The Impact of Anxiety Disorders on Assessment of Myocardial Ischemia and Exercise Stress Test Performance

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- **PURPOSE:** To evaluate the sensitivity of electrocardiogram (ECG) versus single photon emission computed tomography (SPECT) assessments of ischemia in patients with anxiety disorders (AD) and the extent to which patients exhibit poorer exercise performance, compared with patients without AD.
- **METHODS:** Patients referred for nuclear exercise stress testing (N = 2271) underwent a structured psychiatric interview (PRIME-MD) to assess for AD. Exercise performance parameters were assessed during ECG treadmill testing, after which patients underwent SPECT imaging.
- **RESULTS:** Analyses revealed that patients with AD exhibited lower peak exercise systolic blood pressure and rate pressure product than patients without AD. When major depressive disorder was included as an additional covariate, the previous results became trends. Results also indicated a lower rate of electrically positive ECG tests and a higher rate of false-negative diagnoses of myocardial ischemia according to ECG among patients with AD. Including major depressive disorder as a covariate rendered the effects of AD nonsignificant. There was no evidence of reduced exercise performance in patients with AD.
- **CONCLUSIONS:** Findings suggest that AD may be associated with mild impairments in cardiovascular exercise reactivity and may also alter the detection of myocardial ischemia using ECG assessments in patients referred for exercise stress testing. However, the influence of AD appears to be moderated by comorbid depression. Results suggest that exercise test performance and detection of ischemia may be influenced by mood and/or anxiety disorders and that greater efforts should be made to include routine mood and/or anxiety disorder screening as part of exercise stress testing protocols.

K E Y W O R D S

anxiety

depression

exercise stress test

myocardial ischemia

SPECT

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Electrocardiographic (ECG) and single photon emission computed tomography (SPECT) exercise stress tests are the most frequently prescribed tests to assess the presence and severity of coronary artery disease (CAD).[1] We have previously reported that patients with major depressive disorder (MDD), a mood disorder that affects a disproportionately high number of cardiac patients,[2,3] exhibit poor exercise stress test

performance by achieving lower percentage of predicted maximal heart rates (%PMHR), exercise duration, and metabolic equivalents (METs) than patients without MDD.[4] We also reported that ECG assessments of myocardial ischemia (presence of ST-segment depression) are less sensitive than SPECT for the assessment of ischemia in patients with MDD, possibly because of poorer exercise performance.[4,5] To our knowledge, no study has evaluated the association between anxiety disorders (AD) (eg, panic disorder, generalized AD, also common among cardiac patients[6]) and either exercise performance or ischemia assessment in patients referred for diagnostic exercise stress testing. The goal of the present study was to determine the impact of AD on exercise test performance and the relative sensitivity of ECG versus SPECT measures of myocardial ischemia in patients undergoing exercise stress testing. We hypothesized that patients with an AD would exhibit poorer exercise performance than patients without AD and that ECG measures of ischemia would be less sensitive than SPECT measures for the detection of myocardial ischemia in patients with and without AD.

METHODS

Participant characteristics including inclusion and exclusion criteria can be found elsewhere.[4] A total of 2271 consecutive patients referred for SPECT exercise stress tests at the Montreal Heart Institute (MHI) and who had interpretable ECGs during the stress test participated in the study. Written informed consent was obtained from all participants, and the study was approved by the Human Ethics Committee of the MHI.

Procedures

Details of the study procedure can be found elsewhere.[5] Briefly, patients presenting to the Department of Nuclear Medicine of the MHI on the day of their exercise stress test were invited to participate in this study after undergoing standard nuclear (SPECT) exercise stress testing (treadmill, Bruce protocol).[7] Participants were injected with a radioisotope (Tc-99m sestamibi) at peak exercise while ECG measures were continuously recorded. Exercise parameters (%PMHR, duration, METs) and cardiovascular measures (resting, submaximal, and peak exercise heart rate [HR]; systolic and diastolic blood pressure [SBP, DBP]; and rate pressure product [RPP]) were collected during exercise testing using a standard 12-lead ECG configuration (Marquette Medical Systems Inc, Milwaukee, WI) and a manual sphygmomanometer (Welch Allyn Tycos-767 series, Skaneateles Falls, NY). Patients underwent SPECT imaging within 45 minutes of exercising according to standard procedures,[7] after which they met with a research assistant who administered a sociodemographic and medical history interview followed by a brief structured psychiatric interview (Primary Care Evaluation of Mental Disorders [PRIME-MD]) to assess for anxiety and mood disorders. The PRIME-MD uses *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria to generate diagnosis that have been shown to be of comparable reliability ($\kappa = 0.71$), sensitivity (83%), and specificity (88%) to longer interviews including the Structured Clinical Interview for *DSM*.[8-10] All patients were maintained on their usual medication for the duration of testing, with the exception of β-blockers, which are routinely withdrawn for exercise testing.

Ischemia Assessment

Patients were classified as having an ECG-positive test indicating myocardial ischemia (cardiologist interpreted measured horizontal or downsloping ST-segment depression of ≥1 mm [0.1 mV] for ≥1 minute compared to resting baseline).[11] The occurrence of exercise-induced chest pain was also assessed. SPECT-based (Irix-3 model, Philips Inc, Cleveland, Ohio) myocardial ischemia was assessed at peak exercise by experienced nuclear cardiology physicians according to standard procedures.[7] Specifically, to be considered an ischemia response, patients needed to have at least a 2-point change in the stress-rest differential score, which was generated using standard software (Autoquant, Media Cybernetics, Gale Group, Framington Hills, Michigan) and verified by the physician. All borderline cases were reevaluated independently by 2 nuclear cardiology physicians who reached a consensus about a positive or negative diagnosis of ischemia.

Data Reduction and Statistical Analyses

The main effects of the presence of an AD on measures of exercise stress test performance (%PMHR, exercise duration, METs), on baseline, and on peak-exercise cardiovascular measures (HR, SBP, DBP, RPP) were assessed using general linear models. To assess the main effects of an AD on the relative sensitivity of ECG versus SPECT measures of ischemia, diagnostic classifications were split into 2 groups: false negatives, that is, negative ECG ischemia/positive SPECT ischemia, scored as a 1; and everyone else, scored as 0. General linear models were then conducted. All analyses were performed controlling for age, sex, baseline BP, anti-ischemic medication, history of CAD, and %PMHR determined *a priori*. Given the high prevalence of the comorbidity of anxiety with

depression, a second set of analyses were conducted controlling for the same variables mentioned above but including MDD as an additional covariate. All tests were two-sided, and significance was set at .05. Data analysis was performed using SAS v.9.1 (SAS Institute, Cary, North Carolina).

RESULTS

PRIME-MD assessments revealed that 471 patients (21%) had an AD and 1800 (79%) had no AD. Patients with AD were younger and were more likely to be current smokers than patients without AD (Table 1). Patients with AD were also less likely to be taking aspirin and lipid-lowering medication and less likely to have a history of CAD and previous bypass surgery than patients without AD. Patients with an AD were also significantly more likely ($t = -23.7$, $P < .001$) to have MDD (44%) than those patients without an AD (6%). No other group differences were observed.

Table 1 • Participant Demographics and Clinical Characteristics Presented as a Function of Anxiety Disorder Status[a]

	AD (n = 471)	No AD (n = 1800)
Demographics		
Age, mean ± SD,[b] y	54 ± 8.5	57 ± 8.1
Sex, F[b]	43 (203)	30 (540)
Ethnicity, white	99 (466)	99 (1782)
Education, ≥12 y[b]	48 (226)	40 (720)
Cohabitating	67 (316)	72 (1296)
Smoking, current[b]	29 (137)	22 (396)
Smoking, ever	72 (339)	70 (1260)
Medical History		
Hypertension	43 (203)	44 (792)
Hyperlipidemia	59 (278)	60 (1080)
Diabetes	9 (42)	11 (198)
Previous MI	23 (108)	23 (414)
Typical chest pain[b]	16 (75)	11 (198)
Atypical chest pain[b]	48 (226)	35 (630)
History of CAD[b]	41 (193)	50 (900)
History of bypass surgery[b]	9 (42)	14 (252)
Medications		
ACE inhibitors	15 (71)	18 (324)
Vasodilators	35 (165)	30 (540)
β-Blockers	34 (160)	37 (666)
Diuretics	7 (33)	8 (144)
Any anti-BP medication	54 (254)	56 (1008)
Ca-channel blockers	18 (85)	19 (342)
Lipid-lowering medications[b]	44 (207)	51 (918)
Any anti-ischemic	58 (273)	55 (990)
Aspirin[b]	49 (231)	55 (990)

Abbreviations: ACE, angiotensin converting enzyme; AD, anxiety disorder; BP, blood pressure; CAD, coronary artery disease; MI, myocardial infarction.
[a]Values represent % (n), unless otherwise indicated.
[b]Main effect for AD ($P < .05$).

Stress Test Analyses

There was no effect of AD on any resting cardiovascular measures (Table 2). However, patients with AD exhibited significantly lower peak exercise SBP and RPP than patients without AD. When MDD was included as a covariate, the previous results were no longer significant but became trends, with patients with AD tending to have lower peak SBP ($F = 3.61$, $P = .058$) and RPP ($F = 3.40$, $P = .065$) than patients without AD. In addition, there was no effect of AD on any of the exercise performance indices, that is, %PMHR, duration, and METs, irrespective of whether MDD was included as a covariate or not. Finally, among the false-negative group specifically, exploratory analyses revealed that there were no differences in baseline or peak exercise hemodynamics according to AD status, which reflects the pattern observed in the whole group of patients.

Myocardial Ischemia Analyses

There was a main effect of AD ($F = 4.37$, $P = .037$) on ECG assessment of myocardial ischemia such that the rates of ECG-positive tests were significantly lower among patients with AD (40%) than among patients without AD (46%) (Figure 1). However, there were no significant differences in the rates of clinically positive tests (patient reported chest pain at peak exercise) between the AD (22%) and non-AD (19%) groups (Figure 2).

There was no main effect of AD status on rates of SPECT ischemia (43% in the AD group and 42% in the non-AD group; $F = 2.15$, $P = .143$) (Figure 3). However, there was a significant main effect of AD status on the rates of false-negative diagnoses of ischemia ($F = 3.86$, $P = .049$) where ECG was compared with SPECT using SPECT as the gold standard. Specifically, 24% of the patients with AD had an ECG-negative test when their SPECT revealed evidence of ischemia, compared with only 20% of the patients without AD (Figure 4). However, when MDD was included as a covariate, the difference in the rates of ECG-positive tests between patients with and without AD became nonsignificant ($F = 1.26$, $P = .261$) as did the difference in the rates of false-negative ECG diagnoses ($F = 1.00$, $P = .317$). There was no change in the nature of the SPECT ischemia result ($F = 0.33$, $P = .566$).

Table 2 • Participant Resting and Peak Exercise Cardiovascular Measures and Indices of Exercise Performance as a Function of Anxiety Disorder Status

	Mean ± SE			
	AD	Non-AD	F score	*P*
Cardiovascular Measures				
Resting SBP, mmHg	134 ± 0.9	134 ± 0.6	0.02	.881
Peak SBP[a], mmHg	167 ± 1.1	169 ± 0.5	4.65	.031
Resting DBP, mmHg	85 ± 0.5	85 ± 0.3	0.19	.659
Peak DBP, mmHg	85 ± 0.5	85 ± 0.2	1.50	.220
Resting HR, bpm	66 ± 0.5	66 ± 0.3	0.27	.601
Peak HR, bpm	140 ± 0.4	141 ± 0.2	1.22	.269
Resting RPP,[a] U × 10^3	89 ± 1	89 ± 0.6	0.05	.824
Peak RPP,[a] U × 10^3	235 ± 1.8	240 ± 0.9	6.99	.008
Exercise Performance				
% PMHR	85 ± 0.6	86 ± 0.3	0.32	.571
Total METs	9.72 ± 1.3	8.89 ± 0.7	0.49	.486
Total, s	422 ± 4.6	429 ± 2.3	0.84	.358

Abbreviations: AD, anxiety disorder; DBP, diastolic blood pressure; HR, heart rate; METs, metabolic equivalents; PMHR, predicted maximal heart rate; RPP, rate-pressure product; SBP, systolic blood pressure.
[a]Main effect for AD ($P < .05$).

DISCUSSION

Results of the present study showed that patients with AD were significantly less likely to have ECG-positive stress test results than those without an AD, despite the absence of group differences regarding rates of clinically significant chest pain, that is, presence of chest pain during exercise. This finding could be compared with that observed by Channer et al,[12] who assessed ECG results in 87 patients referred for diagnostic exercise treadmill testing. The authors reported that in patients without anxiety or depression but with typical chest pain, the probability of a negative ECG test was 14%, which was significantly lower than in patients who were both anxious and depressed but with atypical pain, which was 97.5%.[12] Even though the present study did not assess typical and atypical chest pain, we observed a significant association between AD and rates of ECG positive, while the rates of positive SPECT tests were not associated with AD status. We also observed false-negative diagnoses

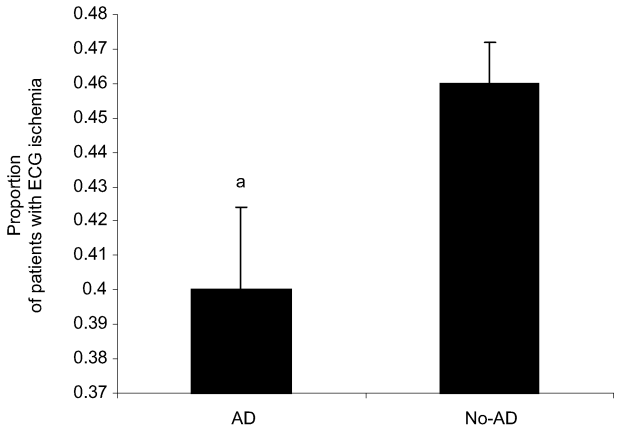

Figure 1. Proportion of positive electrocardiograms (ECG) as a function of anxiety disorder (AD) status.
[a]Main effect of AD ($P < .05$).

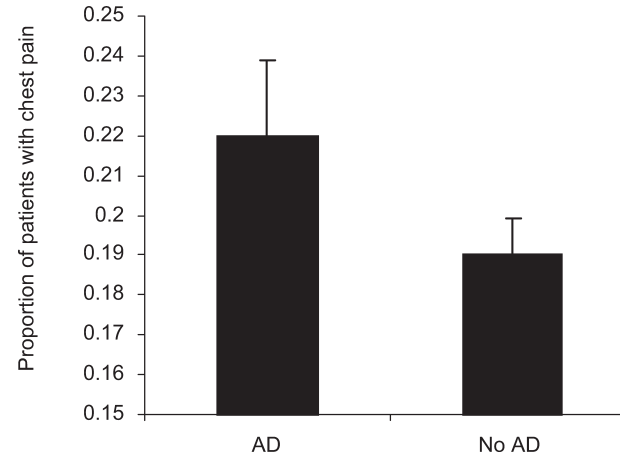

Figure 2. Proportion of clinically significant chest pain as a function of anxiety disorder (AD) status.

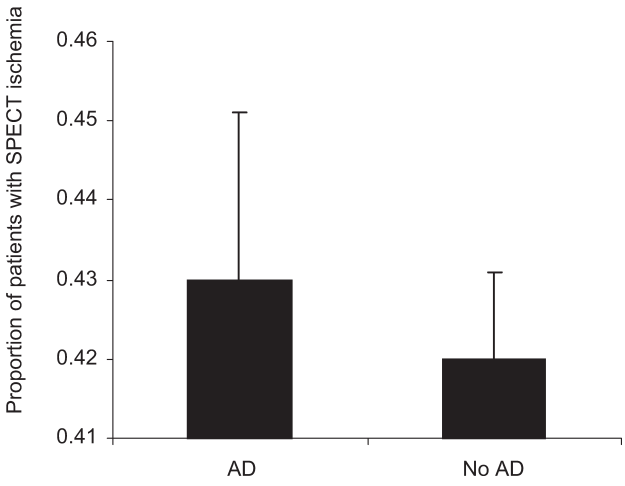

Figure 3. Proportions of single photon emission computed tomography (SPECT) ischemia as a function of anxiety disorder (AD) status.

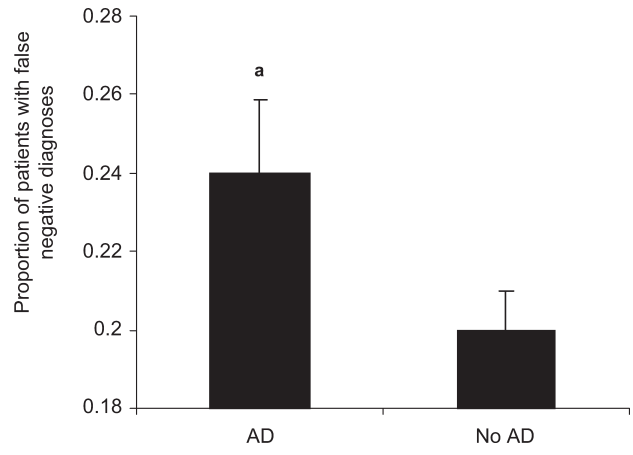

Figure 4. Proportion of false-negative diagnoses as a function of anxiety disorder (AD) status. [a]Main effect of AD ($P < .05$).

(negative ECG with positive SPECT) significantly more often among patients with AD than among patients without AD. These findings suggest that SPECT assessments of ischemia may be more sensitive than ECG assessments in detecting myocardial ischemia among patients with AD, given that ECG assessments may tend to underestimate the presence of myocardial ischemia in anxious patients. Consequently, as we have previously reported,[4] psychological status should be assessed and taken into account by physicians when referring patients for diagnostic exercise stress tests.

A potential explanation for the higher rate of false-negative ECG ischemia diagnoses among patients with AD might be the fact that patients with an AD tend to be more sensitive to increased physiological arousal.[13] As a result, patients may have terminated the exercise test at the first physiological manifestation of ischemia, that is, around the time at which SPECT would have detected the ischemia, which is thought to occur at a lower threshold than ECG ischemia.[14] Although patients may have been able to exercise for longer, the fear of impending symptoms and possibly triggering a cardiac event may have curtailed exercise in patients with AD, which is reflected in achieving lower peak SBP and RPP values. Unfortunately, we do not have data on the exact time of SPECT or ECG ischemia onset, which would have supported this hypothesis.

An alternative explanation to the higher rate of false-negative ECG results among patients with AD can also be postulated, given the fact that the effects of AD on ECG diagnosis of ischemia were altered by the inclusion of MDD as a covariate. This finding suggests that depression may moderate the association between AD and ECG assessment of ischemia. This is consistent with our previous report linking MDD with poorer exercise stress test performance, indexed by the achievement of lower %PMHR, exercise duration, and METs.[4] Patients with MDD were also significantly more likely to have a negative ECG result than patients without MDD. The moderating effect of MDD on AD association with ECG sensitivity is also in accordance with those obtained by Bettinardi et al,[15] who assessed the impact of depression and anxiety on 6-minute walk test performance. Results indicated that depression scores were predictive of worse functional capacity during the test, independent of disease severity. More specifically, patients with higher depression scores achieved shorter walk distances and reported higher fatigue and exertion levels on the Borg index than patients without depression. However, no effects of anxiety levels on those parameters were observed in this study. Depression and anxiety are generally highly comorbid[16-18] and the rate of MDD among patients undergoing exercise stress tests is disproportionately high compared to the general population.[4,19] As such, our data suggest that the effects observed for AD in the present study may be attributable to comorbid depression.

It is interesting to note, however, that although almost half of the patients in the AD group (44%) also had an MDD, they did not exhibit poorer exercise performance than patients in the non-AD group. A potential explanation for this might be that the combination of AD and MDD has an interactive effect on cardiovascular parameters and prognosis and does not simply have a cumulative effect. For example, as some studies have shown that anxious patients exhibit autonomic dysregulations[20-22] and poorer cardiovascular prognosis,[23,24] others have found anxiety to be associated with a better cardiovascular prognosis,[19] better treatment adherence, and more frequent

medical consultations because of fears about the negative consequences of having a disease.[25] Thus, some characteristics of AD, for example, the desire to perform well on the treadmill to ensure a valid diagnostic test, might interact with some characteristics of depression, for example, lack of motivation and activation, and yield a different clinical portrait than what might be expected from the simple addition of their attributable risks or what we would observe in patients with only an AD or MDD.

Results of the present study also indicated that patients with AD exhibited lower peak exercise SBP and RPP during exercise than patients without AD, even after controlling for important covariates, suggesting potential autonomic dysregulation in patients with AD. These impaired sympathovagal responses in anxious patients might be explained by lower baroreceptor sensitivity (BRS). Manabe et al[26] reported that during increased exercise levels, BRS was positively correlated with SBP increases among healthy participants. The authors suggested that normal exercise-induced blood pressure responses are controlled through baroreflex mechanisms. Also, RPP has been reported to be an excellent indicator of BRS.[27] Since our patients with AD exhibited significantly lower peak exercise RPP and SBP values than patients without AD, it is possible that BRS played a role in this finding. This may be important to consider given the fact that decreased BRS has been shown to precede the development of hypertension[28] and is known to be a predictor of mortality among patients with CAD.[29] Moreover, decreased SBP values at peak exercise have been associated with increased all-cause mortality at 5 years among patients referred for exercise stress tests, while higher SBP values have been shown to predict survival in the same cohort.[19]

Lower peak exercise cardiovascular reactivity observed among patients with AD could also be explained by the fact that anxious individuals may have exercised at lower intensities and for a shorter period of time than patients without AD because of fears about provoking physiological symptoms such as chest pain, palpitations, and shortness of breath that may signal the triggering of a cardiac event.[30] However, the facts that patients with AD exhibited comparable %PMHR, exercise duration, and METs to patients without AD and that we included %PMHR as a covariate in our analyses suggest that this explanation is unlikely. It is also important to note that the main effect of AD on peak exercise SBP and RPP became nonsignificant trends when MDD was included as an additional covariate, suggesting that depression may moderate the association between AD and cardiovascular reactivity during exercise.

These results should be interpreted in light of some methodological limitations. Although patients were told not to take their β-blockers prior to exercise testing, compliance with this directive was not systematically assessed by the technician. Also, because angiograms were not available for all patients, an absolute evaluation of CAD severity could not be conducted. Anxiety disorders were assessed following exercise testing; so it is possible that rates of AD may have been inflated because of anxiety carryover effects following exercise. However, we believe that assessing AD prior to exercise would have been associated with even greater anticipatory anxiety; thus, all psychiatric assessments were made approximately 2 hours following exercise testing and after which patients successfully completed their test. Also, the main result was on the border of statistical significance ($P = .049$), and as such, it is possible that in other populations this result may not be reproduced. In addition, because of limited power, we were not able to analyze the unique effects of individual ADs. There is evidence that certain ADs, for example, panic disorder, may be particularly relevant to CAD outcomes because of specific autonomic correlates, for example, associated reductions in heart rate variability.[6,22] As such, it is possible that we have underestimated the impact of specific AD by grouping them together. Finally, specific indications for SPECT tests could not be systematically obtained, either because this information was not available or because it was difficult to interpret owing to multiple indications. Therefore, we cannot generalize findings to patients who were referred for specific indications.

Despite these limitations, this study also has a number of important strengths including being the first to assess the impact of AD on exercise stress test performance and ischemia detection using ECG and SPECT. It also included a large (N = 2271) heterogeneous (eg, 33% female, 48% with history of CAD) sample of patients referred for SPECT exercise stress testing, which may increase generalization of results. In addition, AD and MDD were assessed using a well-validated psychiatric interview (PRIME-MD) that provided clinical diagnoses of psychiatric disorders. The inclusion of MDD as a covariate also permitted a better understanding of the relative contribution of anxiety and depression to the observed effects.

Overall, the findings of this study indicate that exercise stress test performance and detection of ischemia may be influenced by the presence of mood and/or anxiety disorders and that greater efforts should be made to include routine mood and/or anxiety disorder screening as part of exercise stress testing protocols. Future research on the impact of mood and/or anxiety disorders on CVD should assess the unique

contributions of mood and/or anxiety disorders, because of the high rate of overlapping symptoms and comorbidity.

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