn into Vacutainer tubes (BD Biosciences, San Jose, California) coated with ethylenediaminetetraacetic acid for catecholamines, NE, and EPI. Samples were centrifuged, and plasma was stored at −80°C until analysis. Plasma NE and EPI levels were determined using a catecholamine-methyl-transferase–based radioenzymatic assays with a pre-concentration step that extracted catecholamines from 1 ml plasma and concentrated them in 0.1 ml of dilute acid, following previous methods (26). The interassay coefficient of variation was 11%, and the intra-assay coefficient of variance was 6.5%.

Statistical analyses. Calculations were performed using SPSS version 15 (SPSS, Inc., Chicago, Illinois). Cases with missing data were excluded using listwise deletion (27). Skewed data distribution was determined by the Kolmogorov-Smirnov test, and variables not normally distributed were log transformed. We controlled for the cardiovascular risk factors: age, sex, body mass index, and physical function (distance walked in 6 min) in all analyses.

Group differences in sociodemographic and medical characteristics (Table 1) were computed using independent *t* tests or, for categorical data, Kruskal-Wallis tests. Repeated-measures analyses of covariance were performed on CTX data with 2 between factors for group (patients with HF and non-HF controls), 3 within factors for dose of isoproterenol (1, 10, and 100 nmol/l), and 2 within factors for time (before and after exercise). The Greenhouse-Geisser correction was applied to correct for multiple comparisons. Post hoc analyses determined baseline and exercise response differences between patients with HF and non-HF controls.

Linear regression analyses determined associations between circulating catecholamine levels, heart rate, and CTX-I 10 nmol/l (this concentration was chosen because it elicited a middle range of immune responsiveness), controlling for age, sex, body mass index, and physical function. We tested depressive symptom severity modulation according to Baron and Kenny (28): to test for mediation, we entered BDI score as a covariate. To test for moderation, we entered the interaction between BDI score and group (HF status) while controlling for group and BDI score. Similarly, we entered the interaction between BDI score, group, and NE level (or heart rate) while controlling for BDI score, group, and NE (or heart rate). To graphically illustrate our findings, we split BDI scores into ≥10 and <10 and both heart rate and NE into "high" and "low" using median split.

Table 1 Sociodemographic and Medical Characteristics of the Study Subjects

Variable	Patients With HF	Controls	p Value
BDI score	11.5 ± 0.85 (0–34)	5.4 ± 0.88 (0–44)	0.002
Age (yrs)	59.5 ± 1.3 (30–83)	52.2 ± 1.3 (34–84)	0.001
Men	80.8%	47.6%	<0.001
Body mass index (kg/m^2)†	31.7 ± 0.85 (19.4–59.0)	28.3 ± .79 (18.5–54.5)	0.033
Mean arterial blood pressure (mm Hg)*	92.6 ± 2.2 (59.0–141.9)	98.7 ± 1.5 (77.4–123.7)	0.038
Current smokers	16.1%	10.6%	0.32
HF severity			
6-min walking distance (m)	339.2 ± 10.2 (100–624)	493 ± 13.7 (198–975)	<0.001
Ejection fraction (%)	32.0 ± 1.1 (10–70)	Not measured	
NYHA functional class II	85.5%	0%	<0.001
NYHA functional class III	12.7%	0%	<0.001
Medications			
ACE inhibitors	73%	0%	<0.001
Beta-blockers	96.2%	0%	<0.001
CCBs	12.1%	0%	<0.001
Statins	64.3%	0%	<0.001
Aspirin	63.3%	5.7%	<0.001
Diuretics	88%	0%	<0.001
Antiarrhythmic agents	13.8%	0%	<0.001
Digoxin	52.5%	0%	<0.001

Data are expressed as mean ± SEM (range) or as percentages. *Mean arterial pressure was calculated from resting blood pressure readings (1/3 systolic blood pressure + 2/3 diastolic blood pressure). †Body mass index was calculated as weight in kilograms divided by height in square meters.

ACE = angiotensin-converting enzyme; BDI = Beck Depression Inventory; CCB = calcium-channel blocker; HF = heart failure; NYHA = New York Heart Association.

Results

Sociodemographic and medical characteristics of the study groups. Of the 124 subjects who participated in the study, 6 were dropped from analyses because of missing data, including BDI scores (2 subjects with HF) and/or 6-min walk tests (3 non–HF controls and 1 subject with HF). According to Kolmogorov-Smirnov tests, BDI scores and NE were not normally distributed ($p = 0.002$ and $p = 0.005$, respectively). Standard transformation (e.g., square root and log) did not normalize the distribution of BDI scores ($p = 0.011$), while log transformation yielded a normal distribution for NE ($p = 0.51$). However, a normal probability P-P plot suggested that log-transformed BDI scores had a linear pattern with only minor deviations from the line fit to the points on the probability plot, indicating that BDI scores approached a normal distribution. Table 1 presents the biological and medical characteristics of patients with HF and controls. None of the control subjects and 93% of the patients with HF were taking β-blockers, including 67% taking carvedilol, which has β_1-blocking, β_2-blocking, and weak α_1-blocking activity, and 21% taking β_1-specific agents such as metoprolol. No differences were found between patients with HF taking β-blockers or not taking β-blockers for CTX-I at rest ($p > 0.21$) or response to exercise ($p > 0.50$). Although patients with HF had higher BDI scores ($p < 0.001$), 3 of the non-HF subjects and only 1 of the patients with HF were diagnosed with major depressive disorder. BDI scores were 7.5 ± 4.5 for patients with HF taking β_1-specific blockers, 12.8 ± 8.5 for those taking β_1- and β_2-specific blockers, and 13.4 ± 7.1 for those not taking β-blockers. Beta-blocker types or not taking β-blockers did not differ for BDI scores after controlling for New York Heart Association functional class ($p = 0.25$). The lack of an association between β-blocker use and depressive symptoms is consistent with the larger literature in non-HF populations (29).

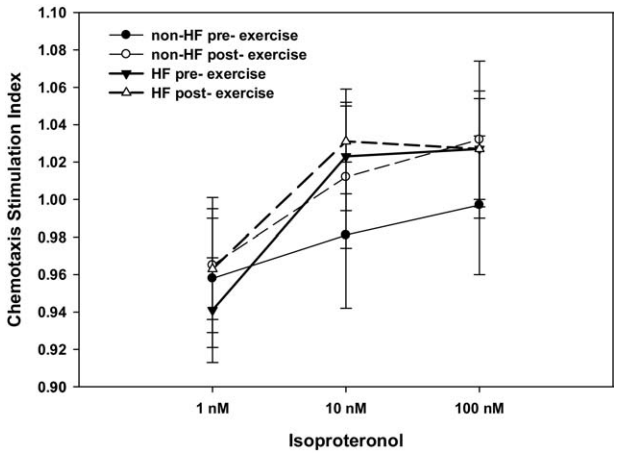

Figure 1 In Vitro Chemotaxis to β-Agonist Before and After Exercise

Stimulation index (chemotaxis to isoproterenol/random migration) in a dose response to isoproterenol in patients with heart failure (HF) and controls at rest and in response to exercise. Data are expressed as mean ± SEM.

Table 2 Regression Outcomes Predicting Changes in CTX-I to 10 nmol/l Response to Exercise With BDI and NE as Potential Moderators

Model	ΔR^2	Coefficients		
		t	p Value	β
Risk factors	0.024			
Age		0.487	0.628	0.001
Sex		0.181	0.857	0.011
BMI		1.361	0.178	0.005
6-min walking distance		0.302	0.764	0.0001
HF status		−3.014	0.004	−0.985
Predictors	0.146			
NE		3.125	0.003	0.171
BDI score		3.119	0.003	0.091
Interactions	0.153			
HF status × NE		2.205	0.031	0.118
HF status × BDI score		3.446	0.001	0.105

The final regression model and coefficients are shown. The regression models were as follows: cardiovascular risk factors (step 1: age, sex, BMI, 6-min walking distance, HF status), predictors of CTX-I (step 2: resting NE and BDI), and interaction variables (step 3: HF status × NE and HF status × BDI score).
BMI = body mass index; other abbreviations as in Tables 1 and 2.

CTX-I at baseline and after exercise. Repeated-measures analysis of covariance indicated that patients with HF and non-HF controls differentially responded to varying doses of isoproterenol (1, 10, and 100 nmol/l) while controlling for age, sex, body mass index, and physical function (HF status-by-dose interaction: $F[6, 112] = 4.2$, $p = 0.018$) after Greenhouse-Geisser correction (Fig. 1). To determine the characteristics of the differences, post-hoc analyses revealed that at rest, patients with HF showed positive CTX-I dose responses (1, 10, and 100 nmol/l), while non-HF controls did not exhibit CTX-I dose responses (HF status-by-dose interaction at rest: $p = 0.002$). However, in response to exercise, both groups had similar positive CTX-I dose responses and did not differ from each other (HF status effect: $p = 0.47$).

Depressive symptoms and CTX-I before and after exercise. Regression analyses revealed that in both groups, higher BDI scores were associated with a trend for lower CTX-I at baseline ($p = 0.099$). In response to exercise, BDI scores appeared to moderate an increased CTX-I response in patients with HF compared with non-HF controls ($t = 3.3$, $p = 0.001$, $\Delta R^2 = 0.11$) (Table 2).

NE, EPI, heart rate, and CTX-I response to exercise: interaction with depression. A linear regression analyses found that higher resting NE levels were associated with greater CTX-I responses to exercise in patients with HF but not in non-HF controls (NE-by-HF interaction: $p = 0.03$, $\Delta R^2 = 0.045$) (Table 2). This suggests that basal sympathetic activation may moderate CTX-I in response to exercise in patients with HF. Meanwhile, baseline EPI levels and HR were not associated with CTX-I in either

group ($p = 0.50$ and $p = 0.95$, respectively). Furthermore, there were no interactions between BDI and NE, EPI, or heart rate for CTX-I in either group.

NE, EPI, and heart rate reactivity to exercise: interaction with depression. Neither NE nor EPI significantly increased from before to after exercise in either group ($p = 0.95$ and $p = 0.29$, respectively), and patients with HF and non-HF controls did not differ in NE or EPI levels in response to exercise ($p = 0.32$ and $p = 0.12$, respectively). BDI scores were also not significantly associated with NE or EPI levels at baseline or in response to exercise.

Heart rate did not differ between patients with HF and non-HF controls at baseline ($p = 0.22$) or in response to exercise ($p = 0.32$). However, exercise produced significant increases in heart rate in both groups ($p = 0.003$, $\Delta R^2 = 0.29$). Furthermore, greater depressive symptom levels were related to higher baseline heart rate, even after controlling for HF status ($p = 0.016$, $\Delta R^2 = 0.045$).

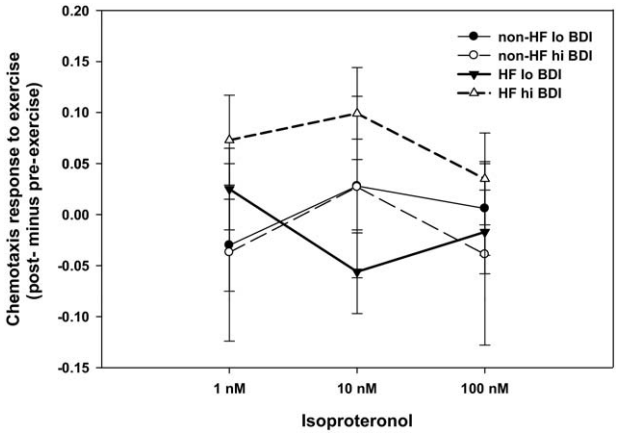

Figure 2 **Chemotaxis Responses to Exercise in Subjects With High and Low Depressive Symptoms**

Change scores (post-exercise minus pre-exercise) and chemotaxis to 3 concentrations of isoproterenol (1, 10, and 100 nmol/l) in patients with heart failure (HF) and non-HF controls. High (hi) versus low (lo) depression was determined by scores of ≥10 and <10 on the Beck Depression Inventory (BDI). Data are expressed as mean ± SEM.

Discussion

The present results suggest that immune cell mobility is likely differentially regulated by neuroendocrine processes in patients with HF compared with non-HF controls. Moreover, elevated depressive symptoms in patients with HF may further augment immune cell motility to neurohormones in reaction to physical exertion. Both at rest and in response to exercise, PBMCs from patients with HF exhibited a CTX-I dose response in vitro. This suggests that patients with HF are sensitive to changes in adrenergic stimuli during both inactivity and activity. Meanwhile, non-HF controls had little response to isoproterenol at rest, whereas in response to exercise, they exhibited an increase in CTX at higher concentrations of isoproterenol. These findings are consistent with observations that physically healthy adults have greater β-adrenergic receptor density and sensitivity responses to acute challenges (11), which may underlie increased homing of lymphocytes to higher concentrations of β-agonists (6,30).

Acute challenges such as exercise tasks create a window into complicated physiological processes (31) and can reveal neuroimmune dysregulation in patients with cardiovascular disease that may be masked under resting conditions (13). Our principal finding was that in response to exercise, patients with HF with higher depression scores had greater PBMC mobility to a β-adrenergic agonist (isoproterenol) compared with non-HF controls (Fig. 2). Meanwhile, patients with HF with lower depression symptoms responded minimally to exercise, which is to be expected in a group taking β-blockers. Thus, patients with HF with high depressive symptoms appeared to override the effects of β-blockers. Our results are consistent with findings that psychological factors are associated with reduced β-blockade efficacy in response to exercise challenge (32).

NE, EPI, and heart rate were assessed to explore endogenous sympathetic and neuroendocrine influences on CTX-I (Table 3). Unexpectedly, NE and EPI levels did not increase during exercise in either patients with HF or non-HF controls. This is likely due to less exertion expenditure from the exercise task in the present study (approximately 65% to 70% of peak oxygen uptake) because of the limited exercise capacity of patients with HF. In contrast, various investigations of non-HF cardiovascular disease patients have used the standard Bruce protocol to obtain peak oxygen uptake to examine catecholamine responses (33). Also unexpectedly, there were no differences observed between patients with HF and non-HF controls for NE or EPI levels or differences between groups in exercise-induced increases in NE and EPI levels. Furthermore, heart rate was lower in patients with HF than in non-HF controls. These results appear in contrast to what is known about HF, being in a state of generalized sympathetic activation (34). However, medications regularly prescribed to treat HF, such as β-blockers, likely reduced sympathetic activity in the patients with HF.

Meanwhile, patients with HF with elevated resting NE levels had an increase in CTX-I in response to exercise, whereas, exercise-induced changes in NE, EPI, and heart rate were not associated with CTX-I (Table 3). These findings are consistent with literature over 2 decades suggesting that acute adrenergic exposure during exercise is not long enough to generate structural changes in lymphocyte adrenergic receptors (10). Instead, the immune cells that reside in lymphatic tissue, and that are released with physical exertion, are likely to already have altered sensitivity to β-agonists. This suggests systemic neuroimmune dysregulation, which may have clinical relevance in that altered β-adrenergic receptor expression dynamics predicts the

Table 3 Correlation Coefficients Among Variables

Variable	Group	Resting HR	Peak HR During Exercise	Average Watts During Exercise	Baseline		Pre- to Post-Exercise		
					NE	EPI	NE	EPI	CTX-I (10 nmol/l)
BDI score	Non-HF	0.394*	0.053	0.003	−0.076	0.064	0.081	−0.139	−0.179
	HF	0.139	0.098	−0.100	−0.006	0.007	0.080	0.087	0.238†
Resting HR	Non-HF	1.00	0.334*	−0.165	0.243	0.135	−0.055	−0.129	0.093
	HF		0.460*	−0.129	0.050	0.184	0.229	0.190	0.146
Peak HR during exercise	Non-HF		1.00	0.441*	0.310*	0.350†	0.258	−0.141	−0.135
	HF			0.160	−0.046	−0.050	0.417*	0.208	0.045
Average watts during exercise	Non-HF			1.00	−0.160	0.074	0.250	−0.098	0.010
	HF				−0.168	0.105	0.029	−0.001	−0.061
Baseline NE	Non-HF				1.00	0.258†	−0.442*	−0.265	0.093
	HF					0.286†	−0.293†	−0.222	0.320†
Baseline EPI	Non-HF					1.00	0.041	−0.357†	−0.125
	HF						−0.151	−0.241	0.151
Pre- to post-exercise NE	Non-HF						1.00	0.457*	−0.259
	HF							0.572*	−0.028
Pre- to post-exercise EPI	Non-HF							1.00	−0.178
	HF								−0.047

*$p < 0.01$ and †$p < 0.05$.
CTX-I = chemotaxis to isoproterenol; EPI = epinephrine; HR = heart rate; NE = norepinephrine; other abbreviations as in Table 1.

development of preclinical states such as greater left ventricular mass and blood pressure (35,36).

Although we found that both depressive symptoms and resting NE levels were positively associated with CTX-I to exercise in patients with HF (Figs. 3 and 4), they were independent of each other. Therefore, the effects of elevated depression symptoms on CTX to β-agonists were likely not directly related to heightened basal NE levels in patients with HF. Instead it may again suggest neuroimmune dysregulation, because chronic psychological distress is known to be associated with down-regulated β-adrenergic receptor expression (37). This in turn would likely reduce chemoattraction sensitivity to β-agonists, as seen in chronically stressed Alzheimer caregivers (25). However, patients with HF with elevated depressive symptoms appear to not follow this expected pattern. Thus, the mechanism that induces increased PBMC mobilization to β-agonists in patients with HF with depression has yet to be determined.

Study limitations. Limitations of this study include a disproportionate number of women in the control group compared with patients with HF. However, sex was

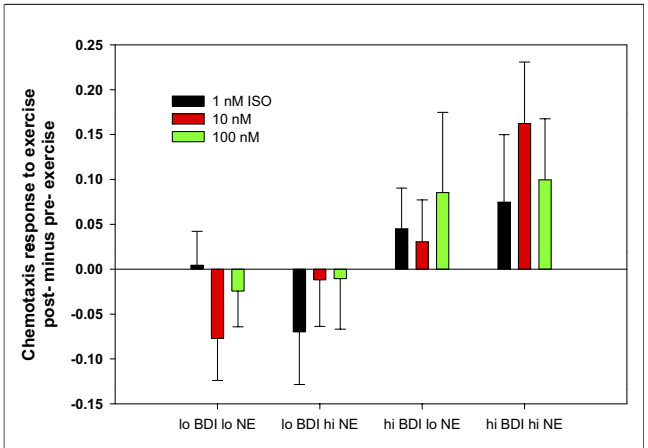

Figure 3 Chemotaxis Responses to Exercise With Differential Depression and NE Levels

Change scores (post-exercise minus pre-exercise) and chemotaxis to 3 concentrations of isoproterenol (ISO) (1, 10, and 100 nmol/l). Data from patients with HF and non-HF controls were combined. High versus low depression was determined by scores of ≥10 and <10 on the BDI. High versus low norepinephrine (NE) levels were determined by a median split. Data are expressed as mean ± SEM. Abbreviations as in Figure 2.

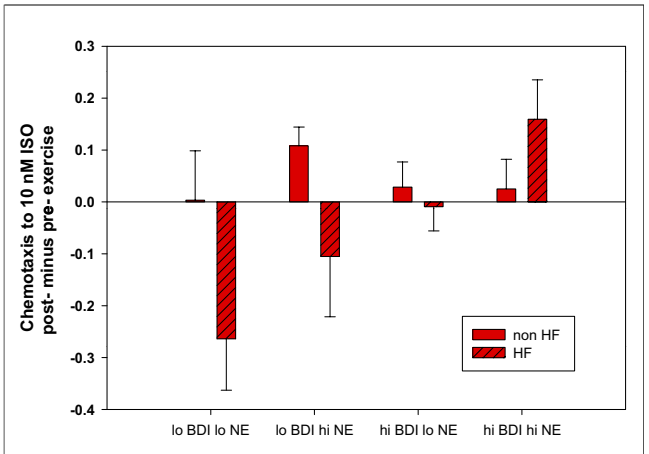

Figure 4 Chemotaxis Responses to Exercise in Patients With HF and Controls

Change scores (post-exercise minus pre-exercise) and chemotaxis to ISO (10 nmol/l). Data from patients with HF and non-HF controls are presented. High versus low depression was determined by median split on the BDI (≥7 and <7 to depict at least 9 subjects per group). High versus low NE levels were determined by median split. Data are expressed as mean ± SEM. Abbreviations as in Figures 2 and 3.

controlled in all analyses, and furthermore, the results were not different when women were removed from the analyses (data not shown). Nonetheless, future studies with larger cohorts of women should be performed to explore whether there are sex differences in neuroimmune modulation in patients with HF with depression. A potential limitation was the heterogeneous population, including patients with HF with preserved systolic function (n = 11) and those with systolic dysfunction (n = 69). However, these groups did not differ in BDI scores ($p = 0.20$), CTX-I at baseline ($p = 0.36$), or response to exercise ($p = 0.79$). It is important to note that the associations found in this study are correlational and therefore may not be causative and are based on relatively few patients. Further study is needed to replicate our findings and research is needed to tease apart the interactions between depression, sympathetic activity, and HF status. In addition, research is necessary to determine if cardiac structural changes are linked with the β-adrenergic-associated immune activation in this group to reveal clinical implications of these results.

Conclusions

Our results suggest that patients with HF with greater depressive symptoms are associated with an augmented CTX-I response to physical exertion. This may indicate an increase in β-adrenergic sensitivity in patients with HF with depressive symptoms that override medications prescribed to reduce sympathetic activity. Furthermore, chronic sympathetic activation and depressive symptoms that occur concomitantly in patients with HF could lead to even greater immune mobility in this group, which may promote increased nonspecific infiltration of immune cells into cardiovascular tissue and result in remodeling. Further understanding of the relationship between depressive symptoms and immune responses to adrenergic agonists may be useful for the development of potential treatments to abrogate increased morbidity and mortality in patients with HF with depression.

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