ORIGINAL REPORT

RELATIONSHIP BETWEEN CARDIOPULMONARY FITNESS AND DEPRESSIVE SYMPTOMS IN CARDIAC REHABILITATION PATIENTS WITH CORONARY ARTERY DISEASE

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Objective: **To identify independent predictors of depressive symptoms in a cohort of patients with coronary artery disease entering cardiac rehabilitation.**

Design: **Cross-sectional cohort study.**

Patients and methods: **Consecutive patients entering a cardiac rehabilitation and secondary prevention programme underwent screening for depressive symptoms using the Center for Epidemiological Studies Depression (CES-D) scale and cardiopulmonary fitness testing to quantify peak oxygen consumption.**

Results: **Of the 366 patients with coronary artery disease, 22.3% reported at least mild (CES-D≥16) and 10.4% reported significant (CES-D≥23) depressive symptoms. Antidepressant medications were being used by 6.3% of patients. Sociodemographic, cardiopulmonary and cardiac characteristics, and medical co-morbidities previously associated with depression accounted for 14.7% of the variance in a multiple linear regression model (F=8.713, *p*<0.001) predicting CES-D scores. Significant independent predictors of CES-D scores were lower peak oxygen consumption, younger age, female sex, lower maximum diastolic blood pressure, angina pectoris and antidepressant use.**

Conclusion: **Reduced physical fitness, younger age, female sex and ischaemic symptoms of coronary artery disease predict higher depressive symptoms in patients entering cardiac rehabilitation.**

Key words: depression, coronary disease, exercise test, rehabilitation, physical fitness.

J Rehabil Med 2008; 40: 213–218

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Submitted April 27, 2007; accepted October 16, 2007

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of disability, mortality and healthcare utilization in developed countries. In Canada, one in 4 men and one in 5 women suffer from some form of heart disease. Depressive symptoms are common in persons with CAD, and they increase the risk of mortality independently of medical risk factors (1) and interfere with cardiac rehabilitation (2).

Despite demonstrated correlations between depressive symptoms and low activity levels (3), relatively few investigations have focused on the association between depressive symptoms and cardiopulmonary fitness in patients with CAD (4). Since a primary focus of rehabilitation is to improve cardiopulmonary fitness, the interaction between fitness and depressive symptoms may be of substantial clinical importance. In addition, CAD is associated with multiple co-morbid medical conditions and risk factors. Hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and symptoms of CAD such as angina pectoris have been associated with an increased prevalence of depression (5–8), and medications used in the management of these conditions, such as β-blockers (9) and statins (10), have been suggested to interact with depressive symptoms.

The goal of this study was to measure the prevalence of depressive symptoms and identify independent predictors of depressive symptoms in patients with stable CAD entering cardiac rehabilitation. Knowing predictors may be useful to clinicians and they can be used to inform future studies designed to understand the aetiology of mood complications in this population. The use of psychotropic medications was also characterized in this population. These findings may help to establish strategies to better manage depressive symptoms associated with CAD within the setting of cardiac rehabilitation and to aid in the optimization of rehabilitation for patients suffering depressive symptoms.

METHODS

Setting

This was a cohort study of 366 patients selected from the Toronto Rehabilitation Institute Cardiac Rehabilitation and Secondary Prevention Program (TRI-Cardiac). The TRI-Cardiac is a university-affiliated rehabilitation facility serving an urban population with a catchment area of approximately 2.5 million. Patients recovering from various manifestations of CAD and those with significant cardiac risk factors, various forms of congenital heart defects or diabetes are accepted at the TRI-Cardiac. Enrolment is based on physician referral only. All participants provide written informed consent for their clinical data to be used in research investigations in accordance with the Research Ethics Board.

Subjects

Patient demographics, cardiac and other medical morbidities, medical history, cardiopulmonary fitness testing data and concurrent medications were obtained by electronic chart review. A clinical cohort of patients with CAD entering rehabilitation was defined based on a history of myocardial infarction (MI), coronary angiographic evidence of ≥50% blockage in at least one major coronary artery, or prior revascularization, such as percutaneous coronary intervention (PCI) procedures or coronary artery bypass graft (CABG) surgery at the time of enrolment at the TRI-Cardiac (Fig. 1). All subjects entered rehabilitation a minimum of 6–8 weeks post-CABG (6 weeks for uncomplicated CABG), a minimum of 6 weeks post-MI, or a minimum of 3 weeks post-PCI. Patients were excluded if they did not perform cardiopulmonary fitness testing, if they were unable to complete the Center for Epidemiological Studies Depression (CES-D) scale, or if their records were otherwise incomplete.

Assessments

Depressive symptoms. All patients were screened for depressive symptoms using the CES-D scale. The CES-D scale has been used extensively in CAD populations (9). The concurrent validity, construct validity and reliability of the CES-D have also been established in community samples (11). In addition, a cut-off score of 16 on the CES-D has demonstrated high sensitivity (100%) and specificity (88%) for detecting Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-IIIR) diagnosed depression in older subjects (12) and an adequate sensitivity (60% major depression and 71% minor depression) and specificity (83% and 83%, respectively) in community samples (13). Importantly, increasing rates of medical illnesses are not related to the number of false positives using the CES-D (12).

Cardiopulmonary fitness. As part of standard clinical protocol, a cardiopulmonary fitness assessment was carried out. Clinical assessment was performed under medical supervision by a multidisciplinary team including trained exercise physiologists. The exercise stress test, as previously described (14), was used to measure cardiopulmonary responses to increasing intensities of exercise. Measures included the anaerobic threshold, peak heart rate, maximum blood pressure and peak oxygen consumption (VO_2 peak). The VO_2 peak is the most reliable and reproducible indicator of cardiopulmonary fitness (15). Resting physiological measurements, including heart rate and blood pressure, and anthropometrics including height, mass, girth, and percentage body fat, were recorded. Body mass index (BMI) and waist-to-height ratio (WHtR) were calculated as per standard definitions. Since body mass is a composite of fat and muscle masses, and reduced ratios of muscle to fat have been previously documented in the depressed elderly (16), BMI may be insufficient as an index of body composition. WHtR is an index of relative central adiposity, which does not rely on the measurement of body mass and may therefore demonstrate superiority as a risk factor.

Statistical analysis. Descriptive statistics were calculated for all variables of interest. Continuous measures, such as age, were summarized using means and standard deviations (SD), whereas categorical measures were summarized using counts and percentages.

To determine which clinical variables were the most significant independent predictors of depressive symptoms, a backward elimination linear regression model was performed. Variables associated with depression or depressive symptoms in previous studies of patients with CAD were entered into the model including the sociodemographic characteristics age, sex, smoking status and marital status, the anthropometric characteristics BMI and WHtR, resting physiology including heart rate, systolic and diastolic blood pressure, and cardiopulmonary fitness parameters, including VO_2 peak, maximum heart rate, and maximum systolic and diastolic blood pressures (4–8, 17–20). Cardiac factors, including history of MI, PCI, CABG, congestive heart failure and cardiac arrest, and the presence of hypertension and angina pectoris, and the medical co-morbidities diabetes, COPD, cancer, renal disease and stroke that have been previously associated with depression or depressive symptoms were also entered (5, 21). Concurrent use of statins (10), β-blockers (9), antidepressant or anxiolytic medications that may affect depressive symptoms was also entered into the model. Parameters below 5% significance were omitted until parameters could no longer be rejected (exit criterion $p > 0.05$). All analyses were two-tailed with results considered significant at $p < 0.05$. All analyses were performed using SPSS statistical software (version 13.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics and incidence of depressive symptoms

The sociodemographic characteristics of patients recruited into this study are summarized in Table I.

Between September 2004 and June 2005, there were 366 patients enrolled. Seventy-six percent were male and 71% were married. The mean age of patients was 63.6 (SD 10.7) years. Of all patients, 22.3% ($n = 82$) showed at least mild (CES-D ≥16) and 10.4% ($n = 38$) showed significant (CES-D ≥23) depressive symptoms (Fig. 1).

Only 6.3% of patients ($n = 23$) were using antidepressant medication and 9.3% ($n = 34$) were using an anxiolytic. The most common medications included selective serotonin reuptake inhibitor (SSRI) antidepressants, the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine, and benzodiazepine anxiolytics. Of patients showing significant depressive symptoms (CES-D ≥ 23, $n = 38$), 31 (82%) were not using an antidepressant and of patients showing at least mild depressive symptoms (CES-D ≥16, $n = 82$), 71 (87%) were not using an antidepressant.

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│           366 Participants selected for study     │
│                 •Evidence of CAD                  │
│      •Complete medical chart and fitness data     │
│  •Completion of the CES-D with 4 or less answers missing │
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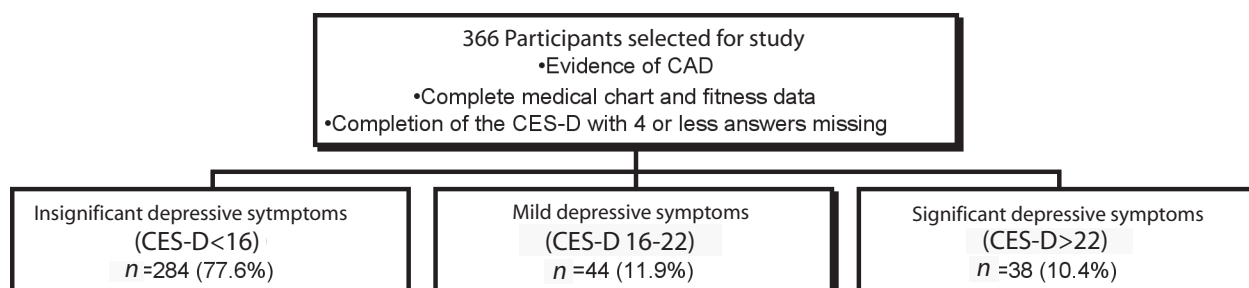| Insignificant depressive sytmptoms (CES-D<16) *n* =284 (77.6%)	Mild depressive symptoms (CES-D 16-22) *n* =44 (11.9%)	Significant depressive symptoms (CES-D>22) *n* =38 (10.4%)

Fig. 1. Definition of cohort with coronary artery disease (CAD). CES-D: Center for Epidemiological Studies Depression Scale.

Table I. *Patient characteristics (n = 366)*

	Prevalence (%)
Sociodemographic	
Age (years)	63.6 (SD 10.7)
Employment	128 (34.9)
Unmarried/divorced/widowed	105 (28.7)
Sex (female)	88 (24.0)
Current smoking status	21 (5.7)
Cardiac factors and diagnoses	
Myocardial infarction	206 (56.2)
PCI	175 (47.8)
Hypertension	170 (46.4)
CABG	136 (37.2)
Valvular heart disease	30 (8.2)
Angina pectoris	29 (7.9)
Conduction deficit	29 (7.9)
Congestive heart failure	23 (6.3)
Cardiac arrest	14 (3.8)
Pacemaker	9 (2.4)
Medical co-morbidities	
Diabetes	103 (28.1)
COPD	27 (7.4)
Cancer	22 (6.0)
Renal disease	18 (4.9)
Stroke	15 (4.1)
Peripheral vascular disease	14 (3.8)
Concomitant medications	
Statins	335 (91.5)
ß-blockers	301 (82.2)
Nitroglycerin	151 (41.3)
Anti-diabetic agents	77 (21.0)
Ca^{2+}-channel antagonists	68 (18.6)
Anti-asthmatic agents	29 (7.9)
Psychotropic medications	
Anxiolytics	34 (9.3)
Antidepressants	24 (6.3)
Other classes	5 (1.4)

PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease.

Physiological and cardiopulmonary characteristics

Patient physiological and exercise characteristics are summarized in Table II. The mean VO_2 Peak was 17.1 (SD 4.7) ml/

Table II. *Patient physiological characteristics*

	Mean (SD)
Anthropometric	
BMI, kg/m^2	28.0 (4.7)
Percentage body fat, %	28.8 (9.1)
Waist-to-height ratio	0.569 (0.074)
Resting physiology	
Resting heart rate, bpm	66.9 (12.7)
Resting systolic BP, mmHg	131.8 (20.2)
Resting diastolic BP, mmHg	72.9 (9.6)
Fitness parameters	
VO_2 peak, ml/kg/min	17.1 (4.7)
Anaerobic threshold, ml/kg	13.2 (3.0)
Maximum heart rate, bpm	113.1 (22.3)
Maximum systolic BP, mmHg	176.6 (28.2)
Maximum diastolic BP, mmHg	79.1 (11.9)

BMI: body mass index; VO_2 peak: peak oxygen consumption; BP: blood pressure.

kg/min, which is approximately 65% of an age-matched norm and considered very poor for patients of this age. The mean BMI was found to be 28.0 (SD 4.7) kg/m^2, which is associated with an increased risk of cardiovascular complications. Of all patients, 45.1% were classified as overweight (BMI between 25 and 30 kg/m^2) and 27.3% were classified as obese (BMI ≥ 30 kg/m^2). The mean WHtR was found to be 0.569 (SD 0.074), which is classified as overweight and characterizes the risk of cardiovascular complications to be significant.

Predictors of depressive symptoms

When sociodemographic variables, cardiac factors, medical co-morbidities, concomitant medications and fitness parameters previously associated with increased depressive symptoms were entered into a backward linear regression, 6 variables remained in the model accounting for 14.7% of the variance (F = 8.713, $p < .001$). Table III contains coefficients obtained in the final regression model. This model suggests that a 1 ml/kg/min decrease in VO_2 peak is associated with a 0.424-point increase in CES-D score, that a one year decrease in age is associated with a 0.17 point increase in CES-D score, and that a 1 mmHg decrease in maximum diastolic blood pressure is associated with a 0.105-point increase in CES-D score. Those with angina pectoris had a 5.8-point higher CES-D score on average than those without angina. Females had a 2.8-point higher CES-D score on average than males. Patients using an antidepressant had a 5.6-point higher CES-D score on average than those not using an antidepressant.

DISCUSSION

A significant correlation between VO_2 peak and CES-D scores was identified in a population of patients with CAD entering rehabilitation. This finding is consistent with the few available reports of correlations between reduced cardiopulmonary fitness and depressive symptoms in patients with CAD (4, 18). A correlation between VO_2 peak and depressive symptoms has also been identified in women showing no clinical evidence of cardiovascular disease (16) suggesting that the relationship between depressive symptoms and fitness may be of broad clinical importance. The present study demonstrates the importance of the VO_2 peak, as it emerged as the strongest predictor of CES-

Table III. *Coefficients of linear regression model predicting CES-D scores* *

Independent variables	Coefficient (B)	Standard error	p
VO_2 peak	–0.424	0.128	0.001
Age	–0.170	0.053	0.001
Angina pectoris	5.848	1.854	0.002
Sex	2.795	1.329	0.036
Maximum diastolic BP	–0.105	0.047	0.026
Antidepressant use	5.607	2.172	0.010

*R = 0.408, R-square = 0.166, adjusted R-square = 0.147,
Standard error of the estimate = 8.302, $p < 0.001$.

VO_2 peak: peak oxygen consumption; BP: blood pressure; CES-D: Center for Epidemiological Studies Depression Scale

D scores, independent of age, sex, medical complications and concurrent medications. This finding may have implications for treatment. It is possible that exercise prescriptions aimed at improving cardiopulmonary fitness may also be beneficial for the improvement of depressive symptoms in persons with CAD. Longitudinal studies show that depressive symptoms tend to decrease over the course of cardiac rehabilitation (22), though it remains unclear which aspects of rehabilitation may be beneficial and whether this improvement is related to an increase in VO$_2$ peak. It is also possible that depression and cardiovascular disease share aetiological underpinnings, such that, rather than treating sequelae, treatment impacting underlying causal factors will be necessary to improve both cardiac outcomes and depressive symptoms.

It has been speculated that psychological features of depression, such as reduced motivation, anhedonia and introversion, could result in an ongoing reduction in physical activity levels and contribute to reduced cardiopulmonary fitness in depressed subjects (16). Sustained inactivity could lead to loss or weakening of muscle tissue or affect neuronal pathways that regulate heart rate and cardiac output. As a limitation of this study, psychological variables, such as the roles of psychosocial wellbeing and social readjustment, were not formally assessed. Cardiac rehabilitation may help to improve VO$_2$ peak by interacting with psychological features of depression, reducing motivational barriers and modifying behaviours not conducive to maintaining both cardiac health and positive affect.

In addition to psychological factors, physiological processes associated with depressive symptoms might interact with physical fitness. Recently, plasma levels of interleukin-6, a circulating pro-inflammatory cytokine, have been inversely correlated with the VO$_2$ peak in asymptomatic men (23). Elevated levels of these cytokines, indicating activation of the inflammatory system, have also been observed in major depressive disorder where they could directly elicit depressive symptoms and thus contribute to reduced physical activity (24). As atherosclerosis and poor CAD prognoses have been associated with inflammatory activation (25), this hypothesis may be particularly relevant. In this report, increased depressive symptoms were found in patients with angina pectoris, which has been associated with increased plasma levels of pro-inflammatory cytokines (26). Elevated levels of pro-inflammatory cytokines have also been associated with feelings of exhaustion (27), which may be related to cardiopulmonary fitness and contribute to depressive symptoms. These potential mechanisms require further investigation.

Only 24% of subjects included in this study were female, in agreement with previous reports that female patients are less likely to enrol in cardiac rehabilitation following acute coronary events (28). This suggests the need to investigate possible gender-biases in patient attitudes towards rehabilitation or in physician referrals to rehabilitation. A significant association between female sex and increased CES-D scores was found, indicating that female sex independently predicted increased depressive symptoms. This is in accord with other reports that females are at increased risk of depressive symptoms among cardiac rehabilitation participants (17). This may be

of particular importance, since female patients and those with higher depressive symptoms are less likely to complete cardiac rehabilitation. However, when female patients and those with significant depressive symptoms complete rehabilitation, they show significant improvements in lipid profile, BMI and exercise capacity (2). This suggests that developing methods to improve adherence to rehabilitation in women and depressed patients may be of substantial clinical benefit. Behaviour change theory has been suggested as a guiding principle in the design of novel individualized physical activity interventions for women, which could be integrated into cardiac rehabilitation. In one small trial, women who were randomized to a self-efficacy based intervention showed improvements in physical activity levels and cardiopulmonary fitness, whereas women randomized to a more traditionally structured exercise programme did not (29). Follow-up intervention has also been shown to protect against symptoms of anxiety and depression in women, while improving long-term risk-factor management (30). Cardiac rehabilitation may be an ideal setting to implement additional female gender-focused support.

Depressive symptoms could also be predicted by younger age. This is consistent with reports of increased psychological distress in younger patients with CAD (31). It is possible that depressive symptoms and CAD share common aetiopathological factors that mediate the association between depression and poorer CAD prognosis. Patients presenting at a younger age with complications of CAD therefore may be more severely affected by a process that also predisposes them to depressive symptoms. This hypothesis is supported by the observation of increased coronary risk factors in younger patients with CAD (31).

Reduced maximum diastolic blood pressure during fitness assessment was independently correlated with CES-D scores, although a correlation with resting diastolic blood pressure was not observed. In studies of older populations, low resting diastolic blood pressure has been associated with depressive symptoms (20), inciting considerable debate concerning possible consequences of aggressive antihypertensive treatment, which may include depressive symptoms and increased risks of cardiac and all-cause mortality (32). However, in this population, the correlation of lower maximum diastolic blood pressure with higher CES-D scores could not be accounted for by controlling for hypertension or the use of antihypertensive medications, and the use of antihypertensives was not associated with low blood pressure. This is consistent with another report associating low resting blood pressure with anxiety and depression independently of antihypertensive treatment (20). Reduced maximal blood pressure during stress testing may be related to depressive symptoms through dysregulation of central neuroendocrine systems. For example, chronic activation of the hypothalamic-pituitary-adrenocortical axis in depressed patients could result in abnormal glucocorticoid feedback regulation of this axis, or desensitization of pressor responses by down-regulation of adrenergic receptors. This could result in the blunted physiological responses to physical exertion observed in CAD patients with depressive symptoms, which is reminiscent of the blunted hypothalamic-pituitary-

adrenocortical responses documented in patients with depression secondary to other medical illness (33). Lower maximum diastolic blood pressure was correlated with CES-D scores even when controlling for age and the use of antidepressant medications.

The rate of antidepressant use in this population was comparable to that reported in other studies of cardiac rehabilitation patients (34). Of patients showing significant depressive symptoms only 18% were using an antidepressant. This suggests that antidepressant medication may be underutilized in this population and that systematic screening for depression at entry into cardiac rehabilitation could help to fulfil an unmet need. It is possible that treatment of depressive symptoms may improve cardiac rehabilitation outcomes. Antidepressant use has been associated with reduced rates of mortality and recurrent MI in post-MI patients with depression (35). Similarly, depression has been associated with a reduced likelihood of completing rehabilitation (22) and treatment of depressive symptoms may interact with adherence to rehabilitation exercise prescriptions. Conversely, adverse risk profiles have been associated with the use of some antidepressants in certain patients with CAD (35), cautioning physicians to choose safe and effective treatments.

Limitations of this study include lack of a diagnostic interview for depression and a lack of recorded psychiatric history. In these patients, it is not known whether psychiatric symptoms preceded or followed acute coronary events. In future studies, it would be interesting to determine if the clinical characteristics of patients with a pre-morbid psychiatric condition differ from those who suffer depressive symptoms for the first time following an acute coronary event. A further limitation was the absence of an assessment of CAD severity. However, available indicators such as cardiac risk factors and medical/surgical histories were not correlated with CES-D scores and did not differ significantly between those who used antidepressants and those who did not, suggesting that differences in the severity of CAD do not account for the observed associations between depressive symptoms and cardiopulmonary fitness.

In summary, depressive symptoms are prevalent among patients with stable CAD entering cardiac rehabilitation and they are frequently untreated. Of the investigated parameters, the most significant independent predictor of depressive symptoms was the VO_2 Peak during cardiopulmonary fitness assessment. Depressive symptoms were also predicted by younger age and female sex. The correlation between depressive symptoms and reduced physiological responses to exercise suggests the need to investigate possible psychological and physiological mechanisms mediating this correlation. An increased focus on psychological/psychiatric screening and intervention may improve the effectiveness of cardiac rehabilitation.

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