Panic Disorder in Patients with Chest Pain and Angiographically Normal Coronary Arteries

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Although patients with angiographically normal or near normal coronary arteries are at low risk for cardiac disease, several follow-up studies have shown that many continue to report recurrent chest pain associated with social and work dysfunction. Three diagnostic entities have been proposed to explain the morbidity of this group: microvascular angina, esophageal motility disorders and panic disorder. The purpose of this study was to test the hypothesis that panic disorder is found frequently in patients with chest pain who have normal epicardial vessels. Ninety-four subjects with angiographically normal coronary arteries were interviewed according to a structured psychiatric protocol within 24 hours of their catheterizations. Thirty-two (34%) fit Diagnostic and Statistical Manual of Mental Disorders (third edition, revised) criteria for current panic disorder. Because panic disorder can be effectively treated, physicians should consider this diagnosis in this group of patients. Current research findings suggest that panic disorder, microvascular angina and esophageal disorders may each form the basis for chest pain in approximately 25% of these patients. Miscellaneous problems account for the other 25%.

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Patients with angiographically normal or near normal coronary arteries have a low risk of cardiac death and a low risk of nonfatal myocardial infarction.[1] Nevertheless, more than 65% of these subjects complain of continuing chest pain and disability over a mean follow-up period of 6.3 years.[1] Each year in the US approximately 500,000 people undergo cardiac catheterization to evaluate symptoms suggestive of coronary artery disease.[2] Approximately 20% of these people are found to have normal or near normal coronary arteries.[1,3] One hundred thousand people each year are told that they have no significant heart disease but are often not offered any treatment alternatives beyond reassurance.

Over the past several years 3 diagnostic entities have been proposed to explain the continuing morbidity of this patient group: microvascular angina,[4] esophageal motility disorders[5] and panic disorder.[6] This article reports the results of interviewing the largest number of angiographically normal subjects studied to date for major psychiatric disorders including panic disorder.

METHODS

Study population: Beginning August 1, 1986, clinical cardiologists at the University of Missouri Hospital referred to this study all patients who were experiencing chest pain but were found to have normal or near normal coronary arteries by cardiac catheterization. Patients with any coronary lesion causing >30% stenosis were excluded from the study. While ≤50% occlusion is generally considered normal or hemodynamically insignificant, in follow-up patients with >30 to 50% stenosis show more coronary events and higher cardiac mortality than those with 0 to 30% stenosis.[1,7] Therefore, ≤30% stenosis is a more conservative definition of hemodynamically insignificant occlusion. Additionally, patients with any other cardiac abnormality such as valvular heart disease (including mitral valve prolapse), cardiomyopathy, congenital heart disease, hypertensive heart disease and pericardial disease were excluded from the study sample.

Study design: Patients were initially screened by a cardiologist (VM) after they were found to have normal or near normal epicardial arteries. Whenever necessary, we reviewed angiocardiogram films to confirm whether the patient fulfilled our angiographic criteria. Verbal consent for the study was obtained by the cardiologist, who then referred the patient to a psychiatrist. The psychiatrist obtained written consent and then interviewed the patient within 24 hours of the procedure. The pa-

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TABLE I Base Rates of Interview Diagnoses and Inter-Rater Relatibilities

Diagnosis	n	(%)	Kappa
Anxiety disorders			
Panic disorder	32	(34.0)	0.81
Simple phobia	10	(11.0)	1.00
Social phobia	0	(0.0)	1.00
Major depression			
Current	11	(12.0)	1.00
Past only	12	(13.0)	1.00
Alcohol abuse			
Current	3	(3.0)	1.00
Past only	10	(11.0)	1.00
Overall kappa			0.95

Kappa coefficients were calculated based on 14 (14.9%) interviews that included both a primary interviewer and an observer.

TABLE II Demographic Data for Patients With Angiographically Normal Coronary Arteries With and Without Panic Disorder

	Current Panic Disorder (n = 32)	No Panic Disorder (n = 62)
M (%)	13 (41)	24 (39)
F (%)	19 (60)	38 (62)
Age (yrs),* mean ± SD	45 ± 12	53 ± 13
Marital status		
Married (%)	21 (66)	45 (74)
Separated/divorced (%)	6 (19)	8 (13)
Never married (%)	1 (3)	1 (2)
Widowed (%)	4 (12)	7 (12)
Social class		
I, II, III, IV (%)	7 (22)	18 (29)
V, VI, VII, VIII, IX (%)	25 (78)	44 (71)

* $p < 0.01$.
SD = standard deviation.

tient was also provided self-report forms that were generally completed at the time of interview or (occasionally) mailed back after discharge. Psychiatric interviews were performed by 3 board eligible psychiatrists trained in the use of the structured clinical interview.

The Structured Clinical Interview Upjohn Version[8] was used for the diagnosis of panic disorder, phobic avoidance (agoraphobia), social phobia, simple phobia and major depression. Diagnosis for alcohol abuse was made using the Diagnostic Interview Schedule alcohol use section.[9] Panic disorder has been shown to be commonly associated with agoraphobia, major depression and alcoholism in psychiatric populations.[10] For a diagnosis of panic disorder, subjects were required to meet the proposed revised Diagnostic and Statistical Manual of Mental Disorders criteria for panic disorder.[11] These criteria include: at least 3 attacks in 3 weeks of discrete periods of intense fear or discomfort, accompanied by at least 4 of the following symptoms: shortness of breath (dyspnea) or smothering sensations; choking; palpitations or accelerated heart rate (tachycardia); chest pain or discomfort; sweating; faintness; dizziness, lightheadedness or unsteady feelings; nausea or abdominal distress; depersonalization or derealization; numbness or tingling sensations (parethesias); flushes (hot flashes) or chills; trembling or shaking; fear of dying; and fear of going crazy or doing something uncontrolled. The symptoms cannot be sustained by any organic factor (such as hyperthyroidism, reaction to caffeine or amphetamine abuse). In addition, subjects were required to have had at least 1 panic attack/week for the past 3 weeks. This latter criterion ensured that subjects with panic disorder would be experiencing an ongoing series of attacks rather than a single cluster and would therefore be more likely to need treatment.

Each participant was also asked to complete the following questionnaires at the time of the interview: the Zung Self-Rating Anxiety Scale,[12] the Beck Depression Inventory,[13] the Marks-Mathews Fear Questionnaire (to test for agoraphobia)[14] and the Brief Symptom Inventory.[15]

Statistical methods: Chi-square tests of association were used to investigate the relation between the interview diagnosis of panic disorder and categorical study variables (sex, social status and other psychiatric diagnoses). Significance levels were evaluated in chi-square analyses using the Fisher exact test with Bonferroni adjustment for multiple comparisons. Continuous variables were contrasted among groups using a 2-tailed Student *t* test for age, and multivariate analyses of variance followed by univariate analyses for self-report questionnaires. Agreement between interviewers on panic disorder and other psychiatric diagnoses were assessed using the kappa coefficient of agreement for nominal scales (kappa). The statistical analysis system was used for all data analyses.

RESULTS

Subjects: Over the 2.2-year data collection period beginning August 1, 1985, 120 consecutive patients who met the study criteria were referred to us. They represented 7% (120 of 1,774) of all patients undergoing coronary angiography for any reason. Twenty-six of these were not included in the final sample either because of refusal (11) or because of incomplete or insufficient information to establish a definitive diagnosis (15). The final study sample, then, included 94 cardiology patients meeting the above criteria (37 men and 57 women), aged 24 to 78 years (50 ± 7, mean ± standard deviation). The 26 patients who qualified but did not participate were compared with the subjects by age and sex. No significant differences between the 2 groups were found nor were any trends obvious. Sixteen subjects did not complete the self-report questionnaires, but were interviewed. These subjects were compared by age and sex with those who did provide these data. No significant differences were found between these 2 groups.

Interview results: Table I lists the base rates for interview diagnoses with their interrater reliability index (K). The overall level of interrater agreement for interview diagnosis is good (overall K = 0.95). Thirty-two of the 94 subjects (34%) met criteria for current panic disorder. Subjects with panic disorder had a mean age of panic symptom onset of 41.9 years (standard deviation 12.3), and a mean duration of panic disorder (time from

TABLE III Current Medications for Patients with Angiographically Normal Coronary Arteries Across Panic Disorder Group Status

	Panic Disorder (n = 31)	No Panic Disorder (n = 63)
Cardiac medications		
Diuretics (%)	7 (22)	18 (29)
Beta blockers (%)	6 (19)	14 (23)
Calcium antagonists (%)	14 (44)	27 (44)
Other antihypertensives (%)	3 (9)	7 (11)
Nitrates (%)	22 (69)	46 (75)
Digitalis derivatives (%)	2 (6)	3 (5)
Antiarrhythmics (%)	0 (0)	2 (3)
Psychiatric medications		
Alprazolam (%)	2 (6)	7 (11)
Other benzodiazepines (%)	7 (22)	24 (39)
Antidepressants (%)	3 (9)	5 (8)
Neuroleptics (%)	0 (0)	0 (0)

TABLE IV Major Depression in Patients with Angiographically Normal Coronary Arteries by Panic Disorder Group Status

	Panic Disorder (n = 32)	No Panic Disorder (n = 62)
Major depression		
Current† (%)	9 (29)	2 (3)
Past or current* (%)	12 (38)	11 (17)
Past only (%)	3 (9)	9 (14)

*p <0.05; † p <0.001.

TABLE V Self-Report Questionnaire Scores for Patients With Angiographically Normal Coronary Arteries With and Without Panic Disorder

	Panic Disorder (n = 32)		No Panic Disorder (n = 62)	
	Mean	SD	Mean	SD
Beck depression inventory*	13.89	8.43	8.40	5.21
Zung self-rated anxiety scale†	52.00	7.81	43.50	7.66
Marks fear questionnaire				
Total score	25.65	15.05	25.39	17.75
Agoraphobia	5.65	6.86	6.04	6.80
Blood/injury	10.30	7.04	9.12	7.57
Social phobia	9.73	5.50	10.24	7.64
Michigan alcohol screening test	2.78	3.80	2.88	7.86
Brief symptom inventory				
General severity inventory*	0.93	0.57	0.57	0.41
Depression*	0.91	0.90	0.47	0.60
Anxiety*	1.08	0.71	0.70	0.57
Phobic anxiety	0.39	0.56	0.22	0.31
Somatization*	1.53	0.61	1.01	0.71
Obsessive-compulsive	0.90	0.80	0.78	0.76
Paranoid ideation*	0.89	0.89	0.48	0.49
Psychoticism*	0.54	0.55	0.24	0.31
Hostility*	0.76	0.58	0.38	0.44
Interpersonal sensitivity*	0.79	0.73	0.56	0.65

* p <0.01; † p < 0.001.
SD = standard deviation.

the age of onset until the interview) of 3.4 years (standard deviation = 6.4). Subjects with panic disorder reported experiencing a mean of 5.2 panic attacks (standard deviation 5.7) in the week before the interview, with the last most severe episode involving a mean of 7.7 panic symptoms (standard deviation 2.9).

Cross-sectional comparisons between those with and without panic disorder: DEMOGRAPHICS: Table II contrasts subjects positive for panic disorder (panic disorder [+]) with those negative for panic disorder (panic disorder [−]) on demographic variables. No chi-square values were found to be significant for sex, social class or marital status. A significant difference for age was found between groups, t (93) = 2.71, p <0.01.

MEDICATIONS: Table III lists current medication use for panic disorder (+) and panic disorder (−) subjects. While no chi-square values were significant in these comparisons, group differences for benzodiazepines did approach significance, chi-square (1 degree of freedom, n = 94) = 2.71, p <0.10. Panic disorder (−) subjects were nearly twice as likely to be prescribed alprazolam or other benzodiazepines as were panic disorder (+) subjects (Table III).

MAJOR DEPRESSION AND ALCOHOLISM: Panic disorder (+) and panic disorder (−) subjects were compared with regard to the presence of major depression (current or past), major depression (current) and major depression (past only). Table IV lists the frequencies (by panic disorder group) relevant to these analyses. Chi-square tests revealed significant differences for major depression (current), chi-square (1 degree of freedom, n = 94) = 13.44, p <0.0001, and major depression (current or past), chi-square (1 degree of freedom, n = 94) = 5.08, p <0.02. Panic disorder (+) and panic disorder (−) subjects were also compared with regard to current or past alcohol abuse, and drinker versus nondrinker status. No significant differences were found in these comparisons.

SELF-REPORT INSTRUMENTS: PANIC DISORDER (+) VERSUS PANIC DISORDER (−) GROUP COMPARISONS: Table V lists means and standard deviations of scores on all self-report measures for panic disorder (+) and panic disorder (−) subjects. The multivariate analysis of variance revealed a significant multivariate main effect for group F(5 degrees of freedom, n = 70) = 4.49, p <0.001. Univariate analyses of variance showed this effect to be associated with the Zung Self-Rating Anxiety Scale, F(1 degree of freedom, n = 75) = 20.64, p <0.001; the Beck Depression Inventory, F(1 degree of freedom, n = 75) = 10.31, p <0.01; and the Brief Symptom Inventory, F(1 degree of freedom, n = 75) = 10.06, p <0.01. Panic disorder (+) subjects scored more symptomatically on self-report instruments measuring depression (Beck Depression Inventory), anxiety (Zung Self-Rating Anxiety Scale) and global psychological distress (the general severity inventory) of the Brief Symptom Inventory).

To assess more specifically the relation between group differences and panic disorder group status, the 9 scales of the Brief Symptom Inventory were contrasted

between the panic disorder (+) and panic disorder (−) groups, using a multivariate analysis of variance. The multivariate statistic for the group comparison was significant, F(9 degrees of freedom, n = 66) = 3.27, p <0.002. Relevant univariate analyses revealed that the psychoticism, somatization, depression, hostility, anxiety and paranoia scales were significantly different for panic disorder (+) versus panic disorder (−) subjects (p <0.01, for all comparisons). For all clinical scales panic disorder (+) subjects scored higher than did panic disorder (−) subjects.

DISCUSSION

In this study we interviewed 94 consecutive consenting patients with angiographically normal coronary arteries according to a structured psychiatric interview. We found that 32 of 94 (34%) fit diagnostic criteria for panic disorder. The self-report questionnaires for anxiety, depression and general symptom severity affirmed the strong differences between the panic disorder (+) group and the panic disorder (−) group.

One limitation of this study is that the interviewers were not blinded to the cardiac status of the subjects. After completion of this trial we interviewed after catheterization 17 consecutive patients with no previous history of coronary artery disease who were found to have significant occlusions (Basha et al, submitted for publication). One of 17 fit panic disorder criteria, a figure consistent with previous studies,[16,17] suggesting panic disorder is unlikely in patients with angina and coronary artery disease.

Some will argue that the panic disorder label is only an interview diagnosis and that there is no biologic discriminator of the disorder. However, its diagnostic validity is supported by reliable challenge tests (carbon dioxide, lactate and yohimbine),[18] effective pharmacotherapy[19] and evidence of familial transmission.[20]

In addition to panic disorder, 2 other possibilities are being explored to understand and treat patients with chest pain and normal epicardial arteries. One possibility is microvascular angina. Cannon and Epstein[4] studied patients with syndrome X and angiographically normal coronary arteries, but they did not require the additional criterion of ST depression >0.1 mV. They found that these patients are likely to demonstrate decreased vasodilatory reserve with atrial pacing or ergonovine challenge. In addition, these patients respond to treatment with calcium antagonists.[4] Another set of explanations involves the esophagus, including motility disorders such as nutcracker esophagus, spasm and hypertonic lower esophageal sphincter, and esophageal reflux.[5]

Although Cannon[21] implied that syndrome X includes all patients with angiographically normal coronary arteries, this syndrome encompasses only about 25% of such patients because approximately 75% of those with normal coronary arteries are judged to have atypical angina.[16,22] Further, as listed in Table III, 44% of all subjects in the current study were receiving calcium antagonists at the time of catheterization, thus suggesting that this treatment is not effective for this group of patients. Although Cannon and Epstein[4] have suggested that nitrates are useful in treating microvascular angina, approximately 70% of patients were taking nitrates (Table III) without apparent relief of symptoms. We therefore conclude that the diagnosis of microvascular angina is likely to apply only to that 25% of patients with angiographically normal arteries who have typical angina.

Esophageal dysfunction may also be associated with chest pain in this group of patients. Katz et al[5] studied a group of noncardiac chest pain patients and found that approximately 25% had an esophageal disorder. The significance of these data remains to be defined because esophageal dysfunction has been reported in 33% of patients following myocardial infarction[23] and 28% of randomly selected subjects.[24]

The data from studies of panic disorder microvascular angina and esophageal disorders suggest that perhaps 25% of the disabilities seen in follow-up studies of patients with angiographically normal coronary arteries could be attributed to each of these 3 diagnostic groups. The final quarter of disability might be attributed to a miscellaneous group of diagnoses including gall bladder disease, pneumothorax, sleep apnea, major depression and many others. This is a preliminary conclusion because much research remains before these relatively new diagnostic entities will be firmly established and accepted in patients with angiographically normal epicardial arteries.

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