Impact of Exercise Training and Depression on Survival in Heart Failure Due to Coronary Heart Disease

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Depression is prevalent in patients with heart failure (HF) and is associated with increased mortality. In patients with coronary heart disease (CHD) without HF, exercise training (ET) can effectively decrease depressive symptoms resulting in improved survival. We evaluated 189 patients with American College of Cardiology/American Heart Association stage C HF due to CHD (mean left ventricular ejection fraction 35 ± 10%) enrolled in a structured ET program from January 2000 to December 2008, including a group of 151 who completed the program and 38 patients with HF who dropped out of rehabilitation without ET. Depressive symptoms were assessed by standard questionnaire at baseline and after ET, and mortality was determined at a mean follow-up of 4.6 ± 2.6 years. Prevalence of depressive symptoms decreased by 40% after ET, from 22% to 13% ($p < 0.0001$). Patients initially classified as depressed who remained depressed after ET had nearly a fourfold higher mortality than patients whose depression resolved after ET (43% vs 11%, $p = 0.005$). Depressed patients who completed ET had a 59% lower mortality (44% vs 18%, $p < 0.05$) compared to depressed dropout subjects not undergoing ET. Survival benefits after ET were concentrated to those patients with depression who improved exercise capacity. In conclusion, depressive symptoms are prevalent in patients with HF and are associated with increased mortality. Structured ET is effective in decreasing depressive symptoms, a factor that correlates with improved long-term survival. © 2011 Published by Elsevier Inc. (Am J Cardiol 2011;107:64–68)

We and others have described the benefits of exercise training (ET) on depressive symptoms in patients with coronary heart disease (CHD) after major CHD events.[1–3] Specifically, ET decreases depressive symptoms and the prevalence of depression by 50% to 70% and in randomized trials decreased depressive symptoms as effectively as antidepressant medications.[4,5] We recently reported a significant improvement in overall survival in depressed patients with CHD when depressive symptoms were successfully decreased after ET.[6] However, a beneficial effect of ET on outcomes in patients with heart failure (HF) whose symptoms of depression decreased has not been reported. The present investigation examined the effects of ET on depressive symptoms and subsequent long-term mortality in patients with HF and evaluates the relation between changes in exercise capacity and clinical outcomes.

Methods

We enrolled patients with a left ventricular ejection fraction <45%, a history of HF (American College of Cardiology/American Heart Association stage C) that was considered by their clinical cardiologist to be stable, who had no previous depression or use of antidepressive medications, and whose HF was due to CHD. All patients were referred by their primary cardiologist after a recent CHD event including acute myocardial infarction (MI), coronary bypass, or percutaneous coronary intervention.

From January 2000 to December 2008, 189 patients met the inclusion criteria. All patients entered the program 2 to 6 weeks after a CHD event, including acute MI (38%), coronary bypass surgery (30%), and percutaneous coronary intervention (45% of patients; some patients had >1 clinical event). Thirty-eight patients dropped out of cardiac rehabilitation within 2 weeks of entry ("dropouts"), all of whom attended <5 sessions of exercise; the remaining 151 patients completed phase II cardiac rehabilitation and ET (completing all 36 sessions over a period of 3 to 7 months, mean 3.8) and formed the "treatment group." All patients completed questionnaires before ET and the treatment group completed questionnaires after ET. Survival status was obtained June 2009, after a mean follow-up of 4.6 ± 2.6 years from the National Death Index. The protocol was approved by the institutional review committee at Ochsner Clinic Foundation (New Orleans, Louisiana).

The Kellner Symptom Questionnaire is a 92-question assessment validated to assess behavioral characteristics including symptoms of depression, anxiety, somatization, and hostility, with a lower score being more favorable for each behavioral symptom (scores can range from 0 to 17 U).[7] The instrument has been validated for its ability to discriminate between psychiatric patients and non-psychiatric patients and for its test–retest and 1/2-split reliabilities.[8] Depressive symptoms were defined to be clinically significant when the depression score exceeded 6, and when

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present, recovery from categorical depression was defined when the depression score was ≤6. The Medical Outcomes Short Form 36 Survey was used to assess quality of life, with a high score indicating a more favorable quality-of-life trait.[9]

Protocol, data collection, and statistical analysis were performed as previously described.[10] Patients were referred to and participated in outpatient phase II cardiac rehabilitation and ET consisting of 36 educational and exercise sessions typically over a 3-month period. Exercise intensity was prescribed within 10 beats of the anaerobic threshold obtained on entry cardiopulmonary exercise testing. Daily lectures and group sessions about CHD risk factors, diet, and HF (symptoms, signs, etc.) were given for patients and spouses. Height, weight, body mass index, and percent body fat were assessed at baseline and 1 week after completing ET. Peak oxygen uptake (Vo_2) was measured by cardiopulmonary stress testing at baseline and on completion of the program as previously reported.[11] Change in peak Vo_2 was calculated as the difference between peak Vo_2 after the program and at baseline.

StatView 5.0.1 (SAS Institute, Cary, North Carolina) was used for statistical analysis. Results are reported as mean ± SD or frequencies expressed as percentages. Differences in continuous variables between 2 groups were assessed by paired Student's *t* test or nonparametric tests as appropriate. Univariate relations between variables were assessed as partial correlations. Two-tailed p value ≤0.05 was considered statistically significant. Logistic regression analysis was performed to determine independent predictors of mortality. Actuarial survival analysis was used to compute cumulative hazard over time.

Results

Mean age of the 189 patients who met the inclusion criteria was 65 ± 11 years, with men comprising 75% of the cohort. Mean left ventricular ejection fraction was 35 ± 10% and mean peak Vo_2 was 15.5 ± 5.0 ml/kg/min. Sixty-one percent of patients were in New York Heart Association class II (23% in class III, 16% in class I). An implantable cardioverter–defibrillator was present in 59 patients (31%). One hundred seventy-four patients (92%) were taking β blockers, 145 (77%) were taking angiotensin-converting enzyme inhibitors, and 21 (11%) were taking angiotensin II receptor blockers. Depressive symptoms were identified in 42 patients (22%) on entry (24% dropouts, 22% treatment; p = NS). Compared to patients in the active treatment group, dropouts had a lower quality-of-life score (88.7 ± 18.9 vs 99.4 ± 18.6; p = 0.05) but were otherwise statistically similar.

Of the 151 patients comprising the treatment group, depressive symptoms were identified in 33 patients (22%) on entry into ET. Table 1 presents baseline differences between treatment subjects based on the presence or absence of significant depressive symptoms. Effects of ET in the depressed cohort are presented in Table 2. After ET the prevalence of depressive symptoms decreased 40% (Figure 1) from 22% on entry to 13% on completion of the program (p <0.0001).

Of the dropouts, depressed subjects had a threefold higher all-cause mortality compared to nondepressed subjects (44% vs 14%, p <0.05).

After completion of ET, treatment group patients initially classified as depressed who remained depressed had a fourfold higher mortality (43% vs 11%, p = 0.005) than depressed patients who converted to a nondepressed status (Figure 2). Depressed patients in the treatment group demonstrated an early and incremental increased mortality compared to nondepressed patients (p = 0.0003) by time-dependent actuarial hazard survival (Figure 3).

By multivariate analysis (Table 3), decreased peak Vo_2 and advancing age were independent predictors of death in

Table 1
Baseline differences in active treatment patients with and without depression at study entry

Variable	Depressed (n = 33)	Nondepressed (n = 118)	p Value
Age (years)	62 ± 12	67 ± 12	0.06
Men	72%	78%	NS
Body mass index (kg/m^2)	28.6 ± 5.0	27.8 ± 4.6	NS
Percent body fat	28.8 ± 6.7	28.5 ± 7.4	NS
Active smoker	0%	1%	NS
Hypertension	34%	32%	NS
Diabetes mellitus	23%	22%	NS
Peak oxygen uptake (ml/kg/min)	14.6 ± 3.9	15.9 ± 4.6	NS
Ejection fraction (%)	34 ± 10	35 ± 10	NS
Depression	11.0 ± 3.7	2.1 ± 1.8	<0.0001
Anxiety	12.2 ± 4.8	3.1 ± 3.2	<0.0001
Hostility	7.8 ± 5.3	1.8 ± 2.6	<0.0001
Somatization	10.0 ± 4.2	6.3 ± 3.5	<0.0001
Quality of life	82.4 ± 12.6	103.7 ± 17.4	<0.0001

Table 2
Effects of exercise training in depressed patients with heart failure (n = 33)

Variable	Before	After	p Value
Body mass index (kg/m^2)	28.6 ± 5.0	28.3 ± 4.7	NS
Percent body fat	28.8 ± 6.7	27.6 ± 5.5	0.05
Peak oxygen uptake (ml/kg/min)	14.6 ± 3.9	15.9 ± 4.7	0.03
Depression	11.0 ± 3.7	5.1 ± 6.1	<0.0001
Anxiety	12.2 ± 4.8	7.0 ± 6.4	<0.0001
Hostility	7.8 ± 5.3	4.3 ± 5.2	0.003
Somatization	10.0 ± 4.2	7.5 ± 5.0	0.0006
Quality of life	82.4 ± 12.6	102.0 ± 19.9	<0.0001

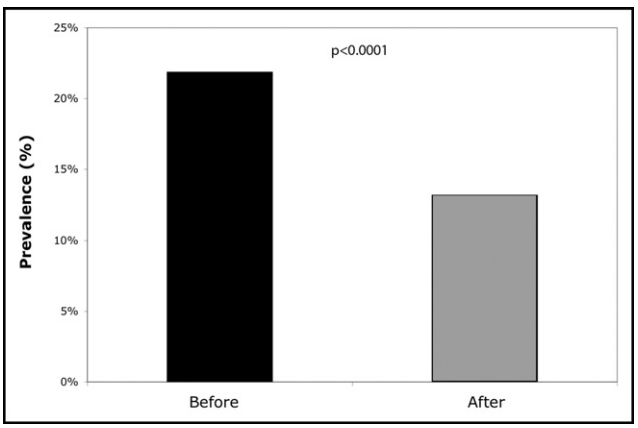

Figure 1. Change in prevalence of depression in patients with heart failure before and after exercise training (n = 151).

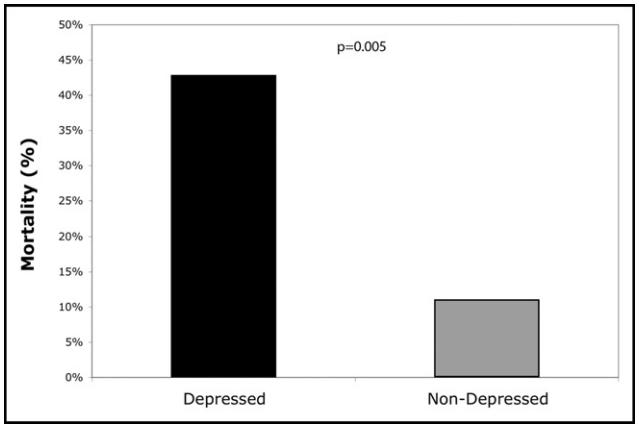

Figure 2. Mortality based on presence or absence of depressive symptoms after exercise training (n = 151).

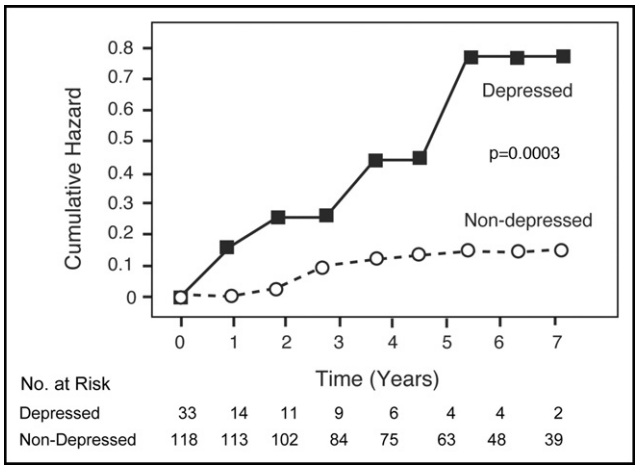

Figure 3. Actuarial hazard for death comparing patients with heart failure with and without depression (n = 151).

Table 3
Multivariate analysis of independent predictors of mortality in patients with heart failure after exercise training (n = 151)

Variable	Chi-square	p Value
Decreased peak oxygen uptake	7.7	0.006
Advancing age	6.3	0.01
Decreased ejection fraction	3.0	0.08
Presence of depression	2.9	0.09

the treatment cohort, whereas decreased ejection fraction and presence of depression were of borderline significance.

To evaluate the impact of ET on survival in depressed subjects, we assessed mortality in all patients (treatment and dropouts) who were identified as being depressed at study entry. Depressed dropouts had a greater than twofold higher mortality than depressed patients who completed ET (44% vs 18%; $p < 0.05$).

Treatment patients were divided into 2 groups based on change in exercise capacity after ET. Patients exhibiting a training effect, demonstrated by an increase in peak Vo_2 after ET, were labeled "Vo_2 gain" and were compared to those with no improvement or a loss in exercise capacity, labeled "Vo_2 loss." Baseline differences between these 2 groups are presented in Table 4. Patients with Vo_2 gain (n = 115) had higher total quality-of-life scores and trended toward having fewer smokers and lower depression scores than patients with Vo_2 loss (n = 36).

Table 4
Baseline differences in patients who improve exercise capacity versus those who do not improve after exercise training

Variable	Vo_2 Gain (n = 115)	Vo_2 Loss (n = 36)	p Value
Age (years)	66 ± 12	67 ± 12	NS
Men	75%	80%	NS
Body mass index (kg/m^2)	27.7 ± 4.8	28.1 ± 4.8	NS
Active smoker	0%	3%	0.08
Hypertension	25%	33%	NS
Diabetes mellitus	21%	22%	NS
Peak oxygen uptake (ml/kg/min)	15.7 ± 4.9	15.7 ± 4.9	NS
Ejection fraction (%)	34 ± 10	35 ± 11	NS
Depression	3.5 ± 4.0	4.9 ± 5.0	0.11
Anxiety	4.6 ± 4.9	5.7 ± 5.7	NS
Hostility	2.7 ± 3.7	3.8 ± 4.9	NS
Somatization	6.8 ± 3.9	7.4 ± 4.1	NS
Quality of life	102.1 ± 17.7	89.8 ± 18.9	0.0009

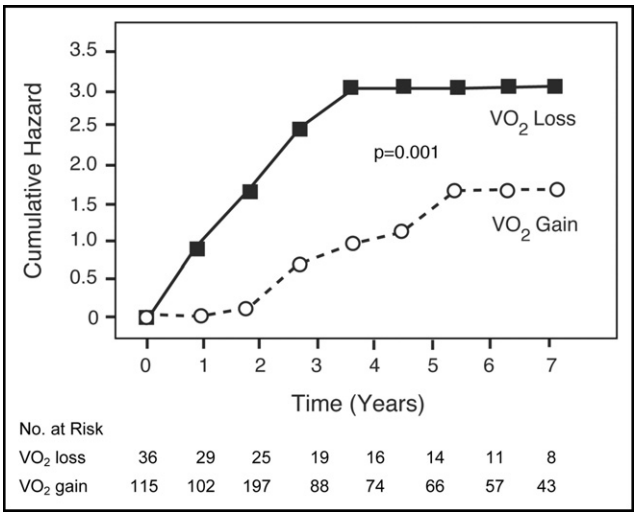

Figure 4. Actuarial hazard for death comparing patients with heart failure who improve exercise capacity (Vo_2 gain; n = 115) to those who do not improve exercise capacity (Vo_2 loss; n = 36) after exercise training.

At follow-up, patients with Vo_2 gain had a 61% lower mortality than patients with Vo_2 loss (13% vs 33%; p = 0.006). Time-dependent actuarial cumulative hazard for survival was assessed in patients with Vo_2 gain and Vo_2 loss (Figure 4). Patients with Vo_2 loss showed an early increase in mortality compared to patients with Vo_2 gain (p = 0.001).

Prevalence of depressive symptoms was assessed in each Vo_2 change group at entry and completion of ET and subsequent mortality was obtained. There were no statistical differences in prevalence of depressive symptoms at baseline between groups. In the Vo_2 loss group, prevalence of depressive symptoms remained unchanged (25% on entry to 23% on completion, p = NS) and the corresponding mortality was relatively high at 33% (Figure 5). In patients with Vo_2 gain, prevalence of depressive symptoms decreased from 21% to

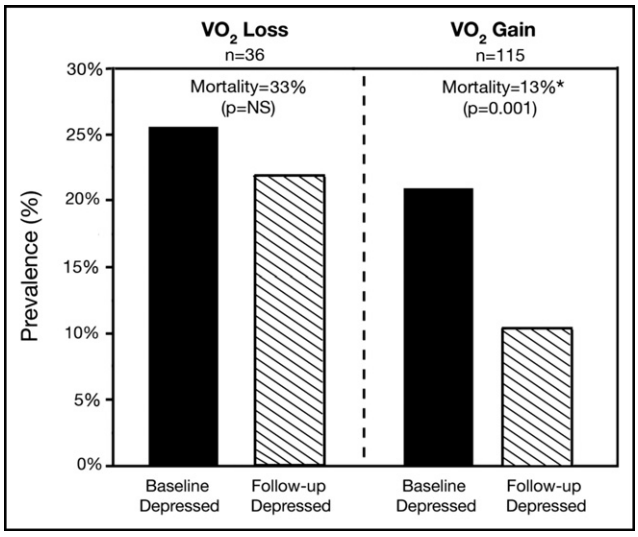

Figure 5. Prevalence of depression and subsequent mortality based on changes in peak oxygen uptake after exercise training (*p <0.001 compared to oxygen uptake loss).

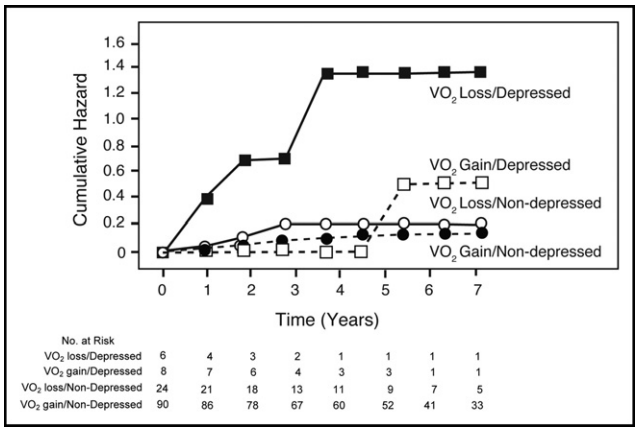

Figure 6. Actuarial hazard for death comparing patients with heart failure with and without depression stratified by change in oxygen uptake after exercise training (p <0.01 between oxygen uptake loss/depressed and all others).

10% (p = 0.001) and subsequent mortality was 13% (p < 0.001 compared to patients with Vo_2 loss). Fifty-seven percent of all patients with improved peak Vo_2 also demonstrated an improvement in their respective depression score.

The impact of depression was then evaluated as a function of change in exercise capacity by examining patients in the 2 exercise change strata separated by depression status using actuarial cumulative hazard for survival (Figure 6). Depressed patients with Vo_2 loss showed an early incremental increased mortality compared to all other groups (p <0.01). Although depressed patients with Vo_2 gain trended toward a higher mortality than all nondepressed subgroups, this difference was not statistically significant.

Discussion

There are several important findings from this investigation. First, clinically unrecognized depressive symptoms are prevalent in the HF population, particularly in patients after major CHD events, and their presence, regardless of age or gender, confers a marked increase in all-cause mortality risk over time. Second, structured ET is an effective method for improving quality of life and decreasing depressive symptoms in patients with HF. Third, patients with HF who improve aerobic capacity, even modestly, have a survival benefit over those whose exercise capacity does not improve. Fourth, the primary beneficiaries of mortality reduction secondary to improvement in exercise capacity are those patients with HF and CHD exhibiting clinically unrecognized depression as discovered by standard questionnaire.

Psychosocial factors including depression are not uncommon in the HF population, with a recent meta-analysis suggesting a point estimate prevalence of 22%, a rate similar to the rate observed in patients with CHD and 2 to 3 times the rate of the general public.[12] Patients with HF and depression perceive the severity of their HF to be worse than objective measurements would indicate and demonstrate greater use of health care services including hospitalization, emergency room visits, and outpatient services, resulting in higher costs of care.[12–16] Moreover, studies evaluating mortality have revealed consistently poorer survival for patients with HF and depression, even when controlling for HF severity.[12,14–17]

Because of poor outcomes reported in the CHD population with depression, there are formal recommendations that patients with CHD be screened for depression and a growing interest in determining whether prognosis can be improved in patients with CHD and HF exhibiting depression.[18] The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial randomized depressed patients after MI, >1/2 of whom had at least a moderate degree of left ventricular dysfunction, to cognitive behavior therapy versus usual care and after an average follow-up of 29 months found improvement in depression and social isolation without any change in survival.[19] Interestingly, in a subsequent publication, the ENRICHD investigators described an association between self-reported exercise after MI and decreased depression; this was further associated with improved survival.[20] Data from randomized trials comparing antidepressive therapies have shown that ET can decrease depressive symptoms as effectively as antidepressant medications.[4,5] Although use of antidepressant medications in patients with HF has been shown to decrease depressive symptoms, studies evaluating their long-term safety have reported mixed results.[14,21–23]

We and others have reported the safety and benefits of ET on conventional and psychological factors in patients with CHD and HF.[6,24] In addition, we recently described a 73% decrease in mortality for depressed patients with CHD who completed an ET program compared to control subjects with CHD and depression.[6] Moreover, the mortality benefit after ET appears to be concentrated to those patients with CHD and adverse psychosocial characteristics including depression, whereas little if any survival advantage was observed in patients who improved exercise capacity but did not have underlying psychosocial distress.[25]

Our findings in the present investigation mirrors the findings observed in the broader CHD population. We confirm that depression carries an adverse prognosis in patients with HF and establish that ET is an effective method for decreasing depressive symptoms in these patients. Moreover, ET offers a mechanism of improving survival in patients with HF, primarily by decreasing the adverse consequences of depression.

The benefit of ET on depressive symptoms is likely multifactorial. Depression has been linked to decreased heart rate variability, blunted baroreflex sensitivity, heightened sympathetic nervous system activity, prolongation of QT interval, increased inflammation, blood hypercoagulability, and endothelial dysfunction, each of which has been associated with adverse clinical outcomes in patients with HF and CHD.[3,14] Moreover, each of these factors has been reported to improve significantly after ET.[24,26,27]

Although a limitation to this study was the lack of a randomized non-ET control group in which depressive symptoms were assessed at 2 points (which makes establishing cause and effect more difficult), we previously demonstrated lack of improvement in most CHD risk factors, including behavioral factors, in control subjects not entering ET after major CHD events.[28] Moreover, data specifically examining depression in patients with CHD over time suggest that the disorder is fairly resistant and likely to remain if left untreated.[29,30] In addition, cardiac rehabilitation and ET is a clinically proved method for decreasing morbidity and mortality in patients with CHD, and a randomized control group not receiving this therapy would be medically unethical.[24] In addition, the instrument used to assess depressive symptoms is not as well established as some other instruments and has not been used in clinical trials of depression. Nevertheless, our incidence rate of depressive symptoms was very similar to that of other investigators and suggests that our sample was representative of patients with HF. More importantly, depressive symptoms demonstrated in this study were associated with markedly increased mortality in patients not completing ET and in those patients with depressive symptoms after ET, thus validating the prognostic impact of this specific assessment.

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