Erschienen in: Biological Psychiatry ; 65 (2009), 9. - S. 801-807

Depressive Symptoms Are Associated with Soluble P-Selectin Reactivity to Acute Exercise in Heart Failure

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Background: To determine the effects of depressive symptom severity on the circulating soluble adhesion molecule response to an acute exercise challenge in patients with heart failure (HF) compared with control subjects.

Methods: Thirty-eight male HF patients and 19 male control subjects (mean age ± SEM: 55.5 ± 1.9) completed the Beck Depression Inventory (BDI) before undergoing a moderate 20-minute bicycle exercise at approximately 65% to 70% VO_{2peak}. Plasma levels of the soluble adhesion molecules P-selectin (sP-selectin) (sCD62P) and soluble intercellular adhesion molecule-1 (sICAM-1) were determined immediately before and after and 10 minutes after exercise.

Results: Higher BDI scores moderated greater increases in sP-selectin levels in response to exercise over time in HF patients as compared with control subjects [$F(1.8/84.5) = 3.25$, $p = .05$]. Post hoc testing revealed that in HF patients, but not in control subjects, higher BDI scores were significantly associated with greater increases in sP-selectin levels over time in response to exercise [BDI by exercise interaction: $F(1.6/49.6) = 5.67$, $p = .010$]. Also, in HF patients, but not in control subjects, higher BDI scores were associated with higher sP-selectin levels at pre-exercise and postexercise time points [main effect BDI: $F(1/31) = 4.86$, $p = .035$].

Conclusions: Our findings suggest that in male HF patients with increasing depressive symptom severity, levels of the adhesion molecule sP-selectin are higher before and after exercise and have greater increases in response to exercise. This could have implications for acute coronary syndromes associated with exercise and thereby may impact mortality.

Key Words: Adhesion molecules, depression, exercise stress, heart failure, sICAM, sP-selectin

Heart failure (HF) is an increasingly prevalent, chronic, progressive, and incurable medical condition that is a major cause of morbidity and mortality (1–3). Although traditional medical risk factors in HF have been identified (4,5), recent reviews suggest a role for depressive symptoms in the development and progression of HF (6,7). Depressive symptomatology varies between 51% in hospitalized HF patients and 69% in recently discharged HF patients (7). Prospective studies indicate that higher levels of depressive symptoms as measured by the Beck Depression Inventory (BDI) in HF patients are independently associated with higher mortality within 3 years (7–9). However, little is known about pathophysiologic mechanisms underlying the increase in adverse outcomes in HF patients with depressive symptoms.

Physical activity may play an important role in the sudden onset of adverse events such as acute coronary syndromes (ACS). Physical exertion occurring within 1 to 2 hours of onset of symptoms has been identified as a potent trigger of acute myocardial infarction (MI) in patients with coronary artery disease (CAD) (10–12). The underlying mechanisms, however, are still unclear. Recent studies suggest that adhesion molecules might be involved in mediating exercise-induced ACS triggering in vulnerable persons. In CAD patients, Kop *et al.* (13) found that treadmill exercise provoked significant immediate responses in the soluble intercellular adhesion molecule-1 (sICAM-1), a membrane-bound adhesion molecule expressed on endothelial cells and leukocytes (14). Moreover, in HF patients, exercise induced profound increases in platelet activation markers such as soluble P-selectin (sP-selectin), an adhesion molecule expressed on platelets and endothelial cells (15). Both intercellular adhesion molecule-1 (ICAM-1) and P-selectin are clinically important because they support increased adhesion and infiltration of leukocytes and platelets in the myocardium in HF patients (14,16–19). Particularly sP-selectin, which is elevated in HF patients (20), seems to be an independent significant predictor of cardiovascular events in HF patients (21). Exercise-induced elevations in either or both of these adhesion molecules may therefore be important in the disease course of HF.

Although sympathoadrenal hyperactivity and reactivity to mental and physical challenges have been suggested to be involved in pathophysiologic mechanisms linking depression and increased mortality in HF, the role of adhesion molecules and other inflammatory measures has received little attention (22,23). Therefore, the objective of the present study was to investigate whether depressive symptoms as assessed by the BDI are associated with exercise-induced changes in adhesion molecule levels in patients with HF and healthy control subjects. Plasma levels of sP-selectin and sICAM-1 were measured immediately before and after and 10 minutes after a moderate exercise task. We hypothesized that higher BDI levels would be associated with greater adhesion molecule increases following exercise in HF patients as compared with control subjects.

Methods and Materials

Study Participants

The study sample consisted of 38 male patients diagnosed with HF and 19 male individuals with no cardiovascular pathology except for elevated blood pressure as a control group.

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Patients were recruited from the San Diego Veterans Affairs Medical Center and the University of California, San Diego (UCSD) Medical Center Heart Failure Program as part of a larger study on the effects of depression on cellular adhesion and inflammation. We recruited the control non-HF individuals from the local community via various advertisements (e.g., newspapers, flyers, brochures, and websites) and word of mouth referrals.

Inclusion criteria for all study participants included age between 30 and 85 years, hypertension <180/110 mm Hg, and men of all ethnicities and races. Inclusion criteria for HF patients included New York Heart Association (NYHA) classes II through IV; symptoms of HF for at least 3 months that had been optimally treated with beta blockers, diuretics, and angiotensin-converting enzyme (ACE) inhibitors; and systolic dysfunction defined by an ejection fraction ≤45% or diastolic dysfunction. Left ventricular ejection fraction (LVEF) was assessed by echocardiography as part of the patient's routine medical evaluation. To assess functional capacity, we used the 6-minute walk test (24). Exclusion criteria included recent myocardial infarction (1 month), recent stroke or significant cerebral neurological impairment, severe chronic obstructive pulmonary disease, inability to exercise, and psychiatric illness other than depression and comorbid anxiety. Subjects were instructed to abstain from taking aspirin for 24 hours prior to the testing session.

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.

Depressive Symptom Severity

On the morning of testing, depressive symptom severity was assessed with the 21-item Beck Depression Inventory where scores ≥10 indicate possible clinical depression (25). The BDI was developed for the assessment of depressive symptoms that correspond to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for major depressive disorder and measures a somatic and a cognitive-affective dimension of depression (26). 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 DSM-IV (SCID) (27) to evaluate for possible major depressive disorder (MDD). If suspected of having MDD, they were presented with a list of options and referred to their treating physician.

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, California). Following a 5-minute to 10-minute quiet rest, resting blood pressure (BP) was taken using an automated BP monitor (Dinamap Compact BP monitor, Critikon, Tampa, Florida) 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 (e.g., 60 bpm). The bicycle protocol consisted of a 5-minute warm-up, 10-minute steady state, and 2-minute cool-down period. To apply the similar exercise intensity in relative to existing fitness levels for all participants, Borg's ratings of perceived exertion (RPE) scale (28) 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 this perceived exertion level was maintained for the 10-minute steady state exercise by adjusting the resistance and speed of cycling. Based on our previous experience (29,30), RPE 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 prior to, immediately following, and 10 minutes postexercise. Exercise was terminated if a subject expressed discomfort, excessive muscle fatigue, chest pain, or shortness of breath or if blood pressure exceeded 220/100 mmHg or dropped below resting levels.

Biochemical Analyses

Blood was drawn into ethylendiaminetetraacetic acid (EDTA)-coated vacutainer tubes (BD Biosciences, San Jose, California) for soluble adhesion molecules (and catecholamines, Supplement 1). Blood samples were centrifuged for 10 minutes at 3000*g* and 4°C and plasma was stored at −80°C until analysis.

Circulating levels of soluble sP-selectin and sICAM-1 were determined following previous methods using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, Minnesota) (31,32). The precision and sensitivity performance values were as follows: sICAM-1: intra-assay coefficient of variation (CV) 4.6%, interassay CV 6.6, sensitivity <.35 ng/mL; sP-selectin: intra-assay CV 5.1%, interassay CV 8.8, sensitivity <.5 ng/mL.

To minimize intra-assay error variance, all samples from an individual subject were analyzed in the same run.

Statistical Analyses

All calculations were performed using SPSS Inc. (version 11.0.1) software packages (SPSS, Chicago, Illinois). Data are presented as mean ± SEM. Results were considered statistically significant at the $p \leq .05$ level and all tests were two-tailed. In both groups, normal distribution of data was verified prior to statistical analyses using the Kolmogorov-Smirnov test. In case of missing data, cases were excluded list-wise. We calculated mean arterial pressure (MAP) from resting BP readings (1/3 systolic BP + 2/3 diastolic BP) and body mass index (BMI) was calculated by the formula weight in kg/(height in m)^2.

Power analyses suggest that a total sample size of $N = 44$ is needed to detect an interaction effect between depressive symptom severity (as measured by BDI) and adhesion molecule changes following exercise (as measured by repeated measurement of adhesion molecules, pre-exercise, postexercise, and 10-minute recovery) in two groups with an expected medium effect size of f = .25 in general linear models with repeated measures with a power of ≥.95, $\alpha = .05$, given the observed intercorrelation among repeated measures of .5 (G-Power, Version 3.0.10, University of Kiel, Kiel, Germany).

To test for group differences in sociodemographic and medical characteristics, we computed univariate analyses of variance (ANOVAs) (Table 1). To test for associations between BDI scores and group characteristics, we calculated Pearson's product-moment correlations for continuous variables and Spearman's rank correlations for ordinal data.

In subsequent analyses, we controlled for the cardiovascular risk factors age, BMI, MAP, and number of smoked cigarettes per

Table 1. Sociodemographic and Medical Characteristics of the Study Subjects

	HF Patients	Control Subjects	*p*
BDI Score	10.2 ± 1.0 (0–26)	4.6 ± 1.3 (0–21)	.001
BDI Score ≥ 10	47.4%	10.5%	
BDI Subscale Somatic Symptoms Score	5.7 ± .4 (0–11)	2.1 ± .5 (0–7)	<.001
BDI Subscale Cognitive/Affective Symptoms Score	4.5 ± .7 (0–16)	2.6 ± .9 (0–14)	.10
Age (years)	59.4 ± 2.4 (31–81)	47.8 ± 2.1 (35–76)	.002
Body Mass Index (kg/m^2)	30.5 ± 1.2 (20.4–51.2)	29.0 ± .8 (23.7–37.7)	.41
Mean Arterial Blood Pressure (mmHg)	80.8 ± 2.3 (56.7–124.2)	93.6 ± 3.1 (74.2–116.7)	.002
Cigarettes Per Day	4.1 ± 2.0 (0–60)	2.2 ± 1.4 (0–20)	.50
Current Smokers	13%	16%	
HF Severity			
6-minute walk test (meter)	362.3 ± 14.9 (170–624)	500.6 ± 19.8 (350–690)	<.001
Ejection fraction (%)	30.1 ± 1.5 (14–54)	—	
NYHA Classification II	89%	0%	
NYHA Classification III	11%	0%	
Concomitant Disease			
Diabetes mellitus	26%	0%	
Medication			
ACE-blocking agents	84%	0%	
Beta blockers	95%	0%	
CCB	3%	0%	
Statin	61%	0%	
Aspirin	50%	5%	
Diuretics	84%	0%	
Anti-arrhythmics	18%	0%	
Warfarin	39%	0%	
Digoxin	61%	0%	

Data are presented as mean ± standard error of means (range) or percentage value.

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

day. We applied the Huynh-Feldt correction for all repeated measures.

General linear models with repeated measures were calculated to test whether exercise induced significant changes over time in soluble adhesion molecule levels in HF patients and control subjects with subject group as independent variable and repeated measures of adhesion molecule levels as dependent variables (Table 2).

Associations with Depressive Symptom Severity. For independent associations between depressive symptom severity and adhesion molecules, we applied the following procedure. To address associations at rest, we calculated linear regression analyses with pre-exercise measures of adhesion molecules as dependent variables and BDI score as continuous independent variable while controlling for the group variable (HF vs. control subjects). To address associations between depressive symptom severity and adhesion molecule changes over time in response to exercise, we calculated general linear models with repeated measures of adhesion molecules as dependent variables. We entered BDI score as independent continuous variable while controlling for the group variable and pre-exercise adhesion molecule levels.

Table 2. Soluble Adhesion Molecule Levels Before and After Exercise in HF Patients and Control Subjects

	Pre-exercise	Postexercise	Recovery
sP-selectin (pg/mL)			
HF patients	55.8 ± 4.6	62.3 ± 6.4	53.1 ± 4.1
Control subjects	62.0 ± 6.9	53.9 ± 9.6	51.8 ± 6.1
sICAM-1 (ng/mL)			
HF patients	322.6 ± 16.9	329.1 ± 17.1	322.6 ± 16.0
Control subjects	243.9 ± 25.5	239.5 ± 25.6	247.9 ± 24.1

Values are means ± SEM.

HF, heart failure; postexercise, immediately after exercise cessation; pre-exercise, immediately before exercise; recovery, 10 minutes after exercise cessation; sICAM-1, soluble intercellular adhesion molecule-1; sP-selectin, soluble P-selectin.

To address whether associations between depressive symptom severity and adhesion molecules differed between HF patients and control subjects, we calculated moderator analyses as described by Baron and Kenny (33), both for resting adhesion molecule levels and for repeated adhesion molecule measures (34). We recalculated the above described regression analyses and general linear models and additionally entered the interaction between group and BDI score as independent variable. In case of significant moderator effects of depressive symptoms, we recalculated the analyses of the respective parameter separate for each group as post hoc test. In HF patients, we additionally controlled for LVEF and NYHA class to test whether the observed associations were mediated by HF severity and for current diabetes mellitus.

In calculations on associations with depressive symptom severity, all included parameters were Z-transformed prior to analyses rendering a mean of 0 and a standard deviation of 1 to allow computation of interaction terms.

To graphically illustrate our continuously calculated significant findings, we categorized the study groups based on their BDI score into four groups of subjects with either high or low BDI score (HF-BDI-high [≥ 8, $n = 21$], HF-BDI-low [< 8, $n = 17$], control subjects-BDI-high [≥ 8, $n = 14$], control subjects-BDI-low [< 8, $n = 5$]) (Figure 1).

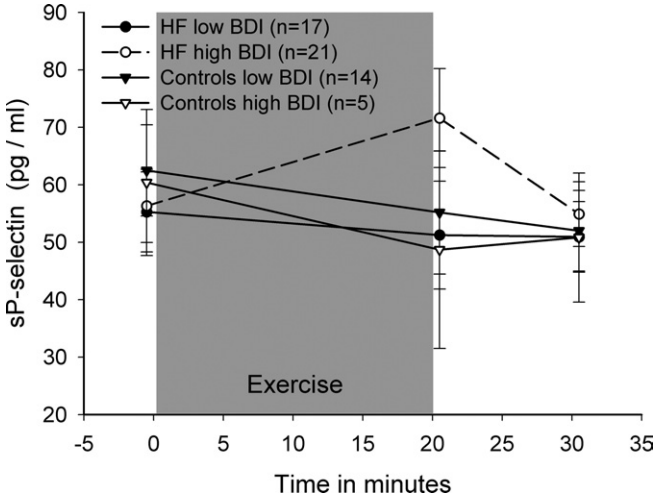

Figure 1. Values are means ± SEM. The figure depicts exercise-induced changes in sP-selectin in HF patients and control subjects with high (≥8) and low (<8) BDI scores. Moderation testing suggests that in the HF group higher depressive symptom scores are associated with higher exercise-induced sP-selectin increases as compared with the control group [$F(1.8/84.5) = 3.25$, $p = .05$, $\eta_p^2 = .06$, f = .26]. In HF patients, but not in control subjects, higher BDI scores were significantly associated with higher sP-selectin levels at pre-exercise and postexercise time points [main effect BDI: $F(1/31) = 4.86$, $p = .035$, $\eta_p^2 = .14$, f = .40] and with greater exercise-induced sP-selectin increases [interaction BDI by exercise: $F(1.6/49.6) = 5.67$, $p = .010$, $\eta_p^2 = .16$, f = .43]. The area shaded in gray marked as "exercise" includes warm-up, 10-minute steady-state cycling, and 2-minute cool-down periods. BDI, Beck Depression Inventory; HF, heart failure; sP-selectin, soluble P-selectin.

Results

Sociodemographic and Medical Characteristics of the Study Groups

Table 1 presents the biological and medical characteristics of the 38 HF patients and the 19 control subjects studied. Most of the patients were NYHA class II and were taking ACE inhibitors, beta blockers, and diuretics, and a high percent of patients was taking digoxin. Heart failure patients walked fewer meters in the 6-minute walk test as compared with control subjects [$F(1/54) = 30.3$, $p < .001$]. Moreover, HF patients were older [$F(1/54) = 10.1$, $p = .002$] and had a lower MAP [$F(1/55) = 10.7$, $p = .002$], probably due to medication intake and/or their underlying LVEF dysfunction. Heart failure patients had higher BDI total scores [$F(1/56) = 11.2$, $p = .001$], as well as higher scores in the BDI subscale somatic symptoms [$F(1/56) = 26.5$, $p < .001$]. None of the study subjects were determined to have major depressive disorder. In both subject groups, BDI score was not significantly associated with cardiovascular risk factors (i.e., age, BMI, resting MAP). In HF patients, BDI score was not significantly associated with medication intake or disease severity indices. None of the medications were associated with either adhesion molecule with the exception of digoxin correlating with sICAM-1 ($r = -.34$, $p = .043$).

Reactivity of Adhesion Molecules to Exercise

Table 2 depicts adhesion molecule baseline and postexercise levels in HF patients and control subjects. Heart failure patients showed higher sICAM-1 levels before and after exercise [main effect group: $F(1/51) = 6.5$, $p = .014$, $\eta^2 = .11$]. However, no other main or interaction effects were significant, either for sICAM-1 ($ps > .38$) or for sP-selectin ($ps > .24$). Cardiovascular risk factors (age, BMI, MAP, and smoking) were controlled.

Depressive Symptom Severity and Adhesion Molecules

As aforementioned, we first tested whether depressive symptom severity was associated with adhesion molecules in both groups (i.e., independent of groups). Second, we investigated whether associations between depressive symptom severity and adhesion molecules differed between HF patients and control subjects by means of moderator analysis. Cardiovascular risk factors (age, BMI, MAP, and smoking) were controlled in all analyses.

At Rest. Regression analyses revealed that independent of groups (HF vs. control subjects), BDI scores were not significantly associated with pre-exercise levels of sP-selectin ($\beta = -.05$, $p = .76$) or sICAM-1 ($\beta = -.07$, $p = .63$) (Figure 1). There was no moderation effect of depressive symptom severity on group differences in pre-exercise adhesion molecule levels ($ps > .23$).

Reactivity to Exercise. To test whether depressive symptom severity was independently (i.e., independent of groups and cardiovascular risk factors) associated with adhesion molecule changes over time in response to exercise, we calculated general linear models with adhesion molecule measures as repeated dependent variables and BDI score as continuous independent variable while controlling for pre-exercise adhesion molecule levels and groups (HF vs. control subjects). Higher BDI scores were significantly associated with greater increases in sP-selectin levels over time in response to exercise [BDI by exercise interaction: $F(1.7/83.3) = 4.31$, $p = .022$, $\eta_p^2 = .08$, f = .29]. Moreover, higher BDI was associated with higher sP-selectin levels at pre-exercise and postexercise time points [main effect for BDI: $F(1/53) = 4.3$, $p = .043$, $\eta_p^2 = .08$, f = .28], but this effect became of borderline significance when controlling for cardiovascular risk factors ($p = .07$). However, there was no association between BDI and sICAM-1 exercise reactivity ($ps > .31$).

Moderation testing revealed that the interaction between group and BDI scores was significantly associated with greater exercise-induced increases in sP-selectin levels [$F(1.8/84.5) = 3.25$, $p = .05$, $\eta_p^2 = .06$, f = .26] but not in sICAM-1 ($p = .21$). This suggests a statistical moderation effect of depressive symptoms: as depicted in Figure 1, higher depressive symptom scores are associated with higher exercise-induced sP-selectin increases in the HF group as compared with the control group. Post hoc testing of this significant moderation effect revealed that in HF patients higher BDI scores were significantly associated with greater increases in sP-selectin levels over time in response to exercise [interaction BDI by exercise: $F(1.6/49.6) = 5.67$, $p = .010$, $\eta_p^2 = .16$, f = .43], even after controlling for LVEF and NYHA class as indicators of HF severity ($p = .018$) and diabetes mellitus ($p = .01$). Also, higher BDI scores were associated with higher sP-selectin levels at pre-exercise and postexercise time points [main effect BDI: $F(1/31) = 4.86$, $p = .035$, $\eta_p^2 = .14$, f = .40]. This association remained significant after controlling for diabetes mellitus ($p = .47$) but became of borderline significance when controlling for LVEF and NYHA class ($p = .059$). None of these associations was observed in control subjects ($ps > .83$). Noteworthy, LVEF [main effect LVEF: $F(1/29) = 5.36$, $p = .028$, $\eta_p^2 = .16$, f = .43; interaction LVEF by exercise: $F(1.8/51.8) = 4.41$, $p = .020$, $\eta_p^2 = .13$, f = .39], but not NYHA ($ps > .86$) or diabetes mellitus status ($ps > .51$), were significantly associated with pre-exercise and postexercise sP-selectin levels.

Discussion

This is the first study to investigate whether in male HF patients and healthy control subjects, depressive symptoms are associated with exercise-induced increases in circulating levels of adhesion molecules expressed on endothelial cells and leukocytes (ICAM-1), as well as on endothelial cells and platelets (P-selectin). Our main finding was that in HF patients, but not in control subjects, higher depressive symptom scores were associated with higher sP-selectin increases in response to exercise over time, peaking immediately after exercise cessation. Moreover, higher levels of depressive symptoms were associated with higher sP-selectin levels at all time points in our HF patients but not in control subjects. These associations were of large effect sizes and independent of both cardiovascular risk factors, indicators of HF severity, and diabetes mellitus status. In other words, in HF patients with increasing depressive symptom severity, sP-selectin levels are not only on a generally higher level before and after exercise but also increase more strongly in reaction to a moderate bicycle exercise. Noteworthy, both BDI subscales (i.e., somatic symptoms and cognitive/affective symptoms) similarly contributed to the observed associations (Supplement 2). In contrast, there were no associations between depressive symptoms and sICAM-1 levels, either at rest or in response to exercise.

Our findings indicate a diverging pattern between depressive symptoms and the two measured soluble adhesion molecules in HF patients, suggesting a role for platelet activation. Soluble P-selectin, but not sICAM-1, relates to platelet activation. P-selectin is constitutively expressed both in the α-granules of platelets and the Weibel-Palade bodies of endothelial cells, with a soluble form present in the plasma (35,36). It plays a crucial role in thrombus formation interconnecting inflammatory, thrombotic, and coagulation activity (35). More precisely, P-selectin translocates to the surface of activated platelets incorporated into a growing thrombus and supports recruitment of circulating leukocytes. It induces expression of tissue factor (TF) on monocytes and mediates binding of platelets to monocytes and neutrophils. As TF binds coagulation factor VII and activates coagulation factors IX and X, P-selectin-induced TF synthesis on monocytes seems to support and maintain the local activation of blood coagulation in the hours following monocyte recruitment (35). Following expression on the platelet surface, P-selectin is rapidly shed. This shedding from platelets is suggested to be the main source of the soluble form found in plasma following thrombotic events (37,38). However, although the P-selectin translocated on activated endothelial cells is recycled back into the cell, part of the soluble P-selectin found in plasma may be of endothelial origin (35,39). Noteworthy, markers of platelet activity other than sP-selectin have also been positively associated with HF and HF severity (40). ICAM-1 is expressed by several cell types, including leukocytes and endothelial cells (14), but to the best of our knowledge, not by platelets. In vitro studies using cultured endothelial cells established that sICAM-1 simply reflects ICAM-1 expression on these cells (41). Thus, in HF patients, depressive symptoms may be associated with higher platelet, but not endothelial, activity before and after exercise, as well as in reaction to exercise.

We observed strong associations between depressive symptoms and higher levels of the measured soluble adhesion molecules in HF patients but not in control subjects. Moreover, low LVEF (as an indicator of HF severity) was significantly associated with repeated sP-selectin levels. Thus, our results suggest that associations between depressive symptoms and higher sP-selectin levels following exercise seem to be specific to HF patients but not control subjects. Noteworthy, depressive symptom severity was significantly lower in control subjects as compared with HF patients. Therefore, we cannot completely rule out that in a non-HF control group with higher levels of depressive symptoms, there might be associations with sP-selectin levels following exercise. Such reasoning is in line with the reported significant associations between BDI scores and repeated sP-selectin levels independent of groups (i.e., main effect of BDI and interaction BDI by exercise). However, it is possible that the latter associations became significant because of the strong associations within the HF group.

The finding of higher platelet activity following exercise in HF patients is in line with a recent study reporting increases in several platelet activation markers, including sP-selectin, in HF patients following exercise (15). Noteworthy, this study used a maximum treadmill graded exercise inducing sP-selectin increases in all patients, whereas we used a moderate exercise testing, inducing increases only in patients with higher levels of depressive symptoms. It is interesting that the depression effect we observed was evident in response to our moderate exercise challenge—one that was not challenging enough to induce an sP-selectin increase in HF patients with little or no depression or control subjects but only in those HF patients with greater depressive symptoms.

Our findings may have clinical implications, since both platelet-derived and endothelial-derived P-selectin play important roles in different phases of atherosclerosis. In addition to its role in thrombus formation and coagulation, platelet-expressed P-selectin may affect later phases of atherosclerosis via the generation of circulating proinflammatory platelet-leukocyte aggregates. These aggregates seem to promote plaque progression and increased levels of these aggregates have been found in stable and acute coronary syndromes (42,43). Endothelial-derived P-selectin supports leukocyte tethering and rolling, which is required for the firm adhesion/activation and transmigration of leukocytes, a critical step in the early phase of the atherosclerotic process (44–46). Changes in platelet activity play an important role in patients with coronary artery disease, since thrombus formation has been shown to be the major cause of ACS in these patients (40,47). The precise role of increased platelet activation in patients with HF, however, is less apparent. It appears to be part of the shift toward a proinflammatory state that is characteristic of heart failure (40,48,49). In this setting, increases in platelet activity would be expected to predispose patients to a thrombotic state. The resultant increase in pulmonary and systemic emboli and myocardial ischemia (particularly in HF patients with underlying CAD) would adversely affect morbidity and mortality in this population. Given the atherogenic properties of sP-selectin and given that physical exertion is suggested to play an important role in the onset of ACS (10–12), our results might suggest a mechanism underlying the association between depressive symptom severity and heightened mortality in HF patients. Heart failure patients with higher levels of depressive symptoms may be particularly susceptible to exercise-induced triggering of ACS because of heightened sP-selectin expression and thereby platetet activation in response to moderate exercise. In line with such reasoning, a recent study by Strike *et al.* (50) similarly suggests a role for heightened platelet activity in mediating ACS triggering. In that study, ACS survivors who had experienced emotional but not exercise-induced ACS triggering in the 2 hours before symptom onset showed elevated propor-

tions of platelet-leukocyte, platelet-monocyte, and platelet-neutrophil aggregates in reaction to psychological stressors. As mentioned earlier, these aggregates can be promoted by sP-selectin. Also, although sP-selectin levels had returned to near resting levels within 10 minutes of exercise cessation, it is likely that the effects on platelet aggregate formation and subsequent platelet proinflammatory activity continued for at least 30 minutes (35,50). Given that a moderate exercise as used in our study might be comparable with the physical activity a patient may perform in daily life and given the known ACS triggering effect of physical exertion, our findings might be of clinical importance.

The molecular mechanisms leading to higher sP-selectin responses to exercise with depressive symptom severity in HF remain to be investigated. Although epinephrine is known to activate platelet activity (36) and although norepinephrine has been suggested to mediate mental stress-induced increases in platelet P-selectin in depressive caregivers (51), our data indicate that the observed associations in our study were neither mediated nor moderated by catecholamine secretion (Supplement 1). This nonsignificant finding could relate to the fact that almost all of our patients were using beta blockers. Although beyond the scope of the present study, a speculative explanation for the observed associations between sP-selectin reactivity to exercise and depressive symptom severity in our HF patients may relate to genetic differences, as a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) has been associated with platelet activation in depression. Other potential explanations include activation of proinflammatory mechanisms and metabolic dysregulation, which are known to increase proclivity to platelet activation and thrombotic events (36,40).

Strengths and limitations of our study are discussed in Supplement 3.

In conclusion, our findings suggest that with increasing depressive symptom severity, levels of the adhesion molecule sP-selectin are not only higher before and after exercise but also show greater exercise-induced increases in male HF patients as compared with control subjects. Future research would benefit from including more measures of platelet activity and address whether our findings have implications for ACS following exercise and thereby mortality in HF patients with higher levels of depressive symptoms.

This work was supported by Grants HL-073355 and HL-57265 (to PJM) and RR-00827 (University of California San Diego [UCSD] General Clinical Research Center Grant) from the National Institutes of Health and by Grant IZKOBO-122843/1 from the Swiss National Foundation (to PHW).

We confirm that we report financial disclosures according to the policy of Biological Psychiatry. None of the authors reported financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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