Depression anticipate patients at risk of poor exercise stress test performance after percutaneous coronary angioplasty: A short-term longitudinal study

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Abstract

Aims

The exercise stress test is commonly used to assess physical capacity and recovery in coronary artery disease (CAD) patients after percutaneous transluminal coronary angioplasty (PTCA). Despite depressive symptoms have been consistently associated with adverse outcomes in CAD patients, they are rarely considered as risk factors of poor exercise test. The present study investigated the influence of depressive symptoms, along with anxiety, sleep problems and perceived health on exercise test in PTCA patients.

Methods

One hundred and sixty-five patients who underwent PTCA completed the Beck Depression Inventory-II (BDI-II), the Beck Anxiety Inventory, the Sleep Condition Index and the 12-item Short-Form Health Survey and, after 20 days, underwent exercise stress test.

Results

Higher BDI-II scores significantly predicted lower maximal workload measured in metabolic equivalents (METs; $\beta = -0.13$; $p = .030$), shorter total exercise duration ($\beta = -5.23$; $p = .034$) and the inability to reach maximum heart rate during exercise test (OR = 1.07; $p = .032$), even after controlling for relevant sociodemographic and biomedical risk factors.

Conclusions

Depressive symptoms specifically predicted worse exercise stress test performance in patients after PTCA, controlling for common risk factors. Focusing on the assessment of depressive symptoms, in addition to sociodemographic and biomedical

risk factors, is essential to anticipate patients at risk of poor physical capacity after PTCA.

Keywords: Depressive symptoms, Coronary artery disease, Exercise stress tests, Percutaneous transluminal coronary angioplasty.

Introduction

Exercise stress testing is a reliable and widely applied method that identifies exercise-related symptoms, evaluates physical capacity and effort tolerance to detect patients with CAD and predict the risk of cardiovascular events (1–4). Most importantly, exercise stress testing is commonly applied for the assessment of cardiac functionality after a revascularization intervention (such as CABG and PTCA; 4,5) and to assess the effectiveness of cardiac rehabilitation interventions (6).

Several factors, the most important being the sociodemographic and biomedical ones, have been reported to impact negatively on exercise stress test outcomes, such as older age, lower body surface area, female sex, previous myocardial infarction (MI) and the presence of comorbidity (3,7). Among behavioral risk factors, poor physical activity has been consistently associated with scarce physical capacity in the general population and (3,5), most importantly, in patients with cardiovascular disorders (7). Indeed, improving physical capacity through physical exercise training is one of the primary outcomes of cardiac rehabilitation after a revascularization intervention (6).

Despite the well-known role of sociodemographic, biomedical and behavioral risk factors, in the last decades, the negative impact on cardiovascular risk of some psychological factors, the most important being depressive symptoms, has been consistently reported. Indeed, depression has been associated with the presence of cardiovascular disorders (CVD; 8), with CAD onset risk (9), premature (10) and all-cause mortality (11) in patients with CAD. The role of depression on adverse cardiovascular outcomes has been explained through both biological and behavioral mechanisms (for a review see (11). More importantly, depression affect patients' physical capacity (7,12,13), as well as the effectiveness of cardiovascular rehabilitation after a

revascularization procedure (14–16). This, in turn, could damage the short and long-term quality of life, as well as the survival rate in patients who underwent revascularization intervention (17).

Remarkably, a limited number of studies focused on how depressive symptoms impact on exercise stress test performance in patients with CAD (18–20) and patients who underwent revascularization intervention (21). In CAD patients depressive symptoms resulted independently associated with poor exercise capacity (18,20), and low exercise tolerance and performance (19). In the only study, to our knowledge, including patients who underwent a revascularization intervention, depressive symptoms were related to impaired heart rate (HR) recovery after exercise stress testing. Nonetheless, this relation did not survive after controlling for patients' physical activity. To notice, the study sample comprised patients who underwent PTCA as well as CABG surgery, patients after MI, and patients with angina (21). In turn, differences in patients' clinical conditions may have confounded the results of this study.

None of these studies included the evaluation of comorbid symptoms such as anxiety, sleep problems and perceived health (18–21). This is surprising considering that depression has much in common with anxiety, sharing diagnostic criteria such as restlessness, agitation, concentration difficulties, and sleep problems (22). More importantly, CAD patients often show depressive symptoms along with abnormal anxiety (23), lower quality of sleep (24), and lower perceived physical and mental health (25). A few studies examined the role of both depression and anxiety on exercise stress testing in patients with chest pain (12,13), and in patients after acute MI (7), reporting mixed results. In patients with chest pain, both anxiety and depression were found to negatively affect exercise stress test performance (13): a poorer exercise stress test was

104 predicted by depression in men and by anxiety in women (12). On the contrary, in
105 patients after acute MI a specific relation between depressive symptoms and exercise
106 stress test performance emerged (7). Therefore, the role of depression, anxiety or
107 comorbid symptoms, such as sleep problems and perceived health, on exercise stress
108 test performance is uncertain.
109 No study so far has specifically focused on the influence of depression – along
110 with anxiety, sleep problems and perceived health – on performance at the exercise
111 stress test in CAD patients who underwent PTCA. The aim of the present (short-term)
112 longitudinal study was to investigate the predictive role of depressive symptoms
113 measured when the patients were referred to a cardiovascular visit to the unit of cardiac
114 rehabilitation (about 25 days after PTCA procedure, T0) on outcomes of exercise stress
115 test performance assessed 15-20 days after T0 (i.e., T1). The measures used to assess
116 performance at the exercise stress test were the maximal workload assessed as
117 metabolic equivalent of task (MET), the total exercise duration (expressed in seconds),
118 and the ability to reach maximum heart rate during the test. It was hypothesized that
119 depressive symptoms, along with anxiety, sleep problems and perceived health, would
120 significantly predict a worse outcome in the exercise stress test in CAD patients who
121 underwent PTCA, even after controlling for sociodemographic, biomedical risk factors
122 and physical activity.
123
124 **Materials and Methods**
125 *Participants*
126 A total of 289 consecutive patients referred to a cardiovascular visit to the Unit of
127 Cardiac Rehabilitation, ULSS 6 Euganea, (Padua, Italy) between March 2019 and

December 2019, were approached to participate in the study. Of the 289 patients approached, 58 (20%) were unable to take part in the study and 10 (3%) declined participation (see Figure 1). Exclusion criteria were: inability to read or to understand Italian; procedure different from PTCA, such as heart valve surgery or CABG surgery; visual or auditory impairments; incomplete data collection; conflicting research protocol; psychiatric illness; life-threatening condition; a history of symptomatic cerebrovascular disease and/or neurological deficit as obtained from patient's medical records and confirmed by medical staff. Two hundred and twenty-one patients were recruited, and 41 patients were excluded since they did not meet inclusion criteria (1 patient was excluded for inability to read or to understand Italian, 12 patients underwent CABG surgery, 15 patients had heart valve surgery and 13 patients underwent combined or another type of cardiac intervention). Therefore, 180 patients met the inclusion criteria and were evaluated. Fifteen patients (5%) were excluded from data analysis because data of stress test exercise were incomplete. The final sample included 165 patients, mostly men (n = 144, 87%), with a mean [standard deviation (SD)] age of 61.88 (9.98) years and a mean (SD) education of 11.93 (4.28) years. None of the patients included in the study were being treated for depression with medications and/or psychotherapy. The study was conducted in accordance with the Declaration of Helsinki, and all procedures were performed with an adequate understanding and written consent of the patients. This study was part of a larger research project

conducted at the Unit of Cardiac Rehabilitation, ULSS 6 Euganea (Padua, Italy) that was approved by the local ethics committee (prot. No. 209498).

Assessment of sociodemographic, biomedical, physical activity and psychological risk factors

The assessment was performed about 25 days (mean [SD] days 25.07 [17.85]) after the revascularization intervention on the same day of the cardiovascular visit at the Unit of Cardiac Rehabilitation. A short semi-structured interview and four questionnaires were administered individually by a trained psychologist in a quiet and isolated room. The semi-structured interview included the evaluation of sociodemographic (age, gender, education and smoking habits) factors, the patient's medical history (including, cardiac risk factors such as the presence of hypertension, atrial fibrillation, diabetes, dyslipidemia, and previous stroke; pharmacological treatment, including β-blockers, antihypertensive, antiarrhythmics, anticoagulants, and ACE-inhibitors; biomedical factors such as days from surgery) and physical activity (number of days in the last week in which patients walked for at least 10 minutes). Mean blood pressure (MBP), mean heart rate (HR), white and red blood cells, levels of glycemia, creatinine, sodium, and potassium, aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alanine aminotransferase (ALT), creatine phosphokinase (CPK), high- and low-density lipoprotein cholesterol (HDL and LDL), total cholesterol and triglycerides were obtained from patient's most recent medical record. Depressive

and anxiety symptoms, sleep problems, and perceived physical and mental health were assessed employing the following standardized questionnaires:

1. The Beck Depression Inventory-II (BDI-II) is a reliable and valid 21 items self-report questionnaire that evaluates the severity depressive symptoms in the last two weeks (26,27). Scores below 13 reflect minimal depressive symptoms, scores from 14 to 19 indicate mild depression, scores from 20 to 28 reflect moderate depression, scores from 29 to 63 suggest severe depression (27).
2. The Beck Anxiety Inventory (BAI; 30,31) has been reported to be a reliable and valid measure of anxiety symptoms in community samples (28). A score below 7 indicates minimal anxiety symptoms, scores between 8-15 reflect mild anxiety, scores between 16-25 reflect moderate anxiety symptoms and scores from 26-63 suggest severe anxiety (29).
3. The Sleep Condition Indicator (SCI) is a brief screening compliant with the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5; 32) to evaluate sleep problems and insomnia in the last month (31). A total score below 16 has been suggested to reflect the minimum criteria for putative insomnia disorder.
4. The 12-item Short-Form (SF-12) Health Survey (32,33) is a valid and reliable measure of general health status in the cardiac population (34,35) and covers

two components of HRQoL: a Physical Component Scale (SF-12 PCS) and a Mental Component Scale (SF-12 MCS).

Indices of stress test performance and cardiovascular measures

The exercise stress test was carried out in a standardized fashion using an electrically braked bicycle ergometer 15 to 20 days after the administration of questionnaires. All patients were tested in the morning in a room with a constant temperature (21-23 °C). Patients' maximal workload (METs), total exercise duration (sec), resting and peak exercise heart rate (HR), mean blood pressure (MBP) and % maximal predicted heart rate (%MPHR; based on the 220-age equation) were evaluated by an experienced cardiologist trained in the administration and the assessment of the exercise test. Patients' ability to reach 85% of maximal age-predicted heart rate was applied as an exercise endpoint that estimates the achievement of an adequate stress level. The exercise stress test was carried out following a standardized multistage protocol following the guidelines (5), with the initial workload set at 25 watts, and 25-watt increments at 3-minute intervals until exhaustion or achievement of maximal heart rate. HR was measured with a standard 12-lead ECG configuration (XSCRIBE 6, Mortara, Casalecchio di Reno, Bologna Italy or CASE v6.7, GE Healthcare, Chicago Illinois), and MBP was measured with a manual sphygmomanometer.

Statistical analysis

Depressive symptoms (BDI-II scores) were compared with a t-test between patients in the final sample (n = 165) and patients who were excluded from the study (12 patients who underwent CABG surgery, 15 patients who had heart valve surgery, 13

patients who underwent combined or another type of cardiac intervention and 15 patients with incomplete stress test exercise data). A series of hierarchical regression models were computed to predict maximal workload (METs) and total exercise duration (sec) from questionnaires scores (i.e., BDI-II, BAI, SCI, SF-12 PCS, SF-12 MCS). Since depressive symptoms are strongly correlated with anxiety symptoms as well as sleep problems and physical and mental perceived health, the association between questionnaires' scores were tested through Pearson's r correlation. To avoid for multicollinearity and to test whether specific symptoms associated with depression (anxiety, sleep problems, perceived physical or mental health) were individually involved in predicting maximal workload (METs) and total exercise duration (sec), five different regression models (i.e., one for each questionnaire) were run for each exercise test outcome. Five binomial logistic regressions were also computed to predict patients' ability to reach exercise endpoint (defined as %MPHR higher than 85; 38) from questionnaires scores (i.e., BDI-II, BAI, SCI, SF-12 PCS, SF-12 MCS). All models were controlled for sociodemographic (i.e., age, sex, smoking habits, and BMI), biomedical variables (i.e., days from surgery, β-blockers therapy, resting MBP, resting HR, CPK levels), and physical activity (i.e., walking). Multicollinearity diagnostics showed that all the variables entered in regression models had acceptable levels of collinearity (variance inflation factor < 4, tolerance > 0.03; 37). Whether a questionnaire's score resulted to significantly predict patients ability to reach exercise endpoint, the Youden index was calculated to identify the criterion for selecting the optimum cut-off point when a diagnostic test (in this case the questionnaire score) identifies a dichotomous result (in this case patients' ability or inability to reach exercise endpoint). All analyses

were performed using Jamovi version 0.9. A *p*-value < .05 was considered statistically significant.

Results

Questionnaires scores

Mean (SD) BDI-II score was 7.32 (6.48). 132 (80%) patients showed minimal depressive symptoms (BDI-II scores 0–13), 21 (13%) patients had mild depression (BDI-II scores 14–19), 8 (5%) patients had moderate depression (BDI-II scores 20–28), and 4 (2%) patients reported severe depression (BDI-II scores 29–63). No differences emerged in depressive symptoms between the patients in the final sample and the patients excluded (mean (SD) = 8.71 (7.48); t = -1.32, *p* = .188).

Mean (SD) BAI score was 8.46 (7.30). 87 (53%) patients showed minimal anxiety symptoms (BAI scores 0–7), 56 (34%) patients had mild anxiety (BAI scores 8–15), 17 (10%) patients showed moderate anxiety (BAI scores 16–25), and 5 (3%) patients had severe anxiety (BAI scores 26–63).

Score at the SCI was mean (SD) 24.63 (6.19), 21 (13%) patients reported a total score above the cut-off reflecting the presence of clinically relevant sleep problems.

Patients perceived physical (SF-12 PCS) and mental (SF-12 MCS) health scores were mean (SD) 42.50 (8.54) and 45.67 (10.74), respectively. Both scores resulted lower compared to those registered by the general population (33).

BDI-II scores were correlated with the questionnaires measuring anxiety (BAI; r = 0.58, *p* < .001), sleep problems (SCI; r = -0.46, p < .001), perceived physical (SF-12 PCS; r = -0.35, *p* =.013) and mental (SF-12 MCS; r = -0.60, *p* < .001) health.

Predictors of maximal workload (METs)

Regarding the exercise stress test mean (SD) maximal workload (METs) was 9.44 (5.56). The final block of the hierarchical linear regression predicting maximal workload (METs) from BDI-II scores controlling for sociodemographic, biomedical variables and physical activity showed that younger age, male sex, no and past smoking, lower resting MBP and HR, CPK levels, more frequent physical activity and lower BDI-II scores predicted higher maximal workload at the stress test (Table 2). Sociodemographic factors (first regression block) accounted for 29% of maximal workload variance, reaching statistical significance for the model ($p < .001$). Biomedical factors (second regression block) accounted for additional 10% of variance ($\Delta R^2 = .10$, $p < .001$). Depressive symptoms alone explained a significant increase of 2% of variance in maximal workload ($\Delta R^2 = .02$, $p = .030$). An increase of eight points on the BDI-II scale predicted a reduction of 1 MET in maximal workload (see Figure 2.a).

The regression models including anxiety symptoms (BAI; Estimate = -0.09, SE = 0.05, 95% C.I. [-0.18 0.01], t = -1.77, $p = .078$), sleep problems (SCI; Estimate = -0.02, SE = 0.58, 95% C.I. [-0.14 0.09], t = -0.43, $p = .669$), physical (SF-12 PCS; Estimate = 0.05, SE = 0.04, 95% C.I. [-0.04 0.13], t = 1.06, $p = .289$) and mental health (SF-12 MCS; Estimate = 0.04, SE = 0.03, 95% C.I. [-0.02 0.11], t = 1.33, $p = .186$) showed no effects of those factors on maximal workload (all p's > . 078).

Predictors of total exercise duration (sec)

The mean (SD) of total exercise duration (sec) was 828.85 (264.23). The final block of the hierarchical linear regression predicting total exercise duration (sec) from BDI-II scores controlling for sociodemographic, biomedical and behavioral variables

yielded a significant effect of younger age, male sex, no and past smoking, higher BMI, CPK, greater physical activity, and lower BDI-II scores in predicting longer total exercise duration (Table 3). Specifically, sociodemographic factors (first regression block) accounted for 44% of exercise duration variance, reaching statistical significance for the model ($p < .001$). The biomedical and behavioral factors (second regression block) accounted for additional significant 8% of variance ($\Delta R^2 = .08$, $p = < .001$). Depressive symptoms alone explained a significant increase of 1% of variance in total exercise duration ($\Delta R^2 = .01$, $p = .034$). The regression models including anxiety symptoms (BAI; Estimate = -2.77, SE = 2.08, 95% C.I. [-6.87 1.34], t = -1.33, $p = .185$), sleep problems (SCI; Estimate = -0.39, SE = 2.48, 95% C.I. [-5.28 4.51], t = -0.16, $p = .876$), physical (SF-12 PCS; Estimate = 2.52, SE = 1.87, 95% C.I. [-1.16 6.21], t = 1.35, $p = .178$) and mental health (SF-12 MCS; Estimate = 2.61, SE = 1.45, 95% C.I. [-0.25 5.47], t = 1.80, $p = .074$) showed no effects of those factors on total exercise duration (all p's > .074).

Predictors of the inability to reach exercise endpoint

One hundred eighteen patients (72%) were unable to reach exercise endpoint (HR > 85% of MPHR). The last block of the first binomial logistic regression yielded that patients' inability to reach exercise endpoint was predicted by higher BMI, lower physical activity, and higher BDI-II scores (Table 4). The inability to reach exercise endpoint was predicted by the presence of higher depressive symptoms (OR = 1.07, 95% CIs = 0.01-0.13, $p = .032$). Sociodemographic factors (first regression block) accounted for 5% of variance explaining the probability of the patients to fail achieving exercise endpoint, not reaching statistical significance for the model ($p = .058$). The Area Under the Curve (AUC) determined by the first block (including sociodemographic

characteristics) was .66 (accuracy = .73, specificity = .06, sensitivity = .99). Biomedical factors (second regression block) did not significantly add explained variance compared to the first block (χ^2 = 9.68, p = .139). Adding biomedical characteristic led to an AUC of .70 (accuracy = .76, specificity = .26, sensitivity = .96). The inclusion of depressive symptoms significantly added 3% explained variance to the model (χ^2 = 5.06, p = .024). The AUC of the final model including depressive symptoms was .73 (accuracy = .77, specificity = .32, sensitivity = .95), indicating that the total model is moderately accurate to identify individuals at risk for patients' inability to reach exercise endpoint (see Figure 2.b).

The regression models including anxiety symptoms (BAI; Estimate = 0.04, SE = 0.03, 95% C.I. [-0.02 0.09], Z = 1.30, p = .195, OR = 1.04), sleep problems (SCI; Estimate = 0.01, SE = 0.03, 95% C.I. [-0.05 0.07], Z = 0.38, p = .704, OR = 1.01), physical (SF-12 PCS; Estimate = -0.01, SE = 0.02, 95% C.I. [-0.06 0.03], Z = -0.48, p = .635, OR = 0.99) and mental (SF-12 MCS; Estimate = -0.01, SE = 0.02, 95% C.I. [-0.05 0.02], Z = -0.81, p = .420, OR = 0.99) health showed no effects of those factors on the inability to reach exercise endpoint (all p's > . 195).[1]

[1] To examine the separate impact of somatic-affective and cognitive symptoms of depression, additional regression models including somatic-affective and cognitive subscale of the BDI-II questionnaire were computed on exercise stress test outcomes. Results showed that somatic-affective subscale significantly predicted the maximal workload in METs (Estimate = -0.17, SE = 0.08, 95% C.I. [-0.34 -0.01], t = -2.05, p = .042) and the inability to reach exercise endpoint (Estimate = 0.96, SE = 0.05, 95% C.I. [0.002 0.19], Z = 2.00, p = .045, OR = 1.10). Cognitive symptoms of depression alone were marginally associated to the maximal workload in METs (Estimate = -0.26, SE = 0.14, 95% C.I. [-0.53 0.01], t = -1.87, p = .064) and the inability to reach exercise endpoint (Estimate = 0.16, SE = 0.08, 95% C.I. [-0.003 0.32], Z = 1.93, p = .054, OR = 1.17). Cognitive symptoms of depression significantly predicted total exercise duration in sec (Estimate = -112.21, SE = 5.82, 95% C.I. [-23.71 -0.71], t = -2.10, p = .038), whereas somatic-affective symptoms of depression were marginally associated to total exercise duration in sec (Estimate = -6.63, SE = 3.59, 95% C.I. [-13.73 0.47], t = -1.85, p = .067).

Concerning optimal cut-off, the analysis showed that a BDI-II score > 9 corresponds to a higher probability for the patient to fail in reaching exercise endpoint (Youden index J = .14, sensitivity = .31, specificity = .83).

Discussion

The present short-term longitudinal study investigated the predictive role of depressive and anxiety symptoms, sleep problems and perceived health on exercise stress test performance in CAD patients after a PTCA intervention. Depressive symptoms were found to negatively affect maximal workload (METs), such that an increase of 8 points on the BDI-II questionnaire predicted a reduction of 1 MET in maximal workload. This is of clinical relevance because METs, as a measure of energy expenditure, have been associated with higher total and cardiovascular mortality (38,39). Specifically, a reduction in exercise capacity by 1 MET was linked to an increase in mortality by 15–19% in a longitudinal study (41). Higher depressive symptoms were associated also with a shorter total duration of the test, such that an increase of eleven-point on the BDI-II scale was associated with a performance about 1 minute shorter. Higher depressive symptoms significantly predicted the inability of a patient to reach exercise endpoint, controlling for sociodemographic, biomedical risk factors and physical activity. Intriguingly, a score higher than nine in the BDI-II was the optimal cut-off corresponding to a significantly higher risk to fail in reaching exercise endpoint.

These results support the predictive role of depressive symptoms on short-term impaired performance at the exercise stress test after PTCA, suggesting a compromised physical capacity. Overall, the current results are in line with those of previous studies reporting that depressive symptoms are associated with poor performance in stress test

exercise in CAD patients (18–20), in patients after a revascularization procedure (21), and in patients after acute MI (7).

Although there is some evidence showing depression-related impaired stress test outcomes, to our knowledge, this is the first study showing specifically the predictive role of depressive symptoms on stress test exercise in CAD patients who underwent PTCA. In previous studies, this association has been shown to survive even after adjusting for sociodemographic and biomedical variables, such as age and sex (19). However physical activity has been overlooked in those studies (18–20). In one study examining a broad sample including patients who underwent a revascularization intervention, the relation between depression and poor exercise stress test did not survive after controlling for physical activity (21). In turn, differences in patients' clinical conditions may have confounded the results.

Of note, in the present study, the negative impact of depression on the exercise stress test in patients after PTCA was not only controlled for the most important sociodemographic and biomedical risk factors but also for physical activity. Accordingly, this suggests that the influence of depressive symptoms on exercise function did not overlap with that of other variables, including cardiovascular functioning and physical exercise. Hence, these findings underline the relevance of including a psychological evaluation of depression, which, in turn, may improve the accuracy of the existing methods used to assess functional status in patients with CAD.

In the present study, 20% of patients had some depressive symptoms (ranging from mild to severe depressive symptoms). The prevalence of depressive symptoms in the present study's sample is consistent with that reported in a recent large meta-analysis (Correa-Rodríguez et al., 2020). Depression was assessed as the patients'

referred severity of depressive symptoms during the past two weeks. It is important to note that subclinical depression shares diagnostic criteria with major depressive disorder, but it satisfies fewer criteria. Depressive symptoms include affective symptoms such as depressed mood or anhedonia as well as somatic symptoms, such as sleep disturbances, alterations in appetite and sexual desire, fatigue, restlessness, agitation (30). Most importantly, diagnostic criteria for depression often overlap with general anxiety disorder criteria (30). In CAD patients depressive symptoms along with anxiety symptoms, are often associated with scarce sleep quality (24) and low perceived physical and mental health (25), making it hard to disentangle whether poor physical capacity is determined by depressed mood or by the presence of a broad psychopathological condition. Present results suggest that higher depressive symptoms are associated with poor exercise stress test performance, whereas anxiety symptoms, sleep problems, and perceived health seems to be unrelated to exercise test outcomes. The few previous studies that investigated the role of psychological symptoms on exercise test performance report mixed findings (7,12,13). In patients with chest pain, both anxiety, and depressive symptoms were found to affect exercise test performance (12,13), on the contrary, in patients after acute myocardial infarction, a specific role of depressive symptoms on exercise test performance emerged (7). Consistent with this finding, the present results suggest that depressed mood could be specifically associated with lower exercise test performance, which in turn could negatively affect the rehabilitation program (14).

In this context, it has to be noted that somatic symptoms of depression are relevant in patients with CAD because cardiovascular symptoms can overlap, at least partially, with those of depression (e.g., fatigue, agitation, lack of energy, sleep

difficulties). In turn, this might dramatically reduce the ability of the clinician to recognize those patients who are at higher risk (40). For these reasons, it has been suggested that the evaluation of patients undergoing cardiac rehabilitation needs to incorporate clinical assessment of depression (41). Indeed, cardiac rehabilitation may be much less effective for cardiac patients with depressive symptoms as compared to patients without depression (14). The lower adherence and effectiveness of rehabilitation programs in depressed patients could contribute to the successive higher risk for readmission (42) and reduced quality of life (43). The inclusion of psychoeducational interventions in cardiac rehabilitation programs has been suggested to improve patients' recovery by reducing cardiovascular risk behaviors (e.g., smoking), anxiety and depression (44). Intriguingly, biobehavioral interventions, such as cardiorespiratory biofeedback training to improve heart rate variability, have been proposed to be included in cardiac rehabilitation programs. Indeed, heart rate variability biofeedback could effectively reduce depressive symptoms and related pathophysiological mechanisms in CAD patients who underwent a revascularization procedure (45).

The current findings should be interpreted in light of some possible methodological limitations. First, 87% of the patients enrolled in the present study were men. Therefore, the present results cannot be generalized to women. Second, data on left ventricular ejection fraction were not available in the present study. Future studies are warranted to verify the role of ejection fraction in the relations between depressive symptoms and exercise stress outcomes. Third, depression was assessed using the BDI-II questionnaire, but not with a complete clinical assessment. Whereas the BDI-II has shown good psychometric properties, has been validated in a large community

population, and covers the most symptomatic elements of depression, it cannot replace a psychiatric evaluation using criteria defined in the DSM (30). However, a substantial number of studies have used the BDI-II as a measure of depression severity in patients with cardiovascular diseases (46). Finally, the present is a short-term longitudinal study focusing on the first month after the PTCA procedure and no follow-ups were performed. Future studies are warranted to evaluate the influence of depression on physical capacity in the long run (e.g., 6 months or 1 year after PTCA).

Conclusion

Depressive symptoms were linked to worse performance in the exercise stress test in CAD patients after PTCA, even after controlling for sociodemographic, biomedical factors and physical activity. Our findings suggest that a comprehensive psychological evaluation of depression along with common risk factors is essential to anticipate which patients are likely to show reduced physical capacity and to benefit less from rehabilitation procedure. An integrated evaluation could improve the ability to identify those patients at high risk of adverse outcomes after PTCA intervention. Finally, with respect to the treatment, biobehavioral interventions designed to target depression are especially needed in cardiac rehabilitation programs to improve the physical capacity of CAD patients.

Author Contributions

EP, SMB, AP, CG and DP contributed conception and design of the study. SB and AP gathered the data and organized the dataset. EP and SMB performed the statistical analysis and wrote the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Table 1 Sociodemographic, biomedical and behavioral characteristics of patients enrolled in the study.

Variable	Patients (N = 165)
Demographic characteristics	
Age (year)	61.88 (9.98)
Gender (Male)	144 (87)
Education (years)	11.93 (4.28)
BMI (Kg/m^2)	27.22 (3.75)
Smoking (no, past, actual)	56 (34), 64 (39), 45 (27)
Cardiac risk factors	
Hypertension	118 (72)
Atrial fibrillation	8 (5)
Diabetes	34 (21)
Dyslipidemia	99 (60)
Stroke	4 (2)
Medications	
β-blockers	133 (81)
Antihypertensive	45 (27)
Antiarrhythmics	5 (3)
Anticoagulants	163 (99)
ACE-inhibitors	86 (52)
Biomedical and behavioral characteristics	
Days from surgery (days)	25.07 (17.85)
Mean Blood Pressure (mmHg)	93.46 (8.34)
Mean Heart Rate (bpm)	63.52 (9.28)
White blood cells (10^9/L)	7.37 (1.89)
Red blood cells (10^{12}/L)	4.72 (0.49)
Platelet (1000/ml)	233.09 (70.62)
Glycemia (mg/dL)	108.79 (28.72)
Creatinine (mg/dL)	1.42 (5.07)
Sodium (mmol/L)	141.13 (2.31)
Potassium (mmol/L)	4.29 (0.39)
AST (U/L)	26.13 (11.24)
GGT (U/L)	31.46 (29.48)
ALT (U/L)	31.10 (17.06)
CPK (U/L)	126.93 (73.82)
HDL (mg/dL)	41.68 (10.29)
LDL (mg/dL)	69.14 (22.34)
Total cholesterol (mg/dL)	120.72 (26.92)
Triglycerides (mg/dL)	108.63 (61.76)
Walking (days in the last week)	4.07 (2.90)

Note: Data are *M (SD)* of continuous and *N* of categorical variables. BMI = Body Mass Index; AST = aspartate aminotransferase; GGT = γ-glutamyltransferase; ALT = alanine aminotransferase; CPK = creatine phosphokinase; HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol.

Table 2 Results of the hierarchical linear regression analysis with independent variables predicting maximal workload in METs.

Predictors of maximal workload in METs							**Overall model test**			**Comparisons between blocks**	
							R^2	**AIC**	***p***	**ΔR^2**	***p***
Block 1 Sociodemographic characteristics							**.29**	**990.75**	**< .001**		
Predictor	**Estimate**	**SE**	**95% C.I. Lower**	**Upper**	**t**	***p***					
Age	-0.27	0.04	-0.35	-0.19	-6.78	< .001					
Sex:											
F – M	-3.77	1.15	-6.04	-1.50	-3.28	.001					
Smoking											
no - actual	2.02	0.98	0.07	3.96	2.05	.042					
past - actual	2.52	0.98	0.58	4.45	2.56	.011					
BMI	-0.13	0.10	-0.34	0.06	-1.38	.169					
Block 2 Biomedical and behavioral characteristics							**.39**	**976.52**	**< .001**	**.10**	**< .001**
Predictor	**Estimate**	**SE**	**95% C.I. Lower**	**Upper**	**t**	***p***					
Age	-0.29	0.04	-0.36	-0.21	-7.36	< .001					
Sex:											
F – M	-2.73	1.12	-4.96	-0.51	-2.43	.016					
Smoking											
no - actual	2.60	0.94	0.74	4.46	2.77	.006					
past - actual	2.52	0.93	0.68	4.35	2.71	.007					
BMI	-0.09	0.10	-0.28	0.10	-0.95	.342					
Days from surgery	-0.02	0.02	-0.06	0.02	-0.87	.387					
β-blockers	-0.24	0.92	-2.07	1.60	-0.25	.799					
MBP	-0.10	0.04	-0.19	-0.02	-2.32	.021					
HR	-0.12	0.04	-0.20	-0.04	-2.92	.004					
CPK	0.01	0.004	0.005	0.02	3.05	.003					
Walking	0.30	0.13	0.04	0.56	2.29	.023					
Block 3 Depressive symptoms							**.41**	**973.42**	**< .001**	**.02**	**.030**
Predictor	**Estimate**	**SE**	**95% C.I. Lower**	**Upper**	**t**	***p***					
Age	-0.27	0.04	-0.35	-0.19	-6.88	< .001					
Sex:											
F – M	-2.61	1.11	-4.81	-0.41	-2.35	.020					
Smoking											
no - actual	2.38	0.93	0.53	4.22	2.55	.012					
past - actual	2.40	0.92	0.58	4.22	2.61	.010					
BMI	-0.11	0.10	-0.30	0.08	-1.17	.243					

Days from surgery	-0.02	0.02	-0.06	0.02	-0.81	.425
β-blockers	-0.18	0.92	-2.00	1.63	-0.20	.841
MBP	-0.11	0.04	-0.20	-0.02	-2.49	.014
HR	-0.09	0.04	-0.18	-0.01	-2.26	.025
CPK	0.02	0.005	0.006	0.02	3.21	.002
Walking	0.28	0.13	0.021	0.53	2.14	.034
BDI-II	-0.13	0.06	-0.24	-0.01	-2.18	.030

Table 3 Results of the hierarchical linear regression analysis with independent variables predicting Total Exercise Duration in sec.

Predictors of Total Exercise Duration in sec							**Overall model test**			**Comparisons between blocks**	
							R^2	**AIC**	***p***	**ΔR^2**	***p***
Block 1 Sociodemographic characteristics							**0.44**	**2225.67**	**<.001**		
Predictor	**Estimate**	**SE**	**95% C.I. Lower**	**Upper**	**t**	***p***					
Age	-12.86	1.7	-16.22	-9.51	-7.6	< .001					
Sex:											
F – M	-285.96	48.52	-381.79	-190.14	-5.9	< .001					
Smoking											
no - actual	88.89	41.53	6.86	170.92	2.14	0.034					
past - actual	116.22	41.42	34.42	198.02	2.81	0.006					
BMI	9.1	4.26	0.69	17.5	2.14	0.034					
Block 2 Biomedical and behavioral characteristics							**0.52**	**2213.43**	**<.001**	**0.08**	**<.001**
Predictor	**Estimate**	**SE**	**95% C.I. Lower**	**Upper**	**t**	***p***					
Age	-13.33	1.65	-16.6	-10.07	-8.1	< .001					
Sex:											
F – M	-246.54	47.73	-340.85	-152.24	-5.2	< .001					
Smoking											
no - actual	114.89	39.89	36.09	193.69	2.88	0.005					
past - actual	117.2	39.41	39.33	195.06	2.97	0.003					
BMI	10.68	4.13	2.52	18.83	2.59	0.011					
Days from surgery	-1.07	0.92	-2.88	0.74	-1.2	0.247					
β-blockers	-10.37	39.45	-88.3	67.57	-0.3	0.793					
MBP	-3.4	1.89	-7.14	0.34	-1.8	0.075					
HR	-4.11	1.73	-7.54	-0.69	-2.4	0.019					
CPK	0.6	0.21	0.19	1.02	2.88	0.005					
Walking	15.93	5.55	4.97	26.89	2.87	0.005					
Block 3 Depressive symptoms							**0.53**	**2210.52**	**<.001**	**0.01**	**.034**

Predictor	Estimate	SE	95% C.I. Lower	95% C.I. Upper	t	*p*
Age	-12.63	1.66	-15.92	-9.35	-7.6	< .001
Sex:						
F – M	-241.39	47.25	-334.73	-148.05	-5.1	< .001
Smoking						
no - actual	105.66	39.66	27.3	184.01	2.66	0.009
past - actual	112.23	39.03	35.13	189.34	2.88	0.005
BMI	9.83	4.1	1.73	17.93	2.4	0.018
Days from surgery	-1	0.91	-2.79	0.79	-1.1	0.272
β-blockers	-8.18	39.01	-85.25	68.89	-0.2	0.834
MBP	-3.66	1.88	-7.37	0.05	-2	0.053
HR	-3.09	1.78	-6.61	0.43	-1.7	0.085
CPK	0.63	0.21	0.22	1.04	3.03	0.003
Walking	14.99	5.5	4.13	25.86	2.73	0.007
BDI-II	-5.23	2.44	-10.04	-0.41	-2.1	0.034

Table 4 Results of the Binomial Logistic Regression Analysis with ability to reach exercise endpoint (defined as 85% of MPHR).

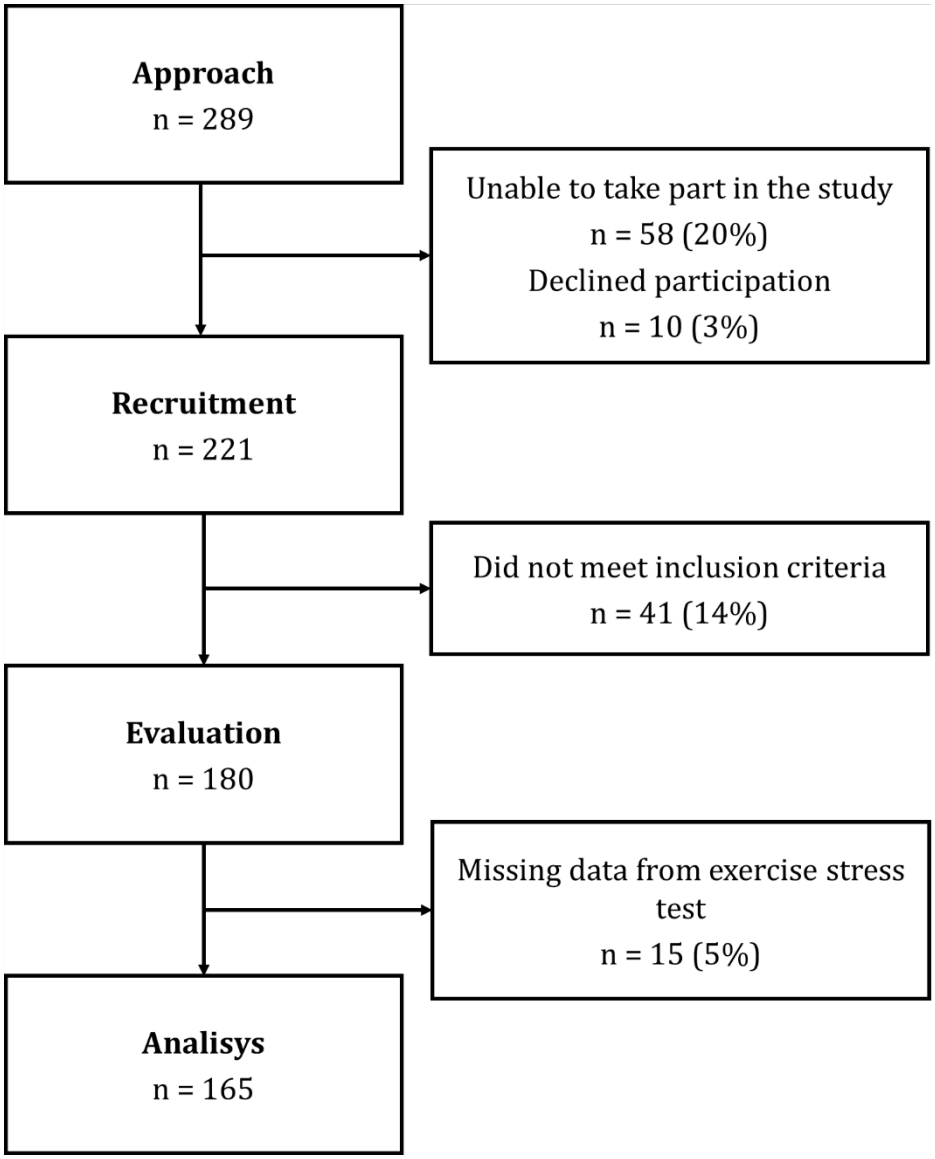
Predictors of the ability to reach Exercise Endpoint								**Overall model test**			**Comparison between blocks**	
								R^2_{McF}	**AIC**	***p***	**χ^2**	***p***
Block 1 Sociodemographic characteristics								**0.05**	**198.49**	**.058**		
Predictor	**Estimate**	**95% C.I. Lower**	**95% C.I. Upper**	**SE**	**Z**	***p***	**Odds Ratio**					
Age	0.004	-0.03	0.04	0.02	0.19	0.846	1.00					
Gender:												
F – M	0.37	-0.73	1.47	0.56	0.67	0.506	1.45					
Smoking												
no - actual	-0.56	-1.48	0.37	0.47	-1.17	0.240	0.57					
past - actual	-0.09	-1.04	0.87	0.49	-0.18	0.859	0.92					
BMI	0.15	0.04	0.26	0.06	2.70	0.007	1.16					
Block 2 Biomedical and behavioral characteristics								**0.10**	**200.80**	**.041**	**9.68**	**.139**
Predictor	**Estimate**	**95% C.I. Lower**	**95% C.I. Upper**	**SE**	**Z**	***p***	**Odds Ratio**					
Age	0.004	-0.04	0.04	0.02	0.20	0.841	1.00					
Gender:												
F – M	0.34	-0.83	1.51	0.60	0.56	0.574	1.40					
Smoking												

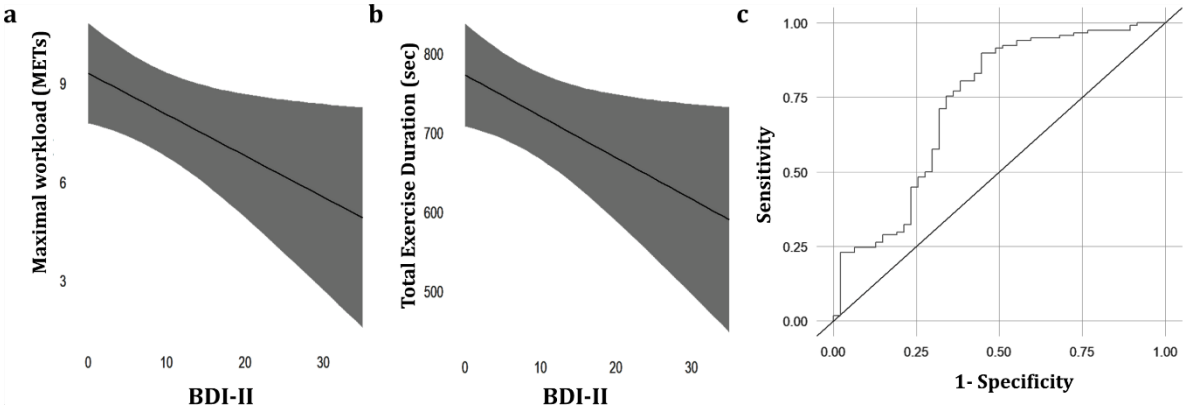
no - actual	-0.73	-1.70	0.25	0.50	-1.46	0.145	0.48				
past - actual	-0.18	-1.18	0.82	0.51	-0.35	0.723	0.83				
BMI	0.17	0.05	0.29	0.06	2.89	0.004	1.19				
Days from surgery	0.002	-0.02	0.02	0.01	0.21	0.836	1.00				
β-blockers	0.75	-0.16	1.66	0.47	1.61	0.108	2.12				
MBP	-0.01	-0.06	0.03	0.02	-0.59	0.554	0.99				
HR	-0.03	-0.07	0.01	0.02	-1.35	0.179	0.97				
CPK	-6.74e−4	-0.01	0.004	0.003	-0.26	0.793	1.00				
Walking	-0.16	-0.30	-0.02	0.07	-2.25	0.025	0.85				
Block 3 Depressive symptoms								**0.13**	**197.74**	**.013**	**5.06**	**.024**
Predictor	**Estimate**	**95% C.I.**		**SE**	**Z**	***p***	**Odds Ratio**				
		Lower	**Upper**								
Age	-0.005	-0.05	0.04	0.02	-0.22	0.828	0.99				
Gender:											
F – M	0.22	-0.96	1.40	0.60	0.37	0.712	1.25				
Smoking											
no - actual	-0.66	-1.65	0.34	0.51	-1.29	0.197	0.52				
past - actual	-0.14	-1.15	0.88	0.52	-0.26	0.794	0.87				
BMI	0.19	0.07	0.31	0.06	3.14	0.002	1.21				
Days from surgery	0.003	-0.02	0.03	0.01	0.25	0.804	1.00				
β-blockers	0.76	-0.18	1.7	0.48	1.59	0.112	2.14				
MBP	-0.01	-0.06	0.04	0.03	-0.46	0.643	0.99				
HR	-0.04	-0.09	0.001	0.02	-1.9	0.057	0.96				
CPK	-0.001	-0.01	0.004	0.003	-0.38	0.700	1.00				
Walking	-0.16	-0.30	-0.01	0.07	-2.13	0.033	0.86				
BDI-II	0.07	0.01	0.13	0.03	2.15	0.032	1.07				

Figure Legends

Figure 1. CONSORT diagram of patient enrolment.

Figure 2.a Plot of the effect of BDI-II scores on the maximal workload (in METs) during the exercise stress test controlled for sociodemographic, biomedical factors and physical activity. **2.b** Plot of the effect of BDI-II scores on the total exercise duration controlled for sociodemographic, biomedical factors and physical activity. **2.c** Receiver operating characteristic (ROC) curve for the identification of patients who failed in reaching exercise endpoint (defined as HR higher than 85% of MPHR). ROC was performed for sociodemographic characteristics, biomedical factors, physical activity and depressive symptoms (n = 165; n =118 patients who failed in reaching exercise endpoint). The area under the curve (AUC) for the total model is 0.74.




a
Maximal workload (METs)
9
6
3
0
10
20
30
BDI-II
b
Total Exercise Duration (sec)
800
700
600
500
0
10
20
30
BDI-II
c
1.00
0.75
0.50
0.25
0.00
Sensitivity
0.00
0.25
0.50
0.75
1.00
1- Specificity