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History of Anxiety Disorders Is Associated With a Decreased Likelihood of Angiographic Coronary Artery Disease in Women With Chest Pain: The WISE Study

Thomas Rutledge, PHD,* Steven E. Reis, MD, FACC,* Marian Olson, MS,* Jane Owens, PHD,* Sheryl F. Kelsey, PHD,* Carl J. Pepine, MD, FACC,† Nathaniel Reichek, MD, FACC,‡ William J. Rogers, MD, FACC,§ C. Noel Bairey Merz, MD, FACC,‖ George Sopko, MD,¶ Carol E. Cornell, PHD,§ Barry Sharaf, MD, FACC,# Karen A. Matthews, PHD*

Pittsburgh, Pennsylvania; Gainesville, Florida; Birmingham, Alabama; Los Angeles, California; Bethesda, Maryland; and Providence, Rhode Island

OBJECTIVES We sought to evaluate the ability of psychiatric anxiety-disorder history to discriminate between women with and without angiographic coronary artery disease (CAD) in a population with chest pain.

BACKGROUND A total of 435 women with chest pain underwent a diagnostic battery including coronary angiography in order to improve testing guidelines for women with suspected CAD.

METHODS Women referred for coronary angiography completed questionnaires assessing prior treatment history for anxiety disorder and current anxiety-related symptoms. Analyses controlled for standard CAD risk factors.

RESULTS Forty-four women (10%) reported receiving prior treatment for an anxiety disorder. This group acknowledged significantly higher levels of autonomic symptoms (e.g., headaches, muscle tension [$F = 25.0$, $p < 0.001$] and higher behavioral avoidance scores (e.g., avoidance of open places or traveling alone by bus [$F = 4.2$, $p < 0.05$]) at baseline testing compared with women without prior anxiety problems. Women with an anxiety-disorder history did not differ from those without such a history with respect to the presence of inducible ischemia or use of nitroglycerin, although they were younger and more likely to describe both "tight" and "sharp" chest pain symptoms and to experience back pain and episodes of nocturnal chest pain. Logistic regression results indicated that the positive-anxiety-history group was more likely to be free of underlying significant angiographic CAD (odds ratio = 2.74, 95% confidence interval 1.15 to 6.5, $p = 0.03$).

CONCLUSIONS Among women with chest pain symptoms, a history of anxiety disorders is associated with a lower probability of significant angiographic CAD. Knowledge of anxiety disorder history may assist in the clinical evaluation of women with chest pain. (J Am Coll Cardiol 2001;37: 780–5) © 2001 by the American College of Cardiology

Among women, the presentation of angina symptoms is neither a sensitive nor a specific marker for coronary artery disease (CAD) (1–3). It has been suggested that the lack of predictive value of symptoms for underlying CAD in women is in part responsible for the less aggressive and comparatively delayed treatment that women receive relative to men (4–6). Although these gender-related disparities in treatment may reduce the number of normal angiograms in women, they may also be associated with a poorer prognosis for the large proportion of women presenting with chest pain or suspected myocardial ischemia that actually have significant CAD (7,8).

Alternative physiological mechanisms, such as coronary microvascular dysfunction (9,10), may provide an explanation for chest pain and myocardial ischemia in many women. Chest pain symptoms may also be related to noncardiac causes, including psychological disorders (11–14). Cross-sectional studies have demonstrated relationships between psychological factors such as high anxiety and life stress with chest pain symptoms in women (15–17). These associations, however, may be interpreted to suggest that stress and anxiety contribute to increased CAD risk (18,19), or that chest pain promotes increased stress and anxiety resulting from symptom-related concerns of illness or death. Evidence pertaining to the relationship between psychological factors and an objective measure of CAD among women with chest pain symptoms would aid in the interpretation of these data, but we are unaware of such findings to date.

In this study, we propose that a history of anxiety symptoms is associated with noncardiac chest pain. Accordingly, we hypothesize that women with chest pain and a

From the *University of Pittsburgh, Pennsylvania; †University of Florida, Gainesville, Florida; ‡Allegheny General Hospital, Pittsburgh, Pennsylvania; §University of Alabama, Birmingham, Alabama; ‖Cedars-Sinai Medical Center, Los Angeles, California; ¶National Heart, Lung, and Blood Institute, Bethesda, Maryland; and #Rhode Island Hospital, Providence, Rhode Island. This work was supported by contracts from the National Heart, Lung, and Blood Institutes, nos. N01-HV-68161, N01-HV-68162, N01-HV-68163 and N01-HV-68164; a GCRC grant M01-RR00425 from the National Center for Research Resources; and grants from the Gustavus and Louis Pfeiffer Research Foundation, The Women's Guild, Cedars-Sinai Medical Center, the Ladies Hospital Aid Society of Western Pennsylvania, and QMED, Inc.

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Abbreviations and Acronyms

BDI = Beck Depression Inventory
CAD = coronary artery disease
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders
HDL-C = high density lipoprotein cholesterol
LDL-C = low density lipoprotein cholesterol
MAPQ = Modified Autonomic Perception Questionnaire
WISE = Women's Ischemia Syndrome Evaluation

psychiatric history of anxiety disorders are less likely to have angiographic CAD than are those women with chest pain symptoms and no anxiety history.

METHODS

Participant recruitment and entrance criteria. The Women's Ischemia Syndrome Evaluation (WISE) is a National Heart, Lung, and Blood Institute-sponsored multicenter study assessing cardiovascular function through state-of-the-art techniques in women referred for coronary angiography to evaluate chest pain or suspected myocardial ischemia (20). Participants completed a battery of symptom and psychological questionnaires at baseline testing, along with quantitative coronary angiography, exercise stress testing and other diagnostic procedures.

Women were eligible for participation in WISE if they were older than 18 years of age and were referred for a coronary angiogram. Exclusion criteria included current pregnancy, cardiomyopathy, recent myocardial infarction or revascularization procedure (percutaneous transluminal coronary angioplasty or coronary artery bypass graft), language barrier preventing questionnaire completion and a history of congenital heart disease, among other criteria. Recruitment for WISE preceded psychological questionnaire development by approximately three months. As a result, the study population reported here represents a total of 435 women from WISE who completed the core diagnostic protocol in addition to the baseline psychological and anxiety questionnaires.

Psychiatric and covariate measures. Participants completed the Modified Autonomic Perception Questionnaire (MAPQ; 21), a five-item behavioral avoidance scale, and the Beck Depression Inventory (BDI; 22) as part of a larger psychosocial questionnaire battery. The MAPQ contains 30 items (scores range from 0 to 120; high scores equal greater sensitivity to sensations) that assess the patient's perception of bodily sensations such as muscle tension, gastrointestinal symptoms and changes in breathing and body temperature, among others. The avoidance scale contained five questions (scores range from 5 to 50; higher scores equal greater avoidance) assessing the avoidance of common situations (traveling by bus, walking alone on busy streets, going into crowded shops, going alone far from home, and large open spaces) because of fear. Finally, the BDI is a widely used 21-item depression measure (scores range from 0 to 48) that assesses both cognitive (e.g., guilt) and physical (e.g., changes in sleep patterns) symptoms of depression. A BDI score of 17 is frequently used to mark the presence of "subclinical" (i.e., not Diagnostic and Statistical Manual of Mental Disorders [DSM-IV] (23) diagnostic for a mood disorder) depression (22). Additional questions assessed whether participants had ever received treatment from a psychologist or psychiatrist for an anxiety disorder (we did not collect data regarding the length, type, precipitating factors or success of the treatment). Coronary artery disease covariate measures included smoking status, total blood cholesterol levels, hypertension status (positive/negative history), body mass index, education, functional capacity as measured by the Duke Activity Status Index (24), age and menopausal status.

Coronary disease severity was judged by three criteria. First, using the quantitative angiogram results, we assigned each participant to a group: "no CAD" ($<$20% maximum stenosis), "nonobstructive CAD" (20% to 49% maximum stenosis) or "obstructive CAD" ($\geq$50% maximum stenosis). Second, each participant was assigned a continuous coronary disease severity score based on a modified Gensini index (25). This severity score was developed with points assigned according to the category of severity of the stenosis (0% to 19%, 20% to 49%, 50% to 69%, 70% to 89%, 90% to 98%, 99% to 100%) adjusting for partial (any filling of the occluded vessel or its distal branches antegrade or retrograde via channels other than the original lumen) and complete collaterals. Scores were then adjusted according to lesion location, with more proximal lesions receiving a higher weighting factor. Finally, we used the raw maximum stenosis score from the participant's angiogram as a third outcome measure. In addition, a total of 343 (68% of the no-anxiety-history participants and 70% of the positive-anxiety-history group) participants also completed one or more noninvasive tests for myocardial ischemia, including exercise and pharmacologic stress testing with or without echocardiographic or radionuclide imaging.

Statistical analyses. Using independent sample t tests, we compared participants with and without a history of anxiety disorders on measured CAD risk factors, angina symptoms and other pain indices (e.g., headaches, back pain, etc.) and anxiety symptoms experienced at baseline testing (i.e., scores on the above autonomic, avoidance and depression scales). The predictive relationship between anxiety-disorder history and the likelihood of angiogram-defined CAD status was first assessed with logistic regression methods predicting anxiety disorder history (0 = no, 1 = yes) on the basis of CAD and demographic covariates at step one followed by the CAD severity categorical variable (0 = no CAD, 1 = nonobstructive CAD, 2 = obstructive CAD) at step two. The obstructive CAD group was used as the reference category; the resulting odds ratios represented the odds of angiogram results falling in the no CAD group relative to the obstructive CAD group, and nonobstructive

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CAD relative to obstructive CAD groups on the basis of anxiety history. Only the first of these ratios was of interest. In addition, because our CAD groupings could be deemed arbitrary, and to demonstrate that relationships based on anxiety history were not an artifact of our CAD grouping method, we used hierarchical linear regression methods to predict continuous CAD severity scores based on the modified Gensini severity index and the patient's quantitative angiogram result. We forced all covariate terms into these equations at step one of each analysis, followed by the yes/no anxiety disorder history variable. All analyses further included a dummy coding for participant's knowledge of their angiogram results (to control for the subset of participants who completed the angiogram test prior to the questionnaire assessment or those with a history of CAD) and the presence/absence of ischemia.

Power analyses, calculated using a two-tailed $\alpha = 0.05$ and a sample size of 435, indicated that our probability to detect large effects between anxiety disorder history and CAD severity (e.g., odds ratios <0.5) was greater than 99%, and that power levels were smaller, but also acceptable (0.75), for effects of moderate magnitude (e.g., odds ratios <0.7).

RESULTS

Table 1 compares women with and without a history of anxiety disorders across measured CAD risk factors, angina and other physical symptoms and psychological characteristics. Women with a history of anxiety disorders (44 of 435 [10%] participants) were younger (53.9 vs. 59.7 years of age), more likely to smoke and had lower LDL-C blood levels. Symptom profiles also differed between groups. Women with a positive anxiety history indicated that their angina episodes were longer and more likely to be relieved by rest, and more frequently endorsed sensations of "tightness" and "sharp, knife-like pain" in describing their chest pain. This subgroup also reported more frequent episodes of angina during sleep. Several other statistical trends were apparent (p values <0.10), including a pattern of seemingly unrelated somatic complaints (back pain and headaches) and a greater chance of experiencing angina while at rest in the positive-anxiety-history subgroup.

Interestingly, despite prior psychological or psychiatric treatment, the positive anxiety group expressed significantly greater distress levels at baseline, as indicated by higher behavioral avoidance scores and markedly greater sensitivity to autonomic symptoms and depression levels. Patients with a positive anxiety disorder history, therefore, were generally much more symptomatic as a group, a pattern that held across psychological measures, cardiac-related symptoms and other forms of physical complaints. It is also noteworthy that a positive anxiety-disorder history was *not* associated with a lower likelihood of having inducible ischemia on noninvasive stress testing (65% vs. 57%, p > 0.3).

Table 2 provides an unadjusted breakdown of the anxiety-disorder history groups according to CAD severity status, Gensini severity scores and quantitative angiogram results. Women with a history of anxiety disorders evidenced significantly less severe disease across each of the three CAD indices in comparison with women with no history of anxiety problems (all p values < 0.05). Based on CAD groupings, women in the positive-anxiety-history group were more than twice as likely (54.5% vs. 25%) to show no CAD (i.e., <20% maximum stenosis) relative to evidence of obstructive CAD (i.e., ≥50% maximum stenosis). In contrast, patients without an anxiety history were almost identically distributed between the no CAD and obstructive CAD categories (37% vs. 35%).

A positive anxiety-disorder history remained an independent predictor of negative angiogram findings and lower CAD severity after controlling for demographic and atherosclerosis risk factors (including age, smoking status, hypertension history, body mass index, menopause status, HDL-C and LDL-C blood levels, education levels and functional capacity) and a dummy coding for previous knowledge of angiogram results. Logistic regression results indicated that women with an anxiety disorder history were

Table 1. A Comparison of Patients With and Without an Anxiety Disorder History on Angina and Other Physical Symptoms, CAD Risk Factors, and Psychological Characteristics (n = 435)

	+ Anxiety History (n = 44)	− Anxiety History (n = 391)
Age*	53.9 (8.7)	59.7 (11.0)
% Daily angina	43.9	38.0
% Using nitroglycerin	50.0	44.6
% Angina from exertion	47.4	55.4
% Sharp, knife-like pain†	40.7	23.3
% Tightness†	66.7	58.9
% Relieved by rest†	77.8	64.7
Length of episodes (min)†	19.0 (24.2)	10.6 (13.3)
% Left arm pain	31.1	37.4
% Angina at rest	75.0	52.8
% Shortness of breath	75.0	69.6
% Angina during sleep†	56.1	39.4
% Headaches	44.2	31.7
% Migraine headaches	33.3	23.4
% Back pain†	54.5	40.1
% Current smokers*	36	16
Body mass index	29.9 (6.8)	29.6 (6.4)
HDL-C	53.8 (12.0)	54.3 (12.3)
LDL-C*	101.6 (37.6)	116.8 (39.7)
% Hypertensive	39	43
% Postmenopausal	77	83
Functional capacity (DASI)	25.1 (5.9)	24.3 (5.5)
BDI*	17.5 (9.8)	9.8 (7.4)
Avoidance scale†	13.9 (12.2)	10.4 (10.6)
MAPQ*	49.2 (15.2)	38.3 (14.7)
HRT use (%)	64.9	52.9
% Ischemic‡	65.0	56.8

*Groups differ at p < 0.01. †Groups differ at p < .05. ‡ Based on results of exercise stress, pharmacologic ECG, dobutamine stress echo, and radionuclide perfusion tests.

BDI = Beck Depression Inventory; CAD = coronary artery disease; DASI = Duke Activity Status Index; ECG = electrocardiogram; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; MAPQ = Modified Autonomic Perception Questionnaire.

Table 2. A Comparison of Women With and Without a History of Anxiety Disorders on Three Indices of CAD Severity

	CAD Group (% [N])*			Continuous Severity Indices (Mean [SD])	
	1 (<20%)	2 (20%–49%)	3 (≥50%)	Gensini-Severity Score†	Maximum Stenosis Score*
− Anxiety history	36.8 (144)	28.1 (110)	35.0 (137)	13.9 (12.8)	37.2 (35.3)
+ Anxiety history	54.5 (24)	20.4 (9)	25.0 (11)	9.0 (7.6)	25.1 (32.4)

*Groups differ $p < 0.05$; †Groups differ $p < 0.01$. CAD groups: 1 = maximum stenosis <20%; 2 = maximum stenosis 20%–49%; 3 = maximum stenosis ≥ 50%.
CAD = coronary artery disease.

nearly three times more likely to be in the lowest category of CAD severity (i.e., <20% maximum stenosis) relative to the category of obstructive CAD (i.e., ≥50% maximum stenosis) compared with women without an anxiety disorder history following covariate adjustment (odds ratio = 2.74, 95% CI 1.15 to 6.53, $p = 0.03$). Using the modified Gensini score as a continuous measure of CAD severity, women with an anxiety-disorder history had significantly lower scores than women without an anxiety-disorder history after adjustment for covariates (adjusted $F = 4.4$, $p = 0.03$). Finally, the inclusion of CAD and demographic covariates results did not affect the relationship between anxiety history and lower disease severity in the form of quantitative angiogram scores (adjusted $F = 5.6$, $p = 0.02$).

DISCUSSION

Our findings suggest that a history of anxiety disorders is associated with a lower likelihood of angiographic CAD among women presenting with chest pain symptoms. Although previous studies have explored relationships between psychological factors and endpoints such as angina during exercise testing (11), the prevalence of psychological distress among patients with angina (12) and the role of psychological factors in silent myocardial ischemia (13,14), the present report is the first investigation to demonstrate a clear association between a history of anxiety disorders and an absence of angiographic CAD in women with chest pain.

It is well known that chest pain symptoms are less reliable markers of CAD among women (1,2), and previous publications derived from this sample proved this to be equally true of women participating in WISE (20). Despite referral for coronary angiography on the basis of chest pain or suspected myocardial ischemia, previously published analyses showed that a full 35% of the WISE cohort had no evidence of CAD (i.e., maximum stenosis <20%) based on angiogram findings. Another 25% of this group showed only modest evidence of nonobstructive CAD (maximum stenosis 21% to 49%) (20). Thus, presenting symptoms were not predictive of angiogram results in women with chest pain.

Our results suggest that anxiety characteristics may be one important factor contributing to false positive cases of angina in women. In this sample, women with a positive history of anxiety disorders expressed more severe clinical symptoms but a substantially reduced probability of angiographic CAD. Based on a categorization of the participants' angiogram scores, members of the positive-anxiety group were more than twice as likely to show no evidence of CAD (i.e., <20% maximum stenosis) than obstructive CAD status (i.e., ≥50% maximum stenosis) relative to participants with no history of anxiety. However, we recognize that our—and arguably any—categorization system for angiogram scores could be subject to bias. For example, a maximum stenosis of 50% (as used in our data) may seem too low to assign to a positive CAD condition, whereas setting the lower end of the angiogram bar higher would result in "CAD-free" participants with at least moderate CAD. In order to circumvent this difficulty, we further examined anxiety relationships with objective continuous measures of CAD: the modified Gensini severity score and the participant's angiogram result. We observed the same pattern of effects across all CAD indices, however, and because these associations proved robust to covariate adjustment, it is unlikely that our findings represent a methodological artifact. The observation that participants with and without a history of anxiety disorders were equally likely to show evidence of ischemia on the basis of noninvasive testing reinforces the potential clinical value of the psychiatric history data.

Limitations and topics for future research. One primary objective of WISE is to better understand contributing mechanisms among women with abnormal diagnostic tests for myocardial ischemia in the absence of coronary atherosclerosis (20). The results presented here offer evidence toward this goal, but several design features limit our ability to draw causal conclusions. For one, existing evidence shows that anxiety-disorder risk is associated with a number of environmental, genetic and personality factors (26). As a result, the associations observed here may be understood in terms of the factors contributing to anxiety-disorder risk and not anxiety-disorder history. We also did not query for a history of depression disorders/treatment in this cohort, and given the well-documented relationship between anxiety and depressive symptoms (11–13,18), this factor may deserve consideration in future studies. There is also the possibility of a referral bias within the WISE sample (i.e., WISE participants may not represent a random sample of women with angina, and anxiety characteristics may affect

treatment-seeking behavior) that may constrain the generalizability of these results. Thus, our findings should not be misconstrued to provide direct evidence for "psychogenic" angina.

Our observation of an association between a *previous* anxiety disorder and *current* angiogram results also raises questions concerning the temporal nature of this relationship. We found that despite prior treatment for their anxiety condition, the subset of women with a positive anxiety history remained highly symptomatic on the basis of physical and psychological questionnaires (questionnaires, however, are not a substitute for an interview-based DSM-IV diagnosis of a mood or anxiety disorder). This pattern may suggest that an anxiety-disorder history among women with chest pain symptoms is a marker of an enduring disposition toward reporting more negative symptom profiles relative to their peers. In contrast, concurrent anxiety symptoms assessed at baseline testing before or after angiogram may reflect more transient factors (e.g., concern about health or potential test results or current life difficulties) and may therefore offer less insight into the long-term symptom reporting style we have shown to be linked to a reduced rate of positive angiogram results.

A pair of additional limitations should also be mentioned briefly. Although the relationship between anxiety-disorder history and CAD status observed here could not be accounted for on the basis of standard atherosclerosis risk factors, our list of potential risk factors was not comprehensive and alternative measures of CAD severity (e.g., electron beam tomography) were not included. Our measure of anxiety history was also rather global and did not allow us to examine relationships with specific anxiety conditions. Although the sample size and prevalence rate of anxiety disorders found in our WISE population would have limited such an examination, anxiety disorders under the classification of the current DSM-IV include conditions ranging from spider phobia to posttraumatic stress disorder but do not include potentially more relevant diagnoses such as somatization disorder or hypochondriasis. The current findings offer no direct insight into these possibilities, but they do suggest that the answers to these questions could be clinically meaningful in future prospective investigations.

Furthermore, the usefulness of measuring anxiety disorder history variables is dependent upon factors affecting the probability of identifying and treating such mental health conditions in the patient's environment. For example, lower socioeconomic standing (although it did not affect the results here) is associated with higher levels of psychological distress but also with relative undertreatment (27,28). Thus, the generalizability of our results is an important issue. WISE is a predominantly middle-class Caucasian (80%) cohort, which may have improved our ability to examine questions about psychiatric treatment history. But because relationships based on anxiety-disorder history may be affected by differences in prevalence or diagnostic reliability, the positive predictive value of anxiety-disorder histories may vary among population groups.

A final caution is warranted regarding the clinical interpretation of these findings. Although we observed a comparatively reduced likelihood of obstructive CAD among women with chest pain who reported a history of anxiety disorders, it is notable that a full 45% of this group nevertheless did show angiographic evidence of moderate, nonobstructive (i.e., maximum stenosis 20% to 49%) or obstructive CAD (i.e., >50% stenosis). We believe this result reinforces the need to carefully evaluate symptoms in women irrespective of psychological history and to consider anxiety-history variables as a topic in future investigations. Furthermore, our results support a lower CAD likelihood in a small (10%) subset of an exclusively female sample and do not suggest that women as a group are less likely to have CAD (which is the leading cause of death among both women and men), or even that an anxious female patient is less likely to show evidence of CAD (i.e., our results reflect a known anxiety-disorder history, not current symptoms).

Conclusions. Our study demonstrates that the presence of an anxiety-disorder history was associated with a significantly lower likelihood of significant angiographic CAD among women with angina. Determining a patient's anxiety-disorder history may assist the clinician in identifying women with angina who are at a lower risk of underlying CAD. Interestingly, the predictive value of anxiety-disorder history proved to be independent of standard CAD risk factors and the results of noninvasive stress testing. Although the retrospective design leaves important questions unanswered, these findings are among the most robust to date in suggesting that a proportion of angina or suspected myocardial ischemia cases among women may be associated with psychological factors.

Reprint requests and correspondence: Dr. Thomas Rutledge, c/o WISE Coordinating Center, 127 Parran Hall, 130 DeSoto Street, Pittsburgh, Pennsylvania 15261. E-mail: dr.tom@musclemail.com.

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