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Relation of Depression to Severity of Illness in Heart Failure (From HF-ACTION [Heart Failure and a Controlled Trial Investigating Outcomes of Exercise)] Training)

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Abstract

Depression is common in patients with heart failure (HF), is prognostic for adverse outcomes, and purportedly related to disease severity. Psychological and physiologic factors relevant to HF were assessed in HF-ACTION, a large, randomized study of aerobic exercise training in systolic HF. We compared the relationship of objective and subjective parameters with scores on the Beck Depression Inventory (BDI) to examine the hypothesis that depressive symptoms are better associated with perception of disease severity than with objective markers of HF severity. At baseline, 2322 of 2331 subjects entered into HF-ACTION completed questionnaires to assess depression (Beck Depression Inventory, BDI) and quality of life (Kansas City Cardiomyopathy Questionnaire, KCCQ). Objective markers of HF severity included ejection fraction (EF), BNP, and peak VO_2, (by cardiopulmonary exercise testing (CPX), with evaluation of duration and respiratory exchange ratio (RER) also performed). Measures more likely to be affected by perceived functional status included NYHA classification and the 6 minute walk test. Objective assessments of disease severity were slightly (VO_2) or not (BNP, EF) related to BDI. By multivariate analysis (KCCQ not included) only age, sex, CPX duration, NYHA, six minute walk distance and peak RER independently correlated with BDI. In conclusion, depression is minimally related to objective assessments of severity of disease in HF, but is associated with patients' (and clinicians') perception of disease severity. Addressing depression might improve symptoms of patients with HF.

Keywords

Depression; Quality of Life; Heart failure; congestive

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HF-ACTION is an NHLBI-sponsored evaluation of structured aerobic exercise training intervention in patients with systolic HF. At baseline, multiple assessments were obtained, including objective markers relevant to heart failure (left ventricular ejection fraction (EF), B-type natriuretic peptide (BNP), and cardiopulmonary exercise testing). Measures believed to be more likely to be affected by perceived functional status (and, thus, considered more subjective and affected by motivation) included NYHA class, six minute walk, and the Kansas City Cardiomyopathy Questionnaire (KCCQ). Depression was assessed using the Beck Depression Inventory (BDI), which has been recommended as one of the preferred instruments in large-scale investigations.[1] We used baseline data from HF-ACTION to evaluate the relationship of depression (as measured by BDI) with both objective and subjective measurements of heart failure. Since it is commonly believed that depression is caused by the difficulties of living with a chronic disease,[2] we examined the opposite hypothesis that depression is more strongly related to subjective heart failure indices than to objective indices.

Methods

The trial design of HF-ACTION has been previously published.[3] Patients with NYHA class II to IV heart failure symptoms, left ventricular EF of 35% or less by echocardiography, and stable medications for at least 6 weeks were eligible. The baseline EF was measured by a core laboratory and was obtained using the biplane, if possible, or single-plane Simpson's method. Where the core laboratory EF was not available, the EF as measured by the site was used.

At baseline, 2322 of the 2331 patients entered into HF-ACTION completed the Beck Depression Inventory (BDI). BDI scores of 10 or greater are considered to represent clinically significant depressive symptoms.[4]

Cardiopulmonary exercise testing (CPX) was performed on all but one of the 2322 patients who completed the BDI. During exercise testing, patients were strongly encouraged to achieve a Borg rating of perceived exertion of greater than 16 (on a scale of 6 to 20) and obtained a respiratory exchange ratio of greater than 1.10. During exercise tests, gas exchange was measured and the data forwarded to the HF-ACTION CPX core laboratory. Determination of peak VO_2, duration of exercise, and peak respiratory exchange ratio (peak RER) was made by the centralized core lab. The majority of tests were performed on a treadmill using a modified Naughton protocol.

The six minute walk test was measured at baseline. Natriuretic peptides (BNP or NT-proBNP) were measured in 820 and 82 patients, respectively. Only the BNP results are reported here. Demographic variables, including age, race, and sex were recorded.

The patients' perceived clinical status was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ).[5] This test has multiple subscales to quantify physical limitations, symptoms, self-efficacy, social interference and quality of life. A higher score reflects better quality of life.

In order to descriptively characterize subjects with a BDI < 10 and those with BDI ≥ 10, the mean and standard deviation for the two groups were computed for demographic variables, exercise variables, and other baseline characteristics. Values were compared using a two-tailed t test or chi-square test. We also examined BDI scores as a continuous measure using univariate regression models, with the above variables as predictors, in order to more fully understand the univariate relationship of BDI scores to each variable.

In the multivariate modeling phase of the analysis, variables with p-values < 0.2 in the univariate regression model were entered into the multivariable model. Etiology, previous HF hospitalization, diabetes, COPD, and medications were not used in the models. Throughout

the multivariate modeling, BDI was treated as a continuous measure. Backwards elimination was used, eliminating the variable with highest p-value until all p-values were below 0.05. The final model had 5 predictors: age and 4 KCCQ variables.

The modeling was then done without KCCQ variables in order to assess the prognostic importance of factors not dependent upon questionnaires. We felt that these factors could more easily be determined to be subjective or objective. In order to check for a sex-race interaction, a model with just sex, race, and their interaction was first examined. Since the P-value for the interaction term was < 0.05, the interaction was used in the multivariate models. The main effects for sex and race were not eliminated in the backwards selection until after their interaction was eliminated.

Results

Depression, as indicated by an elevated BDI >10, was common in this group of HF patients (N=1003; 43%). Table 1 shows the baseline characteristics of patients with a BDI ≥ 10 and those with a BDI < 10. Patients with an elevated BDI score were younger, and slightly more likely to be men and African American.

An elevated BDI was associated with evidence of more subjective symptoms of heart failure. The differences were most striking in KCCQ and NYHA. No differences were noted regarding the more objective measures of disease severity, including LVEF and BNP, and the difference in average peak oxygen consumption was 0.5 mL/kg/min.

Table 2 shows the univariate predictors of BDI. Both EF and BNP did not predict BDI. There was a close relationship between BDI and KCCQ and almost all of its subscores. The effect sizes of the relationship with all other factors were small.

When all variables, including KCCQ, were included in multivariate modeling, the R^2 value was 0.44 and only KCCQ and age remained in the model. Because the KCCQ was closely related to BDI and it is difficult to determine if it is reflecting subjective or objective factors which limit function, we evaluated the independent prognostic importance of the other parameters without including KCCQ. The multivariate predictors of BDI are listed in Table 3. An elevated BDI was independently related to younger age. In addition, independent correlates of BDI included sex, NYHA classification, CPX test duration, and 6 minute walk. Peak RER was also related to depression. Together, these characteristics exhibit a R^2 of 0.086 in the model, suggesting that unmeasured (probably non-cardiac) factors play a predominant role in depression.

Discussion

In this analysis of 2322 patients with extensive characterization at baseline, depression as measured by the BDI was highly associated with reduced quality of life and other subjective assessments of functional status, but not with objective indicators of severity of disease. KCCQ and NYHA, in particular, appeared markedly worse in patients with an elevated BDI, while no measurement unaffected by perception or motivation was independently associated with BDI. The findings of the present study suggest that depression influences the perception of severity of disease to a greater extent than severe heart failure causes depression. One would therefore expect that depressed patients have more symptoms than someone with the same degree of illness but without depression. Addressing the depression might therefore markedly improve symptoms of patients with heart failure.

The findings of this study are important because of the documented high prevalence of elevated BDI scores. Similar to previous smaller studies, [6,7,8,9] 43% of patients in the present study

of out-patient, ambulatory, only moderately impaired heart failure patients obtained clinically elevated scores on the BDI. In this large study applicable to many patients routinely seen by primary care physicians and cardiologists, it is clear that depression is common and its causes and consequences need to be understood.

The results suggest that depression is not directly caused by the severity of heart failure. The measures used in our modeling which were the most objective parameters, BNP and LVEF, were not univariate predictors of BDI in the present study. In contrast, NYHA was the strongest unadjusted predictor other than age and the KCCQ parameters. Both NYHA and KCCQ parameters are subjective and based upon a patient's (and observers') perception. It is important to note that the KCCQ is a subjective questionnaire; most of the domains have been validated against non-objective domains and those affected by motivation, such as NYHA and the six minute walk.[10] Thus, in the present study, BDI was associated chiefly with the measurements highly influenced by perception. Even the very slight association with peak VO_2 might be explained by chronic inactivity or motivation; although all patients had an equally strong stimulus to achieve exhaustive exercise and as a group reached high RER values, the peak RER was lower in depressed patients. Motivation can also explain the association of the BDI with the 6 minute walk.

The present study is consistent with the previous small studies that have evaluated association of subjective and objective markers of depression and severity of disease. For example, in a small study of patients participating in an exercise study, we found that depressed patients appeared to be worse by NYHA, even though their objective parameters (such as EF or peak oxygen consumption) were actually better.[11] A German evaluation of 167 patients in a general medicine practice showed similar results; EF and NT-proBNP did not relate to depression but quality of life measurements were strongly correlated.[12] In patients with coronary artery disease, depressive symptoms were found to be strongly associated with patient-reported health status, but not with EF and ischemia.[13] The present study extends these findings to a much larger and diverse population, and has strong implications for clinical evaluation and treatment of patients.

Many studies have shown the relationship between depression and symptoms.[14] While most observers realize that the interaction is bidirectional,[15] it is usually assumed that the heart failure is causing most of the depression. Since worse quality of life measurements are associated with depression, it is felt that changes in function explain the depression. Rector and colleagues reported, using Val-HeFT data, that dyspnea at rest, dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, fatigue, and New York Heart Association class were all significantly related to Minnesota Living with Heart Failure scores, explaining 41% of the variation in the scores.[16] They state that their study "provides insight into how heart failure affects quality of life." In contrast, the present study, showing a marked influence of depression on another quality of life scale without evidence of differences in severity of disease, suggests that depression probably is a major determinant of quality of life measurements. Interestingly, and consistent with the present study, Rector and colleagues found no relationship in ValHeFT between quality of life and the objective assessments of EF serum creatinine, and BNP.[16]

The present study suggests that physicians might improve HF symptoms (as indicated by quality of life instruments, for example) by addressing depression. Clinicians should evaluate a patient's psychological status and take into account changes in a person's life and environment when increased symptoms are reported; worsening depression could lead to an overestimation of severity of disease. While objective measurements also have limitations, with hemodynamic parameters and EF not reliably predictive of outcome or symptoms, they must be used in the careful evaluation of patients. When objective and subjective factors are not consistent, the practitioner must ascertain the true cardiac status of the patient.

There are limitations to any study attempting to evaluate the relationship of psychological and physiologic parameters. The definition of depression is difficult, and the BDI is only an estimate of its presence. However, it is the most widely used screening tool for assessment of depression in clinical research. Internal consistency of the scale is high (0.86 to 0.88 among psychiatric patients and 0.81 with non-psychiatric subjects), and BDI and clinical ratings of depression are highly correlated in meta-analyses. BDI scores are also correlated with scores on the Minnesota Multiphasic Personality Inventory Depression, Zung Self Rating Depression, Hopelessness, and Hamilton scales.[17] Thus, while not definitive in an individual patient, the BDI should accurately reflect the prevalence of depression in a large population.

These are cross-sectional data, and causation cannot be proven as the relationships between independent variables and the dependent variable may be bidirectional. However, the findings do indicate a poor relationship of BDI and objective indicators of cardiac dysfunction. In contrast, functional and subjective indices are much more closely related to BDI.

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References

1. Davidson KW, Kupfer DJ, Bigger JT, et al. Assessment and Treatment of Depression in Patients with Cardiovascular Disease: National Heart, Lung, and Blood Institute Working Group Report. Psychosomatic Medicine 2006;68:645–650. [PubMed: 17012516]
2. Ferketich AK, Binkley PF. Psychological distress and cardiovascular disease: results from the 2002 National Health Interview Survey. Eur Heart J 2005;26:1923–1929. [PubMed: 15946958]
3. Whellan DJ, O'Connor CM, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Houston-Miller N, Fleg JL, Schulman KA, Piña IL. HF-ACTION Trial Investigators. Heart failure and a controlled trial investigating outcomes of exercise training (HF-ACTION): design and rationale. Am Heart J 2007;153:201–211. [PubMed: 17239677]
4. Beck AT, Ward CH, Mendelsohn M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psych 1961;4:561–71.
5. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245–1255. [PubMed: 10758967]
6. Gottlieb SS, Khatta M, Friedmann E, Einbinder L, Katzen S, Baker B, Marshall J, Minshall S, Robinson S, Fisher ML, Potenza M, Sigler B, Baldwin C, Thomas SA. The Influence of Age, Gender, and Race on the Prevalence of Depression in Heart Failure Patients. J Am Coll Cardiol 2004;43:1542–1549. [PubMed: 15120809]
7. Haveranek EP, Ware MG, Lowes BP. Prevalence of depression in congestive heart failure. Am J Cardiol 1999;84:348–350. [PubMed: 10496452]
8. Jiang W, Kuchibhatla M, Cuffe MS, Christopher EJ, Alexander JD, Clary GL, Blazing MA, Gaulden LH, Califf RM, Krishnan RR, O'Connor CM. Prognostic value of anxiety and depression in patients with chronic heart failure. Circulation 2004;110:3452–3456. [PubMed: 15557372](Epub 2004 Nov 22.)
9. MacMahon KMA, Lip GYH. Psychological Factors in Heart Failure : A Review of the Literature. Arch Intern Med 2002;162:509–16. [PubMed: 11871918]
10. Gottlieb SS, Kop WJ, Thomas SA, Katzen S, Vesely MR, Greenberg N, Marshall J, Cines M, Minshall S. A double-blind placebo-controlled pilot study of controlled-release paroxetine on depression and quality of life in chronic heart failure. American Heart Journal 2007;153:868–873. [PubMed: 17452166]

11. Skotzko CE, Krichten C, Zietowski G, et al. Depression is common and precludes accurate assessment of functional status in elderly patients with congestive heart failure. J Card Fail 2000;6:300–305. [PubMed: 11145754]

12. Müller-Tasch T, Peters-Klimm F, Schellberg D, Holzapfel N, Barth A, Jünger J, Szecsenyi J, Herzog W. Depression is a major determinant of quality of life in patients with chronic systolic heart failure in general practice. J Card Fail 2007;13:818–824. [PubMed: 18068614]

13. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. JAMA 2003;290:215–221. [PubMed: 12851276]

14. Norra C, Skobel EC, Arndt M, Schauerte P. High impact of depression in heart failure: Early diagnosis and treatment options. Int J Cardiol 2008;125:220–231. [PubMed: 17662487]

15. Bekelman DB, Havranek EP, Becker DM, Kutner JS, Peterson PN, Wittstein IS, Gottlieb SH, Yamashita TE, Fairclough DL, Dy SM. Symptoms, depression, and quality of life in patients with heart failure. J Card Fail 2007;13:643–648. [PubMed: 17923356]

16. Rector T, Anand I, Cohn J. Relationships Between Clinical Assessments and Patients' Perceptions of the Effects of Heart Failure on Their Quality of Life. J Card Fail 12:87–92. [PubMed: 16520254]

17. Beck, AT.; Stear, RA.; Garben, MG. The Beck Depression Inventory. Vol. 2. Boston, MA: Houghton Mifflin; 1985. Psychometric Properties of the Beck Depression Inventory: Twenty-Five Years of Evaluation.

Table 1

Characteristics of Subjects with Beck Depression Inventory ≥ 10 and Beck Depression Inventory <10

Variable	Depressed (BDI ≥ 10) (n=1003)	Non-Depressed (BDI<10) (n=1319)
Age (years)	57 ±12	61 ± 13 *
Female	264 (26%)	392 (30%)
Male	739 (74%)	927 (70%)
African American	333 (34%)	414 (32%)
White	603 (61%)	817 (63%)
Other, including multiracial	50 (5%)	71 (5%)
Six minute walk distance (m, n = 2271)	353 ± 107	373 ± 102 *
Cardiopulmonary exercise test duration (min, n = 2301)	9.5 ± 3.9	10.0 ± 4.0 *
Peak oxygen consumption (mL/kg/min, n = 2268)	14.6 ± 4.8	15.1 ± 4.7 *
Ejection Fraction, best available (%, n = 2318)	25.1 ± 7.2	25.3 ± 7.6
Brain Natriuretic Peptide (pg/mL, n = 820)	479 ± 715	456 ± 556
Peak Respiratory Exchange Ratio, Cardiopulmonary exercise test (n = 2253)	1.08 ± 0.11	1.10 ± 0.11 *
KCCQ overall summary score	53 ± 18	77 ± 16 *
KCCQ clinical summary score	61 ± 19	79 ± 16 *
KCCQ physical limitation score (n = 2303)	59 ± 21	77 ± 19 *
KCCQ symptom stability score (n = 2310)	53 ± 18	55 ± 16 *
KCCQ symptom frequency score (n = 2321)	60 ± 23	80 ± 19 *
KCCQ symptom burden score	63 ± 20	83 ± 16 *
KCCQ total symptom score	62 ± 20	82 ± 17 *
KCCQ self-efficacy score (n = 2321)	76 ± 21	85 ± 19 *
KCCQ quality of life score (n = 2321)	43 ± 21	72 ± 19 *

Variable	Depressed (BDI ≥ 10) (n=1003)	Non-Depressed (BDI<10) (n=1319)
KCCQ social limitation score (n = 2281)	46 ± 24	75 ± 23 *
NYHA class		
II	540 (54%)	931 (71%) *
III	448 (45%)	380 (29%)
IV	15 (1.5%)	8 (0.6%)
Ischemic etiology of HF	505 (50%)	687 (52%)
Heart failure hosp. in the last 6 months	274 (28%)	333 (25%)
History of diabetes	341 (34%)	407 (31%)
History of COPD	124 (12%)	125 (10%) *
On an ACE inhibitor	751 (75%)	978 (74%)
On a beta blocker	941 (94%)	1254 (95%)
On an angiotensin II receptor blocker	230 (23%)	312 (24%)
On a loop diuretic	812 (81%)	998 (76%) *
On an anti-depressant	293 (29%)	174 (13%) *

* = $p < 0.05$. n = 2322 unless otherwise stated

Table 2

Univariate predictors of Beck Depression Inventory treated as a continuous variable

Variable	Slope Estimate	Standard Error	R^2	t statistic	P-value
Age (years)	−0.12	0.014	0.0300	−8.5	< 0.0001
Sex	−0.33	0.39	0.0003	−0.83	0.40
Race			0.0017		
Other v. African American	−0.39	0.83		−0.47	0.64
White v. African American	−0.76	0.38		−2.0	0.047
New York Heart Association class (II vs. III/IV)	3.2	0.36	0.0336	9.0	< 0.0001
Ejection Fraction	0.0072	0.024	<0.0001	0.30	0.76
6 minute walk distance (m)	−0.0089	0.0017	0.0119	−5.2	< 0.0001
Cardiopulmonary exercise test duration (min)	−0.18	0.045	0.0067	−3.9	< 0.0001
Peak VO_2 (mL/kg/min)	−0.11	0.038	0.0039	−3.0	0.0029
Peak Respiratory Exchange Ratio, Cardiopulmonary exercise test	−5.4	1.6	0.0050	−3.4	0.0008
Brain natriuretic peptide (pg/mL)	−0.00029	0.0005	0.0004	−0.60	0.55
KCCQ overall summary score	−0.26	0.0066	0.4054	−40	< 0.0001
KCCQ clinical summary score	−0.23	0.0076	0.2904	−31	< 0.0001
KCCQ physical limitation score	−0.17	0.0072	0.2044	−24	< 0.0001
KCCQ symptom stability score	−0.046	0.010	0.0086	−4.5	< 0.0001

Variable	Slope Estimate	Standard Error	R^2	t statistic	P-value
KCCQ symptom frequency score	−0.19	0.0067	0.2554	−28	< 0.0001
KCCQ symptom burden score	−0.21	0.0073	0.2706	−29	< 0.0001
KCCQ total symptom score	−0.22	0.0072	0.2877	−31	< 0.0001
KCCQ self- efficacy score	−0.10	0.0084	0.0584	−12	< 0.0001
KCCQ quality of life score	−0.22	0.0055	0.4192	−41	< 0.0001
KCCQ social limitation score	−0.17	0.0054	0.3122	−32	< 0.0001

Table 3

Multivariate Modeling of Baseline Beck Depression Index Score (excluding KCCQ)

Variable	Slope Estimate	SE	t statistic	P-value
Age	−0.15	0.015	−10	<0.0001
Six minute walk distance	−0.0060	0.0021	−2.8	0.0047
Cardiopulmonary exercise test duration	−0.12	0.057	−2.1	0.033
Peak Respiratory Exchange Ratio	−3.3	1.6	−2.0	0.043
New York Heart Association class (II vs. III/IV)	2.8	0.40	7.0	<0.0001
Sex	−1.1	0.40	−2.9	0.0043