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ORIGINAL RESEARCH

Anxiety Disorders Are Associated With Coronary Endothelial Dysfunction in Women With Chest Pain and Nonobstructive Coronary Artery Disease

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BACKGROUND: Anxiety disorders are the most prevalent mental disorders and are an emerging risk factor for coronary artery disease and its complications. We determine the relationship between having a clinical diagnosis of an anxiety disorder and coronary endothelial dysfunction (CED) using invasive coronary reactivity testing across both sexes.

METHODS AND RESULTS: Patients presenting with chest pain and nonobstructive coronary artery disease (stenosis <40%) at coronary angiography underwent an invasive assessment of CED. Patients were categorized as having a clinical diagnosis of an anxiety disorder at the time of coronary angiography by chart review. The frequency of CED was compared between patients with versus without an anxiety disorder and after stratifying patients by sex. Between 1992 and 2020, 1974 patients (mean age, 51.3 years; 66.2% women) underwent invasive coronary reactivity testing, of which 550 (27.9%) had a documented anxiety disorder at the time of angiography. There was a significantly higher proportion of patients with any type of CED in those with an anxiety disorder in all patients (343 [62.7%] versus 790 [56.4%]; *P*=0.011) that persisted in women but not in men. After adjusting for covariables, anxiety was significantly associated with any CED among all patients (odds ratio [95% CI], 1.36 [1.10–1.68]; *P*=0.004), and after stratifying by sex in women but not in men.

CONCLUSIONS: Anxiety disorders are significantly associated with CED in women presenting with chest pain and nonobstructive coronary artery disease. Thus, CED may represent a mechanism underpinning the association between anxiety disorders and coronary artery disease and its complications, highlighting the role of anxiety as a potential therapeutic target to prevent cardiovascular events.

Key Words: anxiety ■ chest pain ■ coronary endothelial dysfunction ■ ischemia

Impaired psychosocial health is an emerging risk factor for cardiovascular diseases (CVD), including coronary artery disease (CAD) and its complications.[1] Anxiety disorders are the most prevalent mental disorders, affecting nearly 1 in 5 adults in the United States,[2] with women being twice as likely to have an anxiety-related disorder compared with men.[3] Anxiety has been associated with increased mortality in individuals with known CAD.[4] Furthermore, 2 recently published meta-analyses confirmed that psychological factors, including anxiety, are associated with adverse CVD events in patients with[5] and without[6] ischemic heart disease at baseline. However, the role of sex on this association remains unclear.

There are several known differences in the manifestations of CAD between sexes. First, the prevalence of, and mortality from, CAD is higher in men, whereas women tend to develop CAD before menopause, on average 10 years after men.[9] Second, women have fewer traditional CVD risk factors than men.[10] Third, women

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CLINICAL PERSPECTIVE

What Is New?

- Anxiety disorders are significantly associated with coronary endothelial dysfunction in women presenting with chest pain and nonobstructive coronary artery disease.

What Are the Clinical Implications?

- Coronary endothelial dysfunction may represent a mechanism underpinning the association between anxiety disorders and coronary artery disease and its complications, highlighting the role of anxiety as a potential therapeutic target to prevent cardiovascular events.

Nonstandard Abbreviations and Acronyms

%ΔCADAch	percentage change in coronary artery diameter in response to acetylcholine
%ΔCBFAch	percentage change in coronary blood flow in response to acetylcholine
CBF	coronary blood flow
CED	coronary endothelial dysfunction

present with signs and symptoms of ischemia, and tend to experience adverse CVD events, more frequently in the absence of obstructive CAD, which may be explained by a higher prevalence of functional vascular abnormalities, such coronary microvascular dysfunction and coronary endothelial dysfunction (CED).[11–13] CED characterizes early atherosclerosis, and is associated with CVD disease progression, as well as a several-fold increased risk of ischemic cardiac events and stroke.[14–19]

Although the principal target of the pathophysiologic effects of psychosocial risk factors on cardiovascular health appears to be the vasculature, and particularly the endothelium,[20] the precise mechanisms underpinning this relationship remain underrecognized, and challenging to address. Sex-based differences in the prevalence and effects of anxiety could contribute to differences in vascular reactivity and endothelial function between men and women, which, in turn, may affect the differential presentation and progression of ischemic heart disease across sexes. Thus, endothelial dysfunction may explain, at least in part, some of the association between anxiety and adverse CVD events. The significance of the potential link between anxiety and CAD is underscored by the opportunity for early detection and intervention in early atherosclerotic disease. In the current study, we assess the relationship between having a clinical diagnosis of an anxiety disorder and CED using invasive coronary reactivity testing across both men and women, hypothesizing that anxiety is significantly associated with CED in women.

METHODS

The authors of the current study are willing to make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure.

Study Protocol

Patients were referred to our institution by their physician for clinically indicated coronary angiography for the assessment of chest pain or an abnormal stress test result. All patients were then evaluated by a cardiologist at our institution, and those with signs or symptoms of stable cardiac ischemic heart disease or an abnormal noninvasive stress test result were referred for a clinically indicated elective coronary angiogram. Patients with the following criteria were excluded: >40% diameter stenosis in major vessels; acute coronary syndrome; acute renal failure; uncontrolled hypertension; and left ventricular ejection fraction of ≤50% and left ventricular hypertrophy.[13,21–27] This retrospective cross-sectional study was approved by the Mayo Clinic Institutional Review Board, and all study participants gave their informed consent.

Consecutive patients presented to the cardiac catheterization laboratory in the fasting state, and all cardiovascular medications, including nitrates and calcium channel blockers, had been discontinued for at least 24 hours. Routine diagnostic coronary angiography was performed on all patients using standard clinical protocols. Angiograms were reviewed before the infusion of any pharmacological agents. In cases where the severity of stenosis was uncertain, online quantitative coronary angiography was used. All patients underwent evaluation of microvascular endothelial-dependent and endothelial-independent coronary flow reserve, as previously described.[28,29] Following intravenous administration of 5000 to 7000 U of heparin, a Doppler guidewire (Flowire; Volcano), 0.014 inches in diameter, within a 3F Slip-Cath Infusion Catheter (Cook Medical) was positioned into the midportion of the left anterior descending coronary artery, 2 to 3 mm distal to the tip of the infusion catheter. This vessel was chosen for accessibility and because it supplies the largest territory of the myocardium. Heart rate and mean arterial blood pressure were continuously monitored throughout each procedure.[13,21–27]

Baseline mean peak velocity was recorded using the intracoronary Doppler wire, after which acetylcholine

was infused at concentrations of 10^{-6}, 10^{-5}, and 10^{-4} mol/L (to achieve estimated coronary bed concentrations of 10^{-8}, 10^{-7}, and 10^{-6} mol/L, respectively) for 3 minutes at each concentration to assess endothelial-dependent function, as previously described.[13,21–27] Infusions were performed using a Harvard pump to maintain infusion rates of <1% of the estimated coronary blood flow (CBF). Doppler measurements of mean peak velocity were performed after each infusion, followed by repeated coronary angiography. Coronary artery diameter was measured at baseline and after the infusion with acetylcholine, by an independent investigator blinded to Doppler velocity data using a previously described computer-based image analysis system.[30,31] Endothelial-dependent CBF was then calculated using the following, as previously described[28,32]: CBF=(πmean peak velocity/2)(coronary artery diameter/2).[2] The maximal percentage increase in CBF in response to acetylcholine compared with the CBF at baseline was then calculated (percentage change in CBF in response to acetylcholine [%ΔCBFAch]). For quality control, all measurements were performed in the segment 5 mm distal to the tip of the Doppler wire; and following each infusion, the diameter was measured in the same segment of the vessel.[13,21–27]

Definition of Terms

Impaired endothelial-dependent macrovascular function was defined as a coronary artery diameter in response to acetylcholine (percentage change in coronary artery diameter in response to acetylcholine [%ΔCADAch]) of ≤–20%. Impaired endothelial-dependent microvascular function was defined as a maximal percentage increase in CBF in response to any dose of acetylcholine compared with baseline CBF (%ΔCBFAch) of ≤50%.[13,21–24] CED was defined as the presence of impaired endothelial-dependent macrovascular and/or microvascular dysfunction.

Patient Information

Data were collected on conventional cardiovascular risk factors, including hypertension, diabetes, hyperlipidemia, smoking status, and body mass index; biochemical parameters, including fasting blood glucose, hemoglobin A1c, serum total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides; and medication use, including antiplatelet and antihypertensive medication, statins, as well as psychotropic medication, including antidepressants and antipsychotics of any class. Smoking was categorized as a history of current smoking, former smoking, or never smoking; hyperlipidemia was defined by a documented history of hyperlipidemia, treatment with lipid-lowering therapy, a low-density lipoprotein cholesterol level above the target (<130 mg/dL for low-risk patients, <100 mg/dL for moderate- to high-risk patients, <70 mg/dL for very-high-risk patients, and <55 mg/dL for extreme high-risk patients based on 10-year atherosclerotic CVD risk), high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women, or triglycerides >150 mg/dL. Type 2 diabetes was defined as a documented history of or treatment for type 2 diabetes, or a hemoglobin A1c of >6.5, if available. Hypertension was defined as a documented history of or treatment of the condition, a systolic blood pressure measurement of >130 mm Hg, or a diastolic blood pressure measurement of >90 mm Hg. All blood test results included in this study are based on blood samples obtained on the morning of the index procedure. A history of myocardial infarction was also documented and was diagnosed in the presence of at least 2 of the following: (1) typical chest pain for at least 20 minutes; (2) increased creatinine kinase (or the MB fraction) or troponin level; or (3) new ST-segment elevation, Q waves, or left bundle-branch block on ECG. Information was also collected on past medical history, including other vascular diseases (defined as a documented history of peripheral vascular disease, stroke, or transient ischemic attack).[13,21–24] Anxiety disorder was evaluated by patient chart review and was defined by a documented clinical diagnosis of any of the following disorders that were current at the time of coronary angiography: generalized anxiety disorder, panic disorder, phobic anxiety disorders, including social phobia, specific phobia, and agoraphobia, and posttraumatic stress disorder. All diagnoses were made in keeping with criteria established by the *International Classification of Diseases, Tenth Revision* (*ICD-10*).[33]

Statistical Analysis

Patients were retrospectively categorized on the basis of the presence or absence of a diagnosis of an anxiety disorder. The proportions of patients having abnormal endothelial-dependent macrovascular function, measured using %ΔCADAch, abnormal endothelial-dependent microvascular function, measured using %ΔCBFAch, and abnormal any CED were compared across groups in all patients and after stratifying by sex. Continuous variables are presented as a mean (SD), where data are normally distributed, and as a median (quartile 1–quartile 3) for skewed data. Categorical variables are presented as frequencies (percentages). Differences between groups were analyzed using Student *t* test and Wilcoxon rank-sum test for continuous variables and Pearson χ^2 test for proportions. Univariable and multivariable logistic regression models were fitted to assess the association between having an anxiety disorder and endothelial-dependent macrovascular or microvascular dysfunction, and any CED in all patients, and after stratifying by sex. Multivariable analyses were adjusted for conventional CVD risk

Table 1. Summary of Baseline Clinical Characteristics of Patients With and Without a Clinical Diagnosis of an Anxiety Disorder

Characteristics	Anxiety disorder (N=550; 27.9%)	No anxiety disorder (N=1424; 72.1%)	*P* Value
Age, mean (SD), y	50.6 (12.0)	51.5 (12.6)	0.140
Women, n (%)	361 (65.6)	946 (66.4)	0.738
White race, n (%)	511 (92.9)	1223 (85.9)	<0.001*
BMI, mean (SD), kg/m^2	29.3 (6.5)	29.0 (6.4)	0.347
Hypertension, n (%)	238 (43.3)	602 (42.3)	0.688
Diabetes, n (%)	76 (13.8)	139 (9.8)	0.011*
Hyperlipidemia, n (%)	331 (60.2)	762 (53.5)	0.007*
eGFR <60 mL/min per 1.73 m^2, n (%)	68 (12.4)	203 (14.3)	0.269
History of MI, n (%)	92 (17.2)	208 (15.1)	0.250
History of vascular disease, n (%)	61 (11.1)	117 (8.2)	0.050
Family history of CAD, n (%)	330 (60.0)	785 (55.1)	0.050
Smoking status, n (%)			
Never smoked	285 (51.8)	779 (54.7)	
Former smoker	196 (35.6)	476 (33.4)	
Current smoker	68 (12.4)	168 (11.8)	0.632
Total cholesterol, mean (SD), mg/dL	181.4 (40.0)	187.7 (44.4)	0.003*
HDL-C, mean (SD), mg/dL	52.6 (17.0)	54.7 (17.8)	0.018*
LDL-C, mean (SD), mg/dL	102.5 (34.1)	106.5 (38.6)	0.030*
Triglycerides, mean (SD), mg/dL	131.8 (86.3)	133.9 (89.8)	0.638
Psychotropic medication, n (%)	276 (50.2)	457 (32.1)	<0.001*
Systolic blood pressure, mean (SD), mm Hg	125.9 (17.1)	125.8 (17.7)	0.963
Diastolic blood pressure, mean (SD), mm Hg	75.7 (9.6)	76.2 (10.1)	0.291

BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and MI, myocardial infarction.
*P value <0.05.

factors, including age as a continuous variable, a history of hyperlipidemia, hypertension, diabetes, and smoking, and use of psychotropic medications as a categorical variable. A $P<0.05$ was considered significant, and all statistical analyses were performed using JMP 9 software (SAS Institute, Inc, Cary, NC).

RESULTS

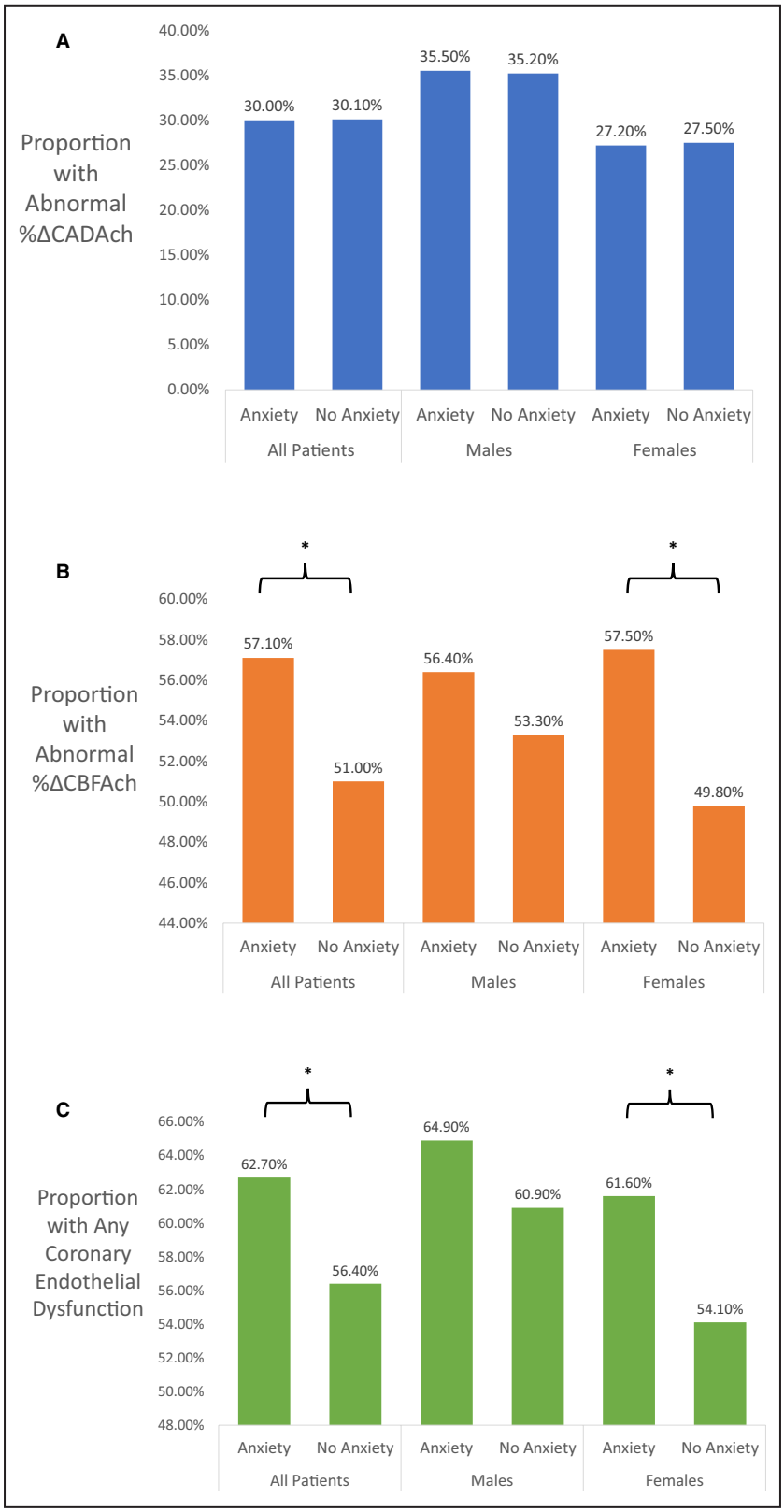
Sample Overview

Between 1992 and 2020, 1974 patients (mean age, 51.3 years; 66.2% women) underwent coronary angiography and invasive testing for CED. A total of 550 patients had a documented anxiety disorder at the time of angiography (27.9%). Table 1 summarizes the baseline characteristics of patients with and without an anxiety disorder. There was a higher proportion of White patients, individuals with diabetes and hyperlipidemia, and those taking psychotropic medications in those with an anxiety disorder versus those without. Study participants with an anxiety disorder also had, on average, lower values of total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol compared with participants without an anxiety disorder.

Proportion of CED in Patients With an Anxiety Disorder

Figure (A) through (C) demonstrate the proportion of patients with abnormal endothelial-dependent

Figure 1. Bar charts demonstrating the different proportions of patients with macrovascular, microvascular, and any coronary endothelial dysfunction in those with vs without an anxiety disorder.
A, Proportion of patients with abnormal endothelial-dependent coronary macrovascular function characterized as a percentage change in coronary artery diameter in response to acetylcholine (%ΔCADAch) of <–20% in patients with compared to without an anxiety disorder across all patients and after stratifying by sex. **B**, Proportion of patients with abnormal endothelial-dependent coronary microvascular function characterized as a percentage change in coronary blood flow in response to acetylcholine (%ΔCBFAch) of <50% in patients with compared to without an anxiety disorder across all patients and after stratifying by sex. **C**, Proportion of patients with any coronary endothelial dysfunction in patients with compared to without an anxiety disorder across all patients and after stratifying by sex. *Signifies statistically significant difference.



macrovascular function, characterized as a %ΔCADAch <–20%, abnormal endothelial-dependent microvascular function, characterized as a %ΔCBFAch <50%, and abnormal any CED in patients with versus those without an anxiety disorder across all patients, as well as separately in men and women. There was no significant difference in the proportion of patients with an abnormal %ΔCADAch (epicardial CED)

Table 2. Univariable Analyses of the Relationship Between the Presence of an Anxiety Disorder and Macrovascular, Microvascular, and Any CED Across All Patients and in Men and Women After Stratifying by Sex

Odds ratio (95% CI)	Abnormal %ΔCADAch	*P* Value	Abnormal %ΔCBFAch	*P* Value	Any CED	*P* Value
All patients						
No anxiety disorder (reference)	N=427 1.00		N=712 1.00		N=790 1.00	
Anxiety disorder	N=165 0.99 (0.80–1.23)	0.961	N=312 1.28 (1.05–1.56)	0.015*	N=343 1.30 (1.06–1.59)	0.011*
Men						
No anxiety disorder (reference)	N=331 1.00		N=463 1.00		N=504 1.00	
Anxiety disorder	N=126 1.01 (0.71–1.44)	0.958	N=206 1.13 (0.80–1.59)	0.476	N=221 1.19 (0.84–1.69)	0.333
Women						
No anxiety disorder (reference)	N=129 1.00		N=249 1.00		N=286 1.00	
Anxiety disorder	N=51 0.98 (0.75–1.29)	0.886	N=106 1.36 (1.07–1.74)	0.013*	N=122 1.36 (1.06–1.74)	0.016*

%ΔCADAch indicates percentage change in coronary artery diameter in response to acetylcholine; %ΔCBFAch, percentage change in coronary blood flow in response to acetylcholine; and CED, coronary endothelial dysfunction.

*P value <0.05.

between patients with anxiety disorders versus those without among all patients or in either men or women after stratifying by sex. There was a significantly higher proportion of patients with an abnormal %ΔCBFAch (microvascular CED) in the group of patients with an anxiety disorder in all patients (312 [57.1%] versus 712 [51.0%]; P=0.015), which remained after stratifying by sex in women but not men (206 [57.5%] versus 463 [49.8%]; P=0.013; and 106 [56.4%] versus 249 [53.3%]; P=0.476). Similarly, there was a significantly higher proportion of patients with any CED in those with versus without an anxiety disorder in all patients (343 [62.7%] versus 790 [56.4%]; P=0.011) that persisted in women but not in men (221 [61.6%] versus 504 [54.1%]; P=0.016; and 122 [64.9%] versus 286 [60.9%]; P=0.333).

Anxiety and CED: Univariable Analysis

Table 2 shows the associations between the presence of an anxiety disorder and CED in all patients and after stratifying by sex in univariable analyses. Anxiety was not associated with macrovascular CED (%ΔCADAch <–20%) among all patients or in either men or women after stratifying by sex. Anxiety was significantly associated with microvascular CED (%ΔCBFAch <50%) among all patients (odds ratio [OR] [95% CI], 1.28 [1.05–1.56]; P=0.015), and after stratifying by sex in women (OR [95% CI], 1.36 [1.07–1.74]; P=0.013) but not in men. Anxiety was significantly associated with any CED among all patients (OR [95% CI], 1.30 [1.06–1.59]; P=0.011), and after stratifying by sex in women (OR [95% CI], 1.36 [1.06–1.74]; P=0.016) but not in men.

Anxiety and CED: Multivariable Analysis

Table 3 shows the associations between the presence of an anxiety disorder and CED in all patients and after stratifying by sex in multivariable analyses after adjusting for age and body mass index as continuous variables, and White race, hypertension, diabetes, hyperlipidemia, smoking, and use of psychotropic drugs as categorical variables. Anxiety was not associated with macrovascular CED among all patients or in either men or women after stratifying by sex. Anxiety was significantly associated with microvascular CED among all patients (OR [95% CI], 1.37 [1.11–1.68]; P=0.003), and after stratifying by sex in women (OR [95% CI], 1.44 [1.12–1.86]; P=0.005) but not in men. Anxiety was significantly associated with any CED among all patients (OR [95% CI], 1.36 [1.10–1.68]; P=0.004), and after stratifying by sex in women (OR [95% CI], 1.40 [1.08–1.81]; P=0.010) but not in men. The formal test for interaction with respect to sex, however, was not significant.

DISCUSSION

In this large population of patients presenting with chest pain and nonobstructive CAD, we show for the first time that invasively determined CED, specifically microvascular CED, was more prevalent in individuals with a diagnosis of an anxiety disorder. This effect was driven by a significant association in women that was not present in men. Furthermore, we show that a current diagnosis of an anxiety disorder was significantly associated with microvascular CED and any CED in both univariable and multivariable analyses after

Table 3. Multivariable Analyses of the Relationship Between the Presence of an Anxiety Disorder and Macrovascular, Microvascular, and Any CED Across All Patients and in Men and Women After Stratifying by Sex

Odds ratio (95% CI)	Abnormal %ΔCADAch	*P* Value	Abnormal %ΔCBFAch	*P* Value	Any CED	*P* Value
All patients						
No anxiety disorder (reference)	N=427 1.00		N=712 1.00		N=790 1.00	
Anxiety disorder	N=165 1.01 (0.81–1.26)	0.907	N=312 1.37 (1.11–1.68)	0.003*	N=343 1.36 (1.10–1.68)	0.004*
Men						
No anxiety disorder (reference)	N=331 1.00		N=463 1.00		N=504 1.00	
Anxiety disorder	N=126 0.99 (0.69–1.43)	0.966	N=206 1.28 (0.89–1.84)	0.180	N=221 1.31 (0.90–1.89)	0.155
Women						
No anxiety disorder (reference)	N=129 1.00		N=249 1.00		N=286 1.00	
Anxiety disorder	N=51 1.01 (0.76–1.34)	0.946	N=106 1.44 (1.12–1.86)	0.005*	N=122 1.40 (1.08–1.81)	0.010*

Multivariable analysis was adjusted for age and body mass index as continuous variables, and White race, hypertension, diabetes, hyperlipidemia, smoking, and use of psychotropic drugs as categorical variables. %ΔCADAch indicates percentage change in coronary artery diameter in response to acetylcholine; %ΔCBFAch, percentage change in coronary blood flow in response to acetylcholine; and CED, coronary endothelial dysfunction.

*P value <0.05.

adjusting for conventional cardiovascular risk factors and the use of psychotropic medications, a relationship that persisted in women but not men. Thus, the current study supports the concept that CED may play a mediating role in the presentation of ischemia in female patients with anxiety disorders, and highlights the need for early detection and potential role of anxiety as a therapeutic target to reduce the risk of CVD events.

Psychosocial Risk Factors for CVD

Despite variations in study design, measures of exposure and outcomes, and patient characteristics, studies have shown significant associations between psychosocial risk factors and adverse clinical events.[34,35] Psychological distress,[36] vital exhaustion,[37] posttraumatic stress disorder,[38] depression,[39] and anxiety[4] have all been shown to be risk factors for CVD. Psychosocial stressors have in fact been shown to have an attributable CVD risk similar to that of diabetes, hyperlipidemia, hypertension, and cigarettes smoking.[40,41] Anxiety disorders affect nearly 1 in 5 adults in the United States,[2] and have been associated with increased mortality in individuals with known CAD,[4] and with adverse CVD events in patients with[5] and without[6] ischemic heart disease in both sexes. The principal site of transduction for the pathophysiologic effects of anxiety disorders on cardiovascular health is thought to be the vasculature, and particularly the endothelium,[20] although the precise mechanisms underpinning this relationship require further clarification.

The mechanism of the link between anxiety and CED may be multifactorial. Monkeys exposed to a new social group, and the inherent changes to social structure and environment, had increased endothelial cell damage and turnover in the thoracic aorta and coronary arteries,[42] and reduced NO availability in arteries with atherosclerosis.[43] Similarly, in humans, a public speaking task[44] and anger provocation[45] were shown to be associated with an increase in circulating endothelial cell-derived microparticles, derived from the membranes of apoptotic endothelial cells. Mental stress more generally may also adversely influence endothelial cell function. In animal studies, acute and chronic stress was associated with lower levels of NO synthase mRNA expression,[46,47] leading to endothelial dysfunction. Mental stress is also associated with oxidative stress and the release of potent vasoconstrictors, such as endothelin[48]and angiotensin II,[49] as well as the upregulation of inflammatory cytokines, such as CRP (C-reactive protein), interleukin-1, interleukin-6, and tumor necrosis factor-α,[50] all of which contribute to endothelial dysfunction. Several studies have also shown a significant relationship between experimentally induced stress and increased peripheral vasoreactivity and microvascular endothelial dysfunction.[51–53] More important, in the current study, we show for the first time that this relationship extends to the coronary arteries of female patients, as anxiety disorders are significantly associated with invasively determined CED in women presenting with chest pain and nonobstructive CAD. CED is considered to be an early marker of atherosclerosis, and is associated with atherosclerotic disease progression, as well as a several-fold increased risk of ischemic cardiac events and stroke.[14–19] Thus,

the findings of the current study suggest that CED may be the underlying mechanism for the increased risk of cardiovascular events in individuals with a diagnosis of an anxiety disorder. Indeed, apical ballooning syndrome, a unique cardiomyopathy that occurs almost exclusively in women and that is typically preceded by strong emotional stress, has also been shown to be associated both CED[54] as well as peripheral endothelial dysfunction.[53] This further highlights the central role that endothelial dysfunction may play in the pathophysiology linking anxiety to CVD. Future prospective studies are required to determine the predictive ability of identifying patients presenting with chest pain with an anxiety disorder to help differentiate those who have CED. Given that the 1974 patients included in the current study sample were examined between 1992 and 2020, it will be possible to determine whether the women with anxiety disorder in this sample have experienced increased mortality and CVD events since study entry compared with those without a history of anxiety disorder. It would also be possible to determine whether those with increased microvascular CED are more likely to experience adverse CVD events, and if so, test whether that increased morbidity/mortality is mediating the adverse clinical outcomes in women with a history of anxiety disorder. We do not currently have data on incident CVD events during follow-up in this study population, but it will be possible to collect such data and then determine whether the increased prevalence of CED in women with history of anxiety disorder found in the current study is one mediator of increased incident cardiovascular events in women with history of anxiety disorder who present with chest pain and nonobstructive CAD.

Sex-Based Differences in the Relationship Between Anxiety and CED

Sex-based differences in the manifestations of CAD are well known. The prevalence of, and mortality from, CAD is higher in men,[7,8] whereas women tend to develop CAD on average 10 years later than men before menopause.[9] Women also have fewer traditional CVD risk factors than men,[10] present with signs and symptoms of ischemia, and experience adverse CVD events more frequently in the absence of obstructive CAD, which may be explained by a higher prevalence of functional vascular abnormalities, such as CED.[11–13] We previously showed that hypothyroidism,[22] elevated uric acid levels, as an index of chronic inflammation,[55] and poor glycemic control in patients with diabetes[21] were more closely associated with microvascular CED in women than men. Sex-based physiological differences may variably influence the impact of potentially injurious factors on vascular function and health, resulting in different clinical presentations and cardiovascular risk across sexes. The findings of the current study build further on this notion when we showed that the presence of an anxiety disorder is significantly associated with microvascular CED in women but not men.

Sex is an important determinant of a variety of psychosocial factors known to influence health. Sex is also known to influence lifestyle habits, such as eating patterns, smoking, alcohol use, and physical exercise.[56] Furthermore, feminine gender roles and personality traits, including anxiety, are associated with an increased risk of recurrent events after acute coronary syndrome.[57] A recent meta-analysis showed that both men and women had a significant association between anxiety and incident ischemic heart disease,[6] with no differences across sexes. A further meta-analysis showed that anxiety was associated with adverse events in men but not in women.[5] This discordance could in part be explained by including studies comprising younger populations, in whom CVD in general is less prevalent in women compared with men, and samples whose manifestation of ischemic heart disease was obstructive CAD, which is more common in men. These meta-analyses also looked at a broad range of psychosocial risk factors, of which anxiety was only one, and for which the definitions and sample sizes varied significantly across studies.[5,6] Although anxiety disorders are typically more prevalent in women compared with men,[2] in the current study we found a similar frequency between sexes. Because of several psychosocial explanations, men typically seek treatment for emotional problems less often than women.[58] The men included in the current study would have had more frequent contact with healthcare professionals to evaluate their signs and symptoms of ischemia, and so may have been more likely to report and be identified with symptoms of anxiety disorders than may have occurred otherwise. The precise role that sex plays on the interplay between psychosocial factors, such as anxiety, and CVD requires further study.

Microvascular Disease and Anxiety

In the current study, we show that anxiety disorders are associated with microvascular, but not macrovascular, CED. Previous studies have shown that environmental stress stimulates inflammatory responses, and the release of vasoactive substances leading to enhanced microvascular permeability in mesenteric vessels in an animal model.[59] Moreover, a recent meta-analysis showed an association between indexes of microvascular dysfunction, including cerebral small-vessel disease, retinal arteriolar diameter, albuminuria, and biomarkers of endothelial function, with the risk of developing late-life depression.[60] Psychosocial risk factors, such as anxiety, may therefore preferentially

affect the endothelium of the microcirculation. Indeed, in angiographically normal epicardial coronary arteries, mental stress is associated with vasodilatation and increased CBF in the setting of mental stress,[61] whereas local vasoconstriction is seen in segments with epicardial atherosclerotic disease.[62] The latter is associated with reductions in CBF above and beyond that explained by epicardial vasoconstriction alone, implicating the role of stress-induced increases in the resistance of the coronary microcirculation. Thus, microvascular CED may form the underlying mechanism for ischemia in patients with anxiety disorders. In this way, anxiety could form a potential therapeutic target to reduce the risk of adverse CVD outcomes, particularly as studies of the clinical utility of psychological interventions, such as stress management[63] and meditation,[64] are emerging. In a randomized clinical trial, for example, group psychosocial stress management training in Swedish women with CAD was associated with a marked reduction in mortality.[65] Indeed, atypical chest pain mediated by CED could be the manifestation of anxiety in women, which, in turn, may lead to an impaired quality of life and recurrent presentations to hospital,[66] underscoring the need to address these symptoms early.

Study Limitations

This study has a few limitations. First, the current study is made up of patients presenting with chest pain who were referred for coronary angiography at a tertiary referral center and thus comprises a select population. Second, the cross-sectional design of this study prohibits a causal association between anxiety and CED. Equally, we cannot establish CED as the underlying mechanism for the incidence of CVD events in patients with anxiety. Thus, the current study is hypothesis-generating, and these additional questions would be better investigated in prospective clinical studies. Third, diagnosis of an anxiety disorder was made retrospectively through chart review and so we cannot exclude misclassification bias and heterogeneity in our sample. Although our multivariable analyses did adjust for the use of psychotropic medications, we did not evaluate the severity of anxiety at the time of coronary angiography, the presence of other potentially confounding psychosocial variables, the timing and duration of diagnosis, or the adequacy of control of symptoms at the time of angiography. However, all patients were evaluated as outpatients on an elective basis and so no patient had unstable symptoms or signs of anxiety that warranted acute hospitalization. We also did not have information on the use of benzodiazepines or cognitive-behavioral therapy and other behavioral strategies to target anxiety.

CONCLUSIONS

Anxiety disorders are significantly associated with CED in women presenting with chest pain and nonobstructive CAD. CED may represent the underlying mechanism or potential therapeutic target for ischemia in patients with anxiety and could underpin the association between anxiety disorders and incident CVD events. Further prospective studies are required to evaluate the potential role of anxiety as a therapeutic target to reduce the risk of cardiovascular events.

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