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Circulating levels of soluble intercellular adhesion molecule-1 (sICAM-1) independently predict depressive symptom severity after 12 months in heart failure patients☆

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ABSTRACT

Objective. To determine whether inflammatory markers prospectively predict depressive symptom severity 12 months later in heart failure (HF) patients. *Methods.* In 30 HF patients we assessed depressive symptom severity by the Beck depression inventory (BDI) at baseline as well as 12 months later. We measured circulating levels of the soluble intercellular adhesion molecule (sICAM)-1, the cytokine interleukin (IL)-6 and the acute phase protein C-reactive protein (CRP) at baseline assessment. *Results.* sICAM-1 ($r = .38$, $p = .045$) but not CRP or IL-6 correlated with BDI scores 12 months later. Hierarchical linear regression analysis revealed that independent of baseline BDI assessment, cardiovascular risk factors, indicators of HF disease severity, and medication intake, sICAM-1 significantly predicted BDI scores 12 months later. sICAM-1 independently explained between 7% ($\beta = .26$, $p = .040$) and 10% ($\beta = .35$, $p = .045$) of the total variance in BDI scores 12 months later. *Conclusion.* The findings from this exploratory analysis suggest that the adhesion molecule sICAM-1 is an independent predictor of depressive symptoms 12 months later in HF patients. Our prospective findings support the suggested role for inflammation in increasing future depressive symptom severity and extend this linkage for the first time to HF.

1. Introduction

A recent hypothesis posits that inflammation can lead to depression and depressive symptoms in vulnerable patients (Dantzer et al., 2008). Heart failure (HF) is a major public health concern associated with both increased incidence of depressive symptoms and clinical depression as well as elevated pro-inflammatory activities indicated by levels of adhesion molecules or inflammatory cytokines (Mari et al., 2002; Parissis et al., 2005; Rutledge et al., 2006; York et al., 2008). Indeed, we and others report cross-sectional associations between inflammation and depressive symptoms or clinical depression in HF patients (Moorman et al., 2007; Parissis et al., 2004; Redwine et al., 2007). However, although elevated biomarkers of inflammation were shown to precede the onset of depressed mood in an aged non-HF population (van den Biggelaar et al., 2007), a prospective relationship between inflammation and depressive symptoms has not yet been studied in HF.

The purpose of this exploratory study was to determine whether different types of inflammatory markers (i.e. an adhesion molecule, an inflammatory cytokine, and an acute phase protein) prospectively predict depressive symptom severity 12 months later in HF patients. We controlled for a variety of potential confounders including cardiovascular risk factors, indicators of HF severity, and medication intake.

2. Methods

2.1. Study participants

The study sample consisted of 30 patients diagnosed with HF. 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 associations between depression, cellular adhesion and inflammation.

Inclusion criteria included age between 30 and 85 years, NYHA classes II through IV, symptoms of HF for at least 3 months which have been optimally treated with beta-blockers, diuretics and ACE inhibitors, and systolic dysfunction defined by an ejection fraction $\leqslant$45% or diastolic dysfunction, hypertension <180/110 mm Hg, and

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patients of all ethnicities and races. 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. Patients were instructed to abstain from taking aspirin for 24 h prior to the testing session. Left ventricular ejection fraction (LVEF) was assessed by echocardiography as part of the patient's routine medical evaluation. To assess functional capacity in the patients, we used the six-minute walk-test (O'Keeffe et al., 1998). Resting BP was taken using an automated BP monitor (Dinamap Compact BP® monitor, Critikon, Tempa, FL).

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.

2.2. Depressive symptom severity

Depressive symptom severity was assessed with the 21-item Beck depression inventory (BDI) (Beck, 1978) (baseline) and 12 months later. In a subsample of 16 patients, we additionally obtained an 18 months follow-up BDI. The BDI scores $\geqslant$10 indicate possible clinical depression, 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 $\geqslant$10 on the initial BDI assessment were administered a modified Structured Clinical Interview for DSM-IV (SCID) (American Psychiatric Association, 1994) 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.

2.3. Blood sampling and biochemical analyses

Blood samples were drawn via venous catheter around 9:00 am at the UCSD General Clinical Research Center. Participants had abstained from food and drink (other than water) for two hours before blood sampling, and from physical exercise, alcohol and caffeinated beverages starting the evening before the blood sampling day. Blood was drawn into EDTA-coated vacutainer tubes (BD Biosciences, San Jose, CA, USA) and centrifuged for 10 min at 3000*g* and 4 °C. Plasma was stored at −80 °C until analysis.

We selected a representative panel of inflammatory markers based on the existing literature (2–5). Circulating levels of soluble intercellular adhesion molecule 1 (sICAM-1) and interleukin-6 (IL-6) were determined following previous methods using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Mpls., MN) (Mills et al., 2000; Rehman et al., 1997). C-reactive protein (CRP) was determined in plasma using the high sensitivity Denka–Seiken assay (Roberts et al., 2001). The precision and sensitivity performance values were: sICAM-1, intra-assay CV is 4.6%, inter-assay CV is 6.6, sensitivity is <0.35 ng/ml; IL-6 intra-assay CV is 2.2%, inter-assay CV is 3.9, sensitivity is <0.71 pg/ml; CRP intra-assay CV is <1.0%, inter-assay CV is 1.6, sensitivity is <0.05 mg/l. To minimize intra-assay error variance, all samples from an individual subject were analyzed in the same run.

2.4. Statistical analyses

All calculations were performed using SPSS Inc. (v11.0.1) software packages (SPSS, Chicago, IL). Data are presented as mean ± -SEM. Results were considered statistically significant at the $p \leqslant .05$ level and all tests were two-tailed. 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 (Faul, 2007) revealed that the optimal total sample size to predict a large effect size of $f^2 = 0.35$ in regression analyses with a power of 0.85 using a maximum of 6 predictors was 29.

We calculated bivariate correlations between the 12-months BDI score and the three inflammatory parameters.

To assess the prospective association of inflammatory measures with depressive symptom severity, we performed separate hierarchical linear regression analyses using the 12-months BDI score as the dependent variable and each of the three inflammatory measures as the independent variable while controlling for baseline BDI. We also controlled for the interaction between baseline BDI and significant inflammatory predictors. Next, to identify potential confounders of significant inflammatory predictors we repeated the initial regression model(s) and tested in further regression steps for potential confounders: In a first step, we controlled for an a-priori defined set of demographic and cardiovascular factors including age, gender, BMI, and MAP. In a second step, we controlled for indicators of HF severity, namely LVEF and meters walked in the 6-min walk test. Third, we controlled for medication intake. To reduce statistical over-controlling, given our sample size, we entered medication in two blocks (block 1: 4 pharmaceuticals, block 2: 5 pharmaceuticals). Noteworthy, to reduce statistical over-controlling given our sample size (Babyak, 2004) we only entered significant predictors of one regression step ($p < .05$) into the next regression step(s) by means of forced inclusion. Non-significant predictors were excluded. We moreover tested the predictive value of our regression model on prediction of BDI scores at 18 months. All regression parameters were Z-transformed prior to analyses rendering variables centered to the mean with a standard deviation of 1, particularly to allow computation of interaction terms.

3. Results

Table 1 presents the biological and medical characteristics of the 30 HF patients 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 statins and digoxin. Although mean BDI scores remained similar from baseline (11.4, SEM ± 1.6) to 12 months later (11.0, SEM ± 1.8), individual BDI scores were increased in 11 patients, decreased in 15 patients, and unchanged in 4 patients. At baseline, according to clinical interview, none of the study patients were determined to have major depressive disorder. We did not perform clinical interviews after 12 months to determine major depressive disorder. Noteworthy, 8 patients had a BDI score of $\geqslant$17 after 12 months.

As depicted in Table 2, sICAM-1 was the only inflammatory measure that correlated with the 12-months BDI-score.

The initial regression models revealed that among the total study group, only sICAM-1 (initial regression model, Table 3) but not CRP ($p = .46$) or IL-6 ($p = .15$) significantly predicted BDI 12 months later. This association was independent of depressive symptom severity at baseline as baseline BDI was entered simultaneously in all of these regression models. Separate recalculation of these initial regression models in the 11 subjects with increasing BDI scores confirmed our initial findings: Only sICAM-1 ($\beta = .52$, $p = .022$, R^2 change = .24), but not CRP ($p = .78$) or IL-6 ($p = .90$) were prospectively associated with BDI at 12 months. In subjects with CRP level >3 mg/L ($N = 11$), higher CRP predicted higher BDI 12 months later independent of baseline BDI ($\beta = .36$, $p = .05$, R^2 change = .13).

Table 3 presents the results of the multiple linear regression analysis for the significant inflammatory predictor sICAM-1. Through all steps of the analysis, sICAM-1 and BDI baseline scores

Table 1
Sociodemographic and medical characteristics of the study subjects.

BDI score	
Baseline	11.4 ± 1.6 (0–31)
12 months	11.0 ± 1.8 (0–34)
Inflammatory markers (baseline)	
sICAM-1 (ng/ml)	315.3 ± 18.6 (120–527)
CRP (mg/L)	3.16 ± .54 (.52–14.8)
IL-6 (pg/ml)	3.79 ± .37 (1.36–9.75)
Age (years)	60.8 ± 2.5 (34–81)
Body mass index (kg/m^2)	31.9 ± 1.8 (20.0–59.0)
Gender (men)	86.7%
Mean arterial BP (mm Hg)	85.4 ± 2.6 (59.0–107.6)
Cigarettes per day	5.2 ± 2.5 (0–60)
Current smokers	22.2%
CHF severity	
Ejection fraction (%)	31.2 ± 1.7 (14–54)
6-min walk test (m)	331.5 ± 20.9 (100–624)
NYHA classification II	86.7%
NYHA classification III	13.3%
Concomitant disease	
Diabetes mellitus	35.7%
Medication	
ACE-blocking agents	78.6%
Beta blockers	96.6%
CCB	10.7%
Statins	57.1%
Aspirin	57.1%
Diuretics	85.7%
Anti-arrhythmics	21.4%
Warfarin	8.5%
Digoxin	57.1%

Data are presented as mean ± standard error of means (range) or percentage value; sICAM-1, soluble intercellular adhesion molecule 1; CRP, C-reactive protein; IL-6, interleukin-6; BP, blood pressure; BDI: Beck depression inventory, CCB: calcium channel blockers.

Table 2
Correlation coefficients (r) between inflammatory measures and BDI scores in HF patients.

Inflammatory measures	BDI score at baseline	BDI score after 12 months	BDI score after 18 months
sICAM-1	.16, p = .41	.38, p = .045*	.63, p = .009**
CRP	.06, p = .77	.14, p = .47	.29, p = .27
IL-6	.35, p = .07	.06, p = .77	.14, p = .60

Values are means ± SEM; sICAM-1, soluble intercellular adhesion molecule 1; CRP, C-reactive protein; IL-6, interleukin-6.
* p < .05.
** p < .01.

but none of the other entered parameters (p's > .32) emerged as significant predictors of depressive symptom severity as measured by BDI 12 months later. sICAM-1 alone independently explained between 7 and 10% of the total variance in BDI scores (R^2 change scores, Table 3). The final model including only significant predictors corresponded to the initial regression model and consisted of sICAM-1 and BDI score at baseline and explained 62% of the total variance in BDI scores at 12 months with sICAM-1 independently explaining 7%. As statins are known to have anti-inflammatory effects we repeated our initial sICAM-1 regression model separately in patients treated with statins compared to those not treated with statins as post-hoc test. In the group without statins, sICAM-1 strongly predicted BDI at 12 months (β = .46, p = .040, R^2 change = .18) whereas it did not in the group with statins (p = .70). We also performed the full multiple linear regression models with all potential confounders for CRP and IL-6 and these models were not significant.

A subset of 16 patients also completed the BDI at 18 months. For this subset of patients, BDI scores were as follows: baseline: 9.9 (SEM ± 2.2); 12 months: 10.1 (SEM ± 2.3); 18 months: 10.4 (SEM ± 2.2). When regressing BDI score at 18 months by entering sICAM-1 and BDI baseline as predictors, results remained similar: sICAM-1 independently explained 10% (β = .37) of the total variance in BDI score at 18 months, but however not in a statistically significant way (p = .10), probably due to the smaller sample size. The total model explained 58% of the total variance in BDI 18 months later (p = .004).

4. Discussion

We found that in HF patients higher sICAM-1, but not IL-6, prospectively predicted higher depressive symptom severity 12 months later. Independent of baseline BDI, higher CRP also predicted higher depressive symptom severity 12 months later in those patients with slightly elevated CRP levels (>3 mg/L). The association between sICAM-1 and depressive symptom severity 12 months later was independent of baseline depressive symptom severity, cardiovascular risk factors, HF severity, and medication intake. Separate reanalyses in patients treated with and without statins suggest that the observed sICAM-1 effect is mostly carried by the non-statin users. Therefore, it can be speculated that the effect would have been stronger if statin use had been excluded from study participation. The findings implicate, limited to HF patients, that sICAM-1 (and possibly CRP) might play a role in future depressive symptom severity. In this cohort of predominately NYHA II

Table 3
Hierarchical linear regression analysis for prediction of BDI scores at 12 months by sICAM-1.

Additionally entered variables per regression step	Significant individual predictor variables with standardized β-coefficient, p-value and R^2 change	Model R^2
Initial regression model		
BDI baseline sICAM-1	BDI baseline (.70, <.001, .48), sICAM-1 (.26, .040, .07)	.62
sICAM-1—by-BDI baseline	BDI baseline (.66, <.001, .36), sICAM-1 (.29, .033, .08)	.63
Control variable testing Step 1		
Age, gender, BMI, MAP	BDI baseline (.70, <.001, .38), sICAM-1 (.30, .047, .08)	.66
Control variable testing Step 2		
6-min walk test (m), ejection fraction (%)	BDI baseline (.71, <.001, .46), sICAM-1 (.28, .043, .08)	.63
Control variable testing Step 3a		
Medication intake block 1 (ACE-blocker, Beta blocker, CCB, statins)	BDI baseline (.65, <.001, .33), sICAM-1 (.30, .041, .08)	.66
Control variable testing Step 3b		
Medication intake block 2 (Aspirin, diuretics, anti-arrhythmics, warfarin, digoxin)	BDI baseline (.55, .005, .21), sICAM-1 (.35, .045, .10)	.63

sICAM-1, soluble intercellular adhesion molecule 1; BDI, Beck depression inventory; BMI, body mass index; MAP, mean arterial blood pressure; CCB, calcium channel blockers.

patients, during the 12 months follow-up, depressive symptoms increased in 37% of the patients, decreased in 50%, and were unchanged in 13%. Given that depressive symptoms are associated with adverse outcomes in HF patients (Rutledge et al., 2006) our findings might be of clinical relevance. sICAM-1 expression can be induced by inflammatory cytokines (Bevilacqua, 1993). In the myocardium of HF patients, upregulation of ICAM-1 and the presence of macrophages expressing inflammatory cytokines have been observed (Deswal et al., 2001). sICAM-1 indicates enhanced expression of adhesion molecules on the cell surface and has been suggested to reflect increased inflammation (Blann et al., 2002). The finding of inflammation predicting future depressive symptoms in vulnerable patients like HF patients is consistent with a very recent review by Dantzer et al.(2008). As an underlying mechanism of this association, inflammatory cytokines (i.e. tumor-necrosis-factor-α and interferon-γ) have been proposed to induce a reduction in serotonin synthesis by increasing indoleamine 2,3-dioxygenase (IDO)-induced reduction of tryptophan to kynurenine (Dantzer et al., 2008). Although we did not observe an association between the cytokine IL-6 and depressive symptom severity, other inflammatory cytokines and their actions may play a role in the observed association between sICAM-1 and future depressive symptom severity in HF patients. Main limitations of the study are that we did not investigate control subjects or other heart conditions. In addition, we assessed inflammatory markers only once and thus could not investigate the possibility of depression predicting inflammation. In sum, our findings suggest a role for inflammatory measures in increasing future depressive symptom severity in HF patients which could be associated with clinical endpoints.

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