Psychosocial Modulators of Angina Response to Myocardial Ischemia

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Background—Although angina is often caused by atherosclerotic obstruction of the coronary arteries, patients with similar amounts of myocardial ischemia may vary widely in their symptoms. We sought to compare clinical and psychosocial characteristics associated with more frequent angina after adjusting for the amount of inducible ischemia.

Methods and Results—From 2004 to 2006, 788 consecutive patients undergoing single-photon emission computed tomography stress perfusion imaging at 2 Seattle hospitals were assessed for their frequency of angina over the previous 4 weeks with the Seattle Angina Questionnaire and for a broad range of psychosocial characteristics. Among patients with demonstrable ischemia on single-photon emission computed tomography (summed difference score ≥2; n=191), angina frequency was categorized as none (Seattle Angina Questionnaire score=100; n=68), monthly (score=61 to 99; n=66), and weekly or daily (score=0 to 60; n=57). Using multivariable ordinal logistic regression, increasing angina was significantly associated with a history of coronary revascularization (odds ratio 2.24, 95% confidence interval 1.19 to 4.19), anxiety (odds ratio 4.72, 95% confidence interval 1.91 to 11.66), and depression (odds ratio 3.12, 95% confidence interval 1.45 to 6.69) after adjustment for the amount of inducible ischemia.

Conclusions—Among patients with a similar burden of inducible ischemia, a history of coronary revascularization and current anxiety and depressive symptoms were associated with more frequent angina. These results support the study of angina treatment strategies that aim to reduce psychosocial distress in conjunction with efforts to lessen myocardial ischemia. (Circulation. 2009;120:126-133.)

Key Words: angina ■ depression ■ anxiety ■ ischemia

A
ngina pectoris is defined as chest, jaw, shoulder, back, or arm discomfort that is aggravated by exertion or emotional stress and relieved by rest or nitroglycerin. Angina typically occurs as a result of atherosclerotic obstruction of >70% in at least 1 large epicardial artery, which leads to an imbalance between myocardial blood supply and oxygen demand. The resultant ischemia causes pain through chemical and mechanical stimulation of sensory afferent nerve endings in the coronary vessels and myocardium. After ambulatory ECG monitoring was studied in the 1970s, however, it became evident that myocardial ischemia does not always result in angina, because 25% to 45% of patients with coronary artery disease (CAD) experience episodes of asymptomatic ischemia. Furthermore, studies of functional limitations in CAD patients have shown little association between coronary anatomy and patients’ health status. These discrepancies between anatomy, physiology, and patients’ experiences of angina warrant further investigation of the mediators of angina so that more comprehensive and cost-effective treatment strategies can be developed.

Clinical Perspective on p 133

Although there are several potential biological explanations for the discrepancy between CAD and angina severity (eg, metabolic neuropathy, ischemic regional nerve injury, defective perception of painful stimuli, and others), several psychosocial factors have also been found to be associated with an increased burden of anginal chest pain. Much of this research, however, has focused on the role of psychosocial factors in chest pain patients with normal coronary arteries. We hypothesized that psychosocial factors may also modulate angina in patients with demonstrable myocardial ischemia. We therefore investigated the association of patient factors, including psychosocial factors, with the frequency of angina in patients with inducible ischemia on single-photon emission computed tomography (SPECT) stress perfusion imaging.
ejection fraction was computed with the use of quantitative gated 367 (50%) of the patients exercised. Patients underwent a 1- or 2-day protocol with the choice of stressor dictated by clinical judgment; testing with myocardial perfusion imaging gated SPECT and had Of the 788 participants, 735 subsequently underwent maximal stress imaging after adjusting for the degree of ischemia so that differences in angina frequency would be independent of the physiological impact of patients' coronary obstructions.

Methods

Patient Population
Study participants were recruited from 1030 consecutive patients scheduled for a clinically indicated outpatient stress test with myocardial perfusion imaging between April 2004 and April 2006 at the University of Washington Medical Center or the Seattle VA Medical Center. Participants were required to be ≥18 years old and able to read English. Questionnaires quantifying the burden of angina and a range of psychosocial factors were mailed to patients ~1 week before their study. Patients who did not complete the questionnaire in advance were offered the opportunity to complete the questionnaire on the day of the test. Of the 1030 patients, 788 (77%) completed the questionnaire and provided baseline clinical data. Institutional research board approval was obtained at each participating hospital, and informed consent was obtained from all patients.

Stress Testing Protocol
Of the 788 participants, 735 subsequently underwent maximal stress testing with myocardial perfusion imaging gated SPECT and had interpretable imaging. Stress testing was performed per institutional protocol with the choice of stressor dictated by clinical judgment; 367 (50%) of the patients exercised. Patients underwent a 1- or 2-day protocol with 201TI or 99mTc tetrofosmin for rest images and 99mTc tetrofosmin for stress images. Myocardial perfusion images were interpreted by board-certified cardiologists blinded to the questionnaire results. For perfusion analysis, the myocardium of the left ventricle was divided into 20 segments, and each segment was scored semiquantitatively with a 5-point scale (0=normal uptake, 1=mild defect, 2=moderately defect, 3=severe defect, and 4=no uptake). The summed rest score and summed stress score were defined as the sum of all the scores on the rest and stress images, respectively. The summed difference score, to assess the magnitude of inducible myocardial ischemia, was derived as the difference between the summed stress and rest scores.

For the purposes of the present study, we were interested in patients with clearly established inducible ischemia, defined as a summed difference score ≥2 (n=191; Figure).18 Left ventricular ejection fraction was computed with the use of quantitative gated SPECT software.17 ST deviation, duration of exercise, metabolic equivalents achieved, and the Duke treadmill score18 were collected for all patients who underwent exercise testing.

Angina Assessment
Before stress testing, patients completed the Seattle Angina Questionnaire, a reliable and valid instrument comprising 5 domains that measure clinically important dimensions of health in patients with CAD.19,20 We focused on the angina frequency domain, which quantifies the frequency and burden of angina over the preceding 4 weeks. Scores range from 0 to 100, with higher scores indicating less frequent angina. On the basis of prior work, angina frequency was categorized as none (Seattle Angina Questionnaire score=100), monthly (score=61 to 99), weekly (score=31 to 60), and daily (score=0 to 30).21 Given the low number of patients with daily angina (n=16), the patients with weekly and daily angina were combined.

Psychosocial Assessment
We selected 5 distinct psychosocial factors to examine as potential mediators of angina frequency based on previously established associations and clinical judgment (Table 1).

Anxiety
The Beck Anxiety Inventory, a measure of global anxiety, is a 21-item reliable and valid self-reported symptom questionnaire for which the respondent is asked to rate how much he or she has been bothered by each symptom over the past week on a 4-point scale from 0 (not at all) to 3 (severely).22 Scores range from 0 to 63, with higher scores indicating more anxiety, and a score of ≥16 denotes moderate clinical anxiety.23 This instrument has been shown to discriminate anxiety and depression better than other anxiety measures.22

Depression
Depressive symptoms were measured with the Center for Epidemiologic Studies Depression scale (CES-D), a 20-item self-reported questionnaire that asks respondents to rate how often they have experienced certain feelings or symptoms during the last week on a 4-point scale from 0 (rarely or none of the time) to 3 (most or all of the time).23 Higher scores signify more depressive symptoms (maximum score of 60), and a score ≥16 is generally used to indicate a probable depressive disorder.24 The Center for Epidemiologic Studies Depression scale has well-established normative, reliability, and validity data23,28 and extensive testing with clinical and nonclinical populations, including those with CAD.29

Neuroticism
Neuroticism reflects the tendency to experience negative affects, including anxiety, sadness, embarrassment, anger, guilt, and disgust. Neurotic individuals are emotional, insecure, impulsive, susceptible to psychological distress, and vulnerable to stress. We assessed this personality trait with a brief version of the neuroticism subscale of the NEO Personality Inventory.24 This reliable and valid self-reported instrument consists of 7 items answered on a 5-point Likert scale from "strongly disagree" to "strongly agree." Higher scores indicate a more neurotic personality (scores range from 7 to 35).24 Neuroticism has been shown to be associated with angina in the absence of CAD.30

Alexithymia
Alexithymia is a cognitive-affective impairment in a person’s ability to identify and verbally express his or her inner feelings. Persons possessing this personality trait focus their attention on external stimuli rather than on emotions, thereby increasing the likelihood of somatic complaints.25 The 20-item Toronto Alexithymia Scale is a widely used self-reported measure of alexithymia, with items presented in a 5-point Likert scale from “strongly agree” to “strongly disagree.”26 Higher scores indicate more alexithymia (scores range from 20 to 100), and a score of ≥61 denotes clinically significant alexithymia.31 Despite some controversy about the ability of an instrument to capture and measure a trait that the subject may lack.

Figure. Flow diagram of patient enrollment.
the ability to report accurately, Lumley et al found evidence to support the validity and reliability of this scale compared with other measures of alexithymia. Alexithymia is associated with chest pain on exercise testing in the absence of ischemia.

Somatosensory Amplification

Somatosensory amplification refers to the tendency to experience a somatic sensation as intense, noxious, and disturbing. The concept of somatic amplification is useful in understanding “functional” somatic disorders and may be important in explaining the severity of somatic amplification is useful in understanding “functional” somatic disorders and may be important in explaining the severity of somatic conditions characterized by somatic symptoms. The Barsky Somatosensory Amplification Scale is a reliable and valid 10-item questionnaire in which respondents rate the degree to which each statement is “characteristic of you in general” on a scale of 1 to 5. Higher total scores indicate greater symptom amplification (scores range from 10 to 50), and scores >30 reflect significant somatosensory amplification.

Statistical Analysis

The primary goal of the present study was to determine the clinical and psychosocial predictors of angina frequency in a group of patients with demonstrable ischemia on SPECT stress perfusion imaging. Baseline demographic, clinical, and psychosocial characteristics were compared across angina frequency groups with the Mantel-Haenszel trend test for categorical variables and the linear trend test for continuous variables. Multivariable ordinal logistic regression models were used to evaluate the clinical and psychosocial predictors of angina frequency. Covariates were selected a priori on the basis of previously demonstrated associations with angina, balancing increased discrimination overfitting. The models included demographic (age, gender), clinical (prior myocardial infarction, prior coronary revascularization [percutaneous coronary intervention, coronary artery bypass grafting], current smoking, summed difference score on SPECT imaging), and psychosocial (anxiety, depression, neuroticism, alexithymia, somatosensory amplification) characteristics. Because the study population was almost entirely white (>90%), race was not included as a covariate. Our primary model evaluated the psychosocial factors as continuous variables, scaled as “per 1/2-SD.” To aid with clinical interpretability, a secondary model analyzed these factors by previously established categories, as described above. For the neuroticism domain of the NEO Personality Inventory, which did not have an established cutoff, a score in the upper quartile (>21 points) was used to indicate a high level of neuroticism.

Ordinal logistic regression, which allows the outcome variable to have >2 categories, was used and assumes a proportional odds ratio (OR) for each predictor for each combination of higher-risk versus lower-risk categories (eg, daily/weekly angina versus monthly or no angina and daily/weekly or monthly angina versus no angina). The validity of the proportional odds assumption, assessed with the Score test, was met for all models.

Although each psychosocial factor in the present analyses assessed a distinct psychological domain or trait, because of the potential overlap between the various factors, it was important to examine the possibility of multicollinearity. When we examined the correlation structure of the psychosocial variables categorized into quintiles, the correlation coefficients were all <0.6. In addition, the variance inflation factor for each variable in the models used in the present study was <10 (high of 2.77), which indicates that multicollinearity was not a significant issue.

All tests of statistical significance were evaluated at a 2-sided significance level of 0.05 with 95% confidence intervals (CIs). All statistical analyses were performed with SAS for Windows version 9.1 (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Population

Among 191 patients with inducible ischemia on stress perfusion imaging, 68 (36%) reported no angina over the previous...
4 weeks, 66 (35%) reported monthly symptoms, and 57 (30%) had weekly or daily angina. The mean age of the study population was 63 years, and patients with more frequent angina were more likely to be younger. Cardiac-related comorbidities and risk factors were common, with 82% having hypertension, 81% with hyperlipidemia, 34% currently smoking, and 14% having diabetes mellitus. With the exception of hyperlipidemia, patients with more frequent angina did not have an increased prevalence of these cardiac risk factors. A preexisting diagnosis of CAD was common among the study population. Although a history of myocardial infarction was not associated with more frequent angina, patients with more frequent angina were more likely to have had prior coronary revascularization (Table 2). Chest pain was the most common indication for stress testing in this population, with 49 patients (26%) reporting typical angina symptoms and 71 (37%) noting atypical chest pain. The remaining 71 (37%) reported other symptoms such as dyspnea on exertion or fatigue.

### Stress Test Results
Detailed results of the nonimaging (for patients who exercised) and imaging sections of the stress tests are shown in Table 3. In general, there were few differences among the angina frequency groups. Although there were no differences in exercise times or metabolic equivalents achieved, patients with more frequent baseline angina were much more likely to report exertional chest pain, with 63% of patients with weekly or daily angina reporting chest pain during treadmill testing compared with 20% of patients with monthly angina and 11% of patients with no angina (P for trend < 0.001). As a result, patients with more frequent angina had lower Duke treadmill scores (weekly/daily angina = 0.1, monthly angina = 2.8, no angina = 4.0; P for trend = 0.022). In the present population of patients who all had demonstrable myocardial ischemia, there was no difference in the magnitude of ischemia across angina frequency groups as assessed by ECG changes, summed rest scores, summed stress scores, or summed difference scores. Angina frequency also was not related to left ventricular size or function.

### Psychosocial Characteristics
All of the assessed psychosocial factors were significantly related to patients’ angina in univariate analyses (Table 4). Anxiety and depression scores were substantially greater in patients with more frequent angina, and more patients exhibited clinical anxiety (score ≥ 16; weekly/daily angina = 44%, monthly angina = 17%, no angina = 6%; P for trend < 0.001) or depressive disorder (score ≥ 16; weekly/daily angina = 64%, monthly angina = 38%, no angina = 22%; P for trend < 0.001). Alexithymia was more common in patients with more frequent angina, with 38% of patients reporting weekly or daily angina classified as having a high level of alexithymia (score ≥ 61) compared with 17% of patients with monthly angina and 14% of those without angina (P for trend = 0.002). Patients with more frequent angina also had higher levels of neuroticism and somatosenory amplification than patients without angina, although the differences across groups were smaller than those observed for the other scales. There were no significant differences in mean scores of each of the psychosocial scales between patients who underwent an exercise stress protocol and those who did not, nor were there differences between those with ischemia on SPECT imaging and those without.

### Association of Patient Factors With Angina Frequency
In multivariable models adjusted for the degree of myocardial ischemia, only previous coronary revascularization (OR 3.06, 95% CI 1.49 to 6.31, P = 0.002), greater anxiety scores (OR 1.39 per 1/2-SD increase in anxiety score, 95% CI 1.11 to 1.74, P = 0.004), and greater depression scores (OR 1.51 per 1/2-SD increase in depression score, 95% CI 1.17 to 1.93, P = 0.001) remained significantly associated with more frequent angina (Table 4). When the psychosocial factors were analyzed as dichotomous variables (instead of continuous scales), patients with at least moderate anxiety symptoms experienced a 4.7-fold increased risk of having more frequent angina (95% CI 1.91 to 11.66, P = 0.001), and patients with clinically relevant depressive symptoms had a 3.1-fold increased risk of experiencing more frequent angina (95% CI 1.45 to 6.69, P = 0.004; Table 5).

### Discussion
Among patients with a similar burden of inducible ischemia on a clinically indicated myocardial stress perfusion imaging study, a history of coronary revascularization, anxiety, and depressive symptoms were independently associated with more frequent angina. In univariate analyses, other psychosocial factors (alexithymia, neuroticism, and somatosenory amplification) were also significantly associated with more frequent angina, but these associations did not remain significant after adjustment for anxiety and depressive symptoms. With the exception of lower Duke treadmill scores, a conse-
sequence of differences in chest pain reporting during the stress test, there were essentially no differences in the stress test results of patients with more frequent angina compared with those having less angina, which supports previous studies that demonstrated a weak correlation between the degree of myocardial ischemia and the burden of angina.37 Although traditional medical models cannot explain much of the variability in patients’ angina, the present results suggest that psychosocial factors may significantly modulate patients’ anginal response to myocardial ischemia.

The prevalence of psychosocial distress in the patient population in the present study was quite high; 21% had at least moderate anxiety, 40% had clinically significant depressive symptoms, 22% exhibited high levels of alexithymia, and 27% had significant somatosensory amplification. Previous estimates of the prevalence of significant depressive symptoms have ranged from 20% to 32% in patients with chronic stable angina12,38 to 17% to 47% in patients after myocardial infarction.39 Although the prevalence of the other psychosocial factors in patients with ischemic angina has rarely been documented, in 1 study of 69 patients with refractory angina, 55% of patients demonstrated clinical anxiety,38 which is not dissimilar from the 44% of patients in the present study with daily or weekly angina who had at least moderate anxiety. The present study thus supports past research that has demonstrated a high prevalence of psychological distress in patients with symptomatic CAD.

In addition to describing the high levels of psychological distress in patients with ischemic heart disease sent for stress perfusion testing, the present study extends previous research on potential modulators of the angina response to myocardial ischemia. In support of the present finding of more frequent angina in patients with significant depressive symptoms, Krittayaphong et al,40 in a study of 58 patients with exercise-induced ischemia, demonstrated that depressive symptoms were associated with a shorter time to onset of angina and longer duration of angina during treadmill testing. Patients with diabetes mellitus and coronary artery bypass grafting surgeries were excluded from that study because it was suspected that these factors may influence the perception of pain. More recently, in the Heart and Soul Study, Ruo et al11 demonstrated that depression was associated with a nearly

### Table 3. Stress Test Results by Severity of Angina

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Monthly</th>
<th>Weekly/Daily</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonimaging results, n*</td>
<td>28</td>
<td>30</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>ST-segment deviation, %</td>
<td></td>
<td></td>
<td></td>
<td>0.655</td>
</tr>
<tr>
<td>None</td>
<td>29.6</td>
<td>30.0</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>&lt;1 mm</td>
<td>33.3</td>
<td>23.3</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>1–1.99 mm</td>
<td>14.8</td>
<td>33.3</td>
<td>25.8</td>
<td></td>
</tr>
<tr>
<td>≥2 mm</td>
<td>22.2</td>
<td>13.3</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td>Exertional chest pain, %</td>
<td>10.7</td>
<td>20.0</td>
<td>62.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise duration, min</td>
<td>7.6</td>
<td>6.8</td>
<td>7.3</td>
<td>0.229</td>
</tr>
<tr>
<td>Metabolic equivalents achieved</td>
<td>7.9 (4.9)</td>
<td>7.4 (3.7)</td>
<td>7.9 (3.8)</td>
<td>0.173</td>
</tr>
<tr>
<td>Duke treadmill score</td>
<td>4.0 (5.5)</td>
<td>2.8 (7.1)</td>
<td>0.1 (7.3)</td>
<td>0.022</td>
</tr>
<tr>
<td>Imaging results, n</td>
<td>68</td>
<td>66</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Summed rest score</td>
<td>4.7 (7.6)</td>
<td>4.2 (8.3)</td>
<td>4.3 (9.9)</td>
<td>0.774</td>
</tr>
<tr>
<td>Summed stress score</td>
<td>11.7 (10.0)</td>
<td>11.7 (9.5)</td>
<td>11.3 (10.5)</td>
<td>0.841</td>
</tr>
<tr>
<td>Summed difference score</td>
<td>7.0 (5.8)</td>
<td>7.5 (5.5)</td>
<td>7.1 (4.9)</td>
<td>0.933</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>51.1 (18.2)</td>
<td>54.8 (12.4)</td>
<td>53.0 (16.8)</td>
<td>0.507</td>
</tr>
<tr>
<td>After stress</td>
<td>53.0 (13.9)</td>
<td>50.1 (16.4)</td>
<td>49.4 (18.1)</td>
<td>0.218</td>
</tr>
<tr>
<td>End-diastolic volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>108.3 (59.9)</td>
<td>112.3 (51.5)</td>
<td>95.1 (44.7)</td>
<td>0.165</td>
</tr>
<tr>
<td>After stress</td>
<td>124.6 (60.5)</td>
<td>113.2 (58.1)</td>
<td>110.6 (52.9)</td>
<td>0.179</td>
</tr>
<tr>
<td>End-systolic volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>54.1 (45.7)</td>
<td>53.6 (39.6)</td>
<td>45.6 (34.8)</td>
<td>0.243</td>
</tr>
<tr>
<td>After stress</td>
<td>66.4 (62.1)</td>
<td>55.6 (42.7)</td>
<td>55.3 (39.3)</td>
<td>0.213</td>
</tr>
</tbody>
</table>

All values are mean (SD) unless otherwise indicated.

*Nonimaging results reported only in the exercising patients.

### Table 4. Psychosocial Characteristics by Severity of Angina

<table>
<thead>
<tr>
<th>Psychosocial Characteristic</th>
<th>None</th>
<th>Monthly</th>
<th>Weekly/Daily</th>
<th>P For Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>5.3 (9.6)</td>
<td>8.5 (9.0)</td>
<td>15.5 (12.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>10.7 (9.8)</td>
<td>14.4 (10.0)</td>
<td>20.8 (11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>16.4 (5.5)</td>
<td>16.2 (6.1)</td>
<td>19.0 (7.3)</td>
<td>0.023</td>
</tr>
<tr>
<td>Alexithymia</td>
<td>49.2 (10.6)</td>
<td>49.9 (10.7)</td>
<td>55.4 (12.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Somatosensory amplification</td>
<td>25.3 (6.2)</td>
<td>27.1 (5.7)</td>
<td>27.6 (6.3)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

All values are mean (SD).
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2-fold increased risk of having more frequent angina, as well as greater physical limitation due to angina and worse disease-specific quality of life. Although ischemia was assessed in that study with stress echocardiography, it was analyzed only as a dichotomous variable and was not included in any of the final models (owing to lack of univariate association with the outcome variables), which limits their insights into the incremental association of depressive symptoms above and beyond patients’ physiological ischemia. In addition, although the entire study population had established CAD, only 33% had demonstrable ischemia on imaging. The relationship between angina and psychosocial factors other than depression has been limited primarily to patients without obstructive CAD. Thus, by including only patients with established ischemia, adjusting for the degree of ischemia on a continuous scale, and evaluating a broad array of psychosocial factors, the present study adds substantially to the evidence base for the altered anginal response in patients with CAD.

There are several potential mechanisms by which depression and anxiety could modulate the anginal response to myocardial ischemia. Given their previously demonstrated role in nonischemic angina, each of the psychological factors in the present study may contribute to increased pain reporting in patients with myocardial ischemia; however, these self-reported psychological factors may also be associated with observable differences in visceral pain processing within the nervous system. The pathways through which myocardial ischemia produces angina are complex and not completely understood, with many sites in the peripheral and central nervous system where the relationship between myocardial ischemia and angina may be modified. In the setting of other chronic medical conditions, depressive and anxiety disorders have also been found to be associated with amplification of medical symptoms, which has been hypothesized to occur as a result of decreased activity in the descending pain inhibitory circuits of the central nervous system. More study is needed, however, to elucidate the neurophysiological mechanisms through which psychological distress can modify the processing of pain associated with myocardial ischemia.

The present study has several important limitations. First, we relied solely on SPECT stress perfusion imaging to assess inducible ischemia. Although SPECT stress perfusion imaging has excellent sensitivity and specificity (88% and 77%, respectively), false-positive and false-negative results are possible, which could bias our findings. Second, the present results should be considered in light of the study population, which was composed primarily of white men from the Seattle area. It is not known whether our results would be generalizable to other populations. Third, there was an understandable difference in antianginal medication use among patients with varying severities of angina, which could have influenced the relationship between angina and psychosocial distress. Fourth, given that there is some overlap between the psychosocial variables (eg, many patients with depression also have anxiety), it is unclear whether the present multivariable regression model is able to fully separate them. However, the correlation coefficients between quintile categories of the psychosocial characteristics were all < 0.6, and the variance inflation factors were all < 4, which indicates that multicollinearity was unlikely to be a significant issue in the multivariable regression model. Finally, and most importantly, because all data are presented cross-sectionally, causal priority cannot be attributed to 1 factor over another. Thus, it

### Table 5. Association of Clinical and Psychosocial Factors With Severity of Angina in Multivariable Ordinal Logistic Models (Odds of Being in a More Severe Angina Frequency Group)

<table>
<thead>
<tr>
<th>Demographic and clinical factors</th>
<th>Psychosocial Factors as Continuous Variables</th>
<th>Psychosocial Factors as Dichotomous Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Female</td>
<td>0.98 (0.95–1.01)</td>
<td>0.98 (0.95–1.01)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>0.48 (0.17–1.41)</td>
<td>0.52 (0.18–1.47)</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>0.87 (0.41–1.82)</td>
<td>0.88 (0.43–1.80)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.06 (1.49–6.31)</td>
<td>2.95 (1.44–6.03)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.66 (0.28–1.59)</td>
<td>0.65 (0.27–1.53)</td>
</tr>
<tr>
<td>Summed difference score</td>
<td>0.96 (0.49–1.88)</td>
<td>0.84 (0.44–1.62)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychosocial factors</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>1.39 (1.11–1.74)</td>
<td>4.72 (1.91–11.66)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.51 (1.17–1.93)</td>
<td>3.12 (1.45–6.69)</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>0.83 (0.67–1.04)</td>
<td>0.58 (0.23–1.41)</td>
</tr>
<tr>
<td>Alexithymia</td>
<td>0.97 (0.79–1.18)</td>
<td>1.78 (0.77–4.11)</td>
</tr>
<tr>
<td>Somatosensory amplification</td>
<td>1.06 (0.90–1.25)</td>
<td>1.25 (0.63–2.47)</td>
</tr>
</tbody>
</table>

C-statistic for continuous variable model = 0.758; C-statistic for dichotomous variable model = 0.740.

*ORs are per 1/2-SD of the respective instrument score.
is unclear whether these psychosocial factors are truly modulating the anginal response to ischemia or whether the increased anginal burden that results from other unmeasured factors is causing an intensification in psychosocial distress. At a minimum, however, the present study highlights the high prevalence of these psychosocial factors among patients with more frequent angina and supports recognition of the presence of these factors so that a proper treatment plan may be developed. Whether or not treatment of depression or anxiety will reduce the burden of angina in these patients is still unknown, because clinical trials have not yet consistently shown a benefit to treatment of psychological disorders in patients with CAD.47

The strong association between depression and anxiety symptoms and increased angina symptom burden in the present study emphasizes the need for prospective observational studies and treatment trials that could demonstrate the value of a multimodal, biopsychosocial approach to understanding and treating patients with chronic CAD. To date, American cardiology has considered angina almost entirely as an issue of physiological imbalances between myocardial oxygen supply and demand. Hence, the primary treatment goal for ischemic heart disease has been to eradicate or reduce myocardial ischemia through pharmacological and revascularization therapies. In contrast, European physicians use a broader range of treatments for refractory angina, including spinal cord stimulation, sympatheticectomy, opioids, cognitive-behavioral therapy, and multidisciplinary rehabilitation programs similar to those used for other chronic pain syndromes.48 Although treatment of the biological factors responsible for myocardial ischemia must remain a cornerstone of antianginal therapy owing to the mortality risk associated with this ischemia, the present results support the study of angina treatment strategies that additionally aim to recognize and reduce psychosocial distress, particularly in patients with refractory symptoms.

Conclusions

Among patients with inducible myocardial stress perfusion imaging study, the prevalence of psychosocial distress in patients with greater angina frequency was high, with 44% of patients with weekly or daily angina having clinically significant anxiety and 64% having clinically significant depressive symptoms. A history of coronary revascularization, anxiety, and depressive symptoms were associated with more frequent angina, independent of the amount of physiological ischemia. The present results suggest that psychological characteristics are associated with angina frequency, independent of the magnitude of myocardial ischemia. Further study is needed to determine the effectiveness of a multimodal approach to the patient with angina, which includes therapies to reduce the impact of these factors in addition to treatments that seek to lessen myocardial ischemia.

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Disclosures

Dr Spertus owns the copyright to the Seattle Angina Questionnaire. The remaining authors report no conflicts.

References

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**CLINICAL PERSPECTIVE**

Although angina is often caused by atherosclerotic obstruction of the coronary arteries, prior studies have demonstrated little association between coronary anatomy and the severity of patients’ chest pain. Several psychosocial factors have been found to be associated with increased anginal chest pain, but much of this research has focused on chest pain in patients with normal coronary arteries. We hypothesized that psychosocial factors may modulate angina in patients with demonstrable myocardial ischemia. We therefore investigated the association of psychosocial factors with angina frequency in patients with inducible ischemia on single-photon emission CT stress perfusion imaging after adjusting for the degree of ischemia. We assessed 788 consecutive patients undergoing clinically indicated single-photon emission CT stress perfusion imaging for their frequency of angina over the previous 4 weeks and for a broad range of psychosocial characteristics. Among patients with inducible ischemia (n = 191), a history of coronary revascularization, anxiety, and depressive symptoms were independently associated with more frequent angina, after adjustment for the amount of inducible ischemia. In univariate analyses, other psychosocial factors (alexithymia, neuroticism, and somatosensory amplification) were also associated with more frequent angina, but these associations did not remain significant after adjustment for anxiety and depressive symptoms. Our results suggest that psychosocial characteristics are associated with angina frequency, independent of the magnitude of myocardial ischemia, and support further study to determine the effectiveness of angina treatment strategies that aim to reduce psychosocial distress in conjunction with efforts to lessen myocardial ischemia.
Psychosocial Modulators of Angina Response to Myocardial Ischemia
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