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Follow-up Status of Patients With Angiographically Normal Coronary Arteries and Panic Disorder

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Cardiology patients with normal coronary angiography demonstrate continuing and substantial social, health, and work disability. We hypothesized that the diagnosis of panic disorder would mark those for whom continuing disability is most likely. We interviewed 72 such patients at the time of their normal angiogram, and then again an average of 38 months later. Those with panic disorder (n = 36) demonstrated significantly more disability at follow-up than did the other study patients. We conclude that those patients with normal angiograms who have panic disorder are more disabled than those who do not have panic disorder. Panic disorder in psychiatric samples has been shown to be highly treatable. Therefore, early identification and treatment of panic disorder in this group is likely to minimize the suffering associated with this condition.

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AS MANY as 150 000 of the half million individuals who undergo cardiac catheterization each year in the United States are found to have no significant coronary artery disease.[1,2] Since the early 1970s, a number of investigations have evaluated the prognostic implications of normal coronary arteries (NCA) in follow-up periods ranging up to 10 years. Early studies found that such patients demonstrate a good prognosis with regard to long-term survival.[3-7] Many authorities thus assert that normal angiography signifies a benign condition requiring no treatment.

Although not contradicting findings of a low mortality risk for patients with NCA, more recent follow-up studies have documented that normal coronary findings provide a marker for serious long-term disability. These studies document that approximately half or more of patients with NCA continue to report problems such as regular chest pain, a persistent belief that they have heart disease, ongoing use of heart medications, and lowered capacity to work and to perform daily activities.[8-13] The cause and treatment of disability in patients with NCA is currently unknown.[14]

Panic disorder occurs in 33% to 46% of patients with NCA,[15-17] and may account for some of the long-term problems seen in these patients. This psychiatric condition, according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*,[18] is diagnosed in individuals experiencing at least four panic attack episodes (each including a minimum of four of the symptoms listed in Table 1) in a 4-week period that are not sustained by any organic factor (eg, hyperthyroidism, reaction to caffeine or other stimulants), and that do not occur exclusively on exposure to a specific phobic stimulus. In patients with NCA, chest pain is one of the panic symptoms.

Two lines of research further point toward the idea that panic disorder marks patients with NCA for long-term disability. First are those studies showing that panic disorder is associated with long-term disability in samples of psychiatric patients.[19,20] Second, Bass et al[15] found that disability in patients with NCA 1 year after angiogram was highly associated with psychiatric morbidity. Although they did not assess panic disorder specifically, these authors found that those patients with high levels of somatic psychiatric symptoms reported more chest pain, sought medical help more often, and reported more social deficits at follow-up than did other patients with NCA.

We conducted this study in order to test the prediction that patients with NCA and panic disorder are at a greater risk for long-term disability following a normal angiogram than are patients with NCA alone. To test this hypothesis, we carried out a follow-up study of psychiatric diagnosis, functional status, and self-perceived illness in a group of patients with NCA whom we had previously interviewed immediately following their angiograms.[16] Because panic disorder is a highly treatable condition,[21] the confirmation of this hypothesis would have the practical effect of suggesting intervention strategies for a subset of dysfunctional patients with NCA.

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Table 1.—Panic Attack Symptoms*

Shortness of breath (dyspnea) or smothering sensations
Choking
Palpitations or accelerated heart rate (tachycardia)
Chest pain or discomfort
Sweating
Faintness
Dizziness
Nausea or abdominal distress
Depersonalization or derealization
Numbness or tingling sensations (parasthesias)
Flushes (hot flashes) or chills
Trembling or shaking
Fear of going crazy or doing something uncontrolled

*Panic attack is defined as a period of intense fear or discomfort accompanied by at least four of the listed symptoms.

METHODS

Subjects

Study Population.—From August 1, 1985, through October 13, 1987, 120 patients with chest pain undergoing cardiac catheterization at the University of Missouri (Columbia) Cardiology Division were found to have less than 30% stenosis of all major epicardial arteries and no other cardiac abnormalities (eg, valvular heart disease including mitral valve prolapse, cardiomyopathy, congenital heart disease, hypertensive heart disease, and pericardial disease). Ninety-four of these patients formed the baseline sample described earlier.[16]

We obtained follow-up information from 72 of the 94 baseline patients a mean of 38 months (SD, 6.5 months) after the baseline assessment. Of the 22 patients for whom we did not obtain follow-up data, we were unable to locate 19, two refused to participate, and one had apparently died of cancer. Thus, the final follow-up sample consisted of 72 patients (48 women and 24 men) whose ages ranged from 27 years to 79 years (mean, 56 years; SD, 11.8 years).

Study Groups.—For all study analyses, the follow-up subjects were dichotomized based on whether they met criteria for a lifetime history of panic disorder based on the Structured Clinical Interview from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*.[22] Thirty-six patients with a mean age of 59 years (26 women and 10 men) were classified as positive for a lifetime history of panic disorder (panic disorder group). The remaining 36 patients (mean age, 61 years; 22 women and 14 men) were found to be negative for a lifetime history of panic disorder (no panic disorder group). Statistical comparisons showed that the groups had similar gender distributions; however, patients in the panic disorder group were significantly younger than those in the no panic disorder group ($F[1,71] = 14.30$, $P<.001$).

Follow-up Study Measures

Measures of Disability.—In order to assess psychosocial function, we administered the Social Adjustment Scale (Self-report Version) (SAS-SR).[23] The SAS-SR is a 54-item self-report measure that inquires about six role areas (work, social and leisure, extended family, marital relations, parental, and nuclear family). Additionally, an overall measure of social adjustment is provided by considering the scores in each role area together in the Overall Global summary score. The SAS-SR has been shown to have good reliability and validity as compared with patient and informant interviews covering the same information.[23]

We assessed study subjects' functional cardiac status utilizing a shortened version of the Specific Activities Scale (SAS).[24] Items on this measure ask about subjects' ability to perform specific activities of known metabolic equivalent requirements. Respondents are classified into one of four ordinal level categories based on the activity with the highest metabolic equivalent requirement that they indicate that they can perform without difficulty (eg, level I indicates that ordinary activity does not cause undue fatigue; level IV indicates inability to perform virtually any physical activity without discomfort).[24]

Based on a questionnaire developed at Duke University, Durham, NC, for follow-up studies of patients with NCA,[11] we obtained data regarding subjects' medical and mental service utilization (eg, medications, consultations, procedures), beliefs regarding their current health status, and changes they have perceived in their health since the time of their angiogram (ie, baseline phase).

Psychological Functioning and Psychiatric Diagnostic Status.—Patients were interviewed for current or past diagnoses of panic disorder, major depression, and alcohol abuse and dependence during both the baseline and follow-up phases of this study.[22] Assessment of the interrater reliability (κ) for the baseline and follow-up interviewers (conducted by J.L. and M.G.K., respectively) was determined by having both interviewers separately assess a subset of 15 subjects (20% of the total) from the follow-up phase. These separate interviews of the same patient showed good diagnostic agreement ($\kappa = .76$).

In order to determine subjects' level of psychological symptoms, patients were asked to fill out the Brief Symptom Inventory.[25] The Brief Symptom Inventory is a 53-item self-report inventory of symptoms that provides a Global Severity Index, a sensitive overall indicator of current distress level.[25] Subjects also filled out the Zung Self-rating Anxiety Scale[26] and the Marks-Mathews Fear Questionnaire.[27]

Procedures.—After patients were found to have angiographically NCA (ie, <30% stenosis), they were interviewed and baseline measures were taken within 24 hours.[16]

Approximately 3½ years later, the follow-up information was gathered. Informed by a graded set of techniques for locating study subjects outlined by Russell Noyes, MD (written communication, March 1989), we attempted to recontact all 94 patients assessed during the baseline phase. Seventy-two patients (77%) participated in the follow-up.

On telephone contact, we attempted to set up an appointment for the patients to come to our clinic ($n = 21$) or, if this was not possible, to do the Structured Clinical Interview over the telephone and complete questionnaires that were mailed to them ($n = 51$). Studies have shown that diagnostic interviews conducted over the telephone demonstrate good interrater reliability when compared with those conducted face-to-face.[28] The persons conducting follow-up Structured Clinical Interviews were blind to patients' baseline diagnostic status; patients were paid for their participation.

RESULTS

Assessment for Sampling Bias

Using data gathered at baseline, we compared those patients who participated in the follow-up phase ($n = 72$) with those who did not ($n = 22$), in order to evaluate whether subject loss was systematic (ie, biased vs random). These comparisons showed that participants and nonparticipants did not differ significantly in terms of gender, social class, psychiatric status, or psychological functioning. However, statistical comparisons did reveal that follow-up participants were significantly older at baseline (mean, 52.4 years; SD, 11.9 years) than were nonparticipants (mean, 43.7 years; SD, 13.3 years) ($t[83] = 3.04$, $P<.01$). These findings suggest that, although subject loss was generally unsystematic, older subjects were more likely to be in the follow-up phase than were younger subjects.

Disability in Panic Disorder Patients vs Other Patients With NCA

Our major study hypothesis was that the disability experienced would be most notable in the panic disorder group. Table 2 shows the percentage of patients with and without panic disor-

Table 2.—Functional Status at Follow-up for Those With and Without Panic Disorder (Measures of Disability)*

Measure of Disability	Panic Disorder, % (n = 36)	No Panic Disorder, % (n = 36)	χ^2
Chest pain			
In the past week	71.9	33.3	9.24†
During rest	66.7	23.3	11.89‡
During sleep	30.0	0.0	10.81‡
Worse since catheterization	21.9	7.4	5.31
View of own health and vigor			
Health worse since catheterization	31.3	3.3	8.75†
Ability to perform physical activity worse since catheterization	27.3	3.3	9.62†
Moderate to strong belief that they are suffering from heart disease	30.6	8.3	5.68§
Difficulty doing tasks ranging from ordinary activities to nearly everything	47.2	19.4	6.25†
Other psychiatric disorders			
Depression (since catheterization)	22.2	8.3	2.68
Alcohol abuse (since catheterization)	22.2	6.3	3.23
Medication use			
Cardiologic	58.3	38.9	2.72
Psychiatric	33.3	15.6	2.75
Type of treatment sought since catheterization			
Psychiatric	21.9	4.8	1.61
Medical (any)	93.9	93.3	0.01
Hospitalization	42.4	26.7	1.72
Work status since catheterization			
Changed work situation due to health	20.6	6.7	2.56
Unemployed (nonhomemaker)	39.4	33.3	0.69
Total No. of workdays missed last year due to panic disorder symptoms	16.2	2.0	4.25§

*We employed a conservative α level of .01 to control for experimentwise error due to multiple comparisons. The measure of disability "Total No. of workdays missed last year due to panic disorder symptoms" is expressed as a mean value, and the statistic used is an F test.
†P < .01.
‡P < .001.
§P < .05.

der reporting impairment at follow-up (ie, chest pain, view of own health and physical limitations, lifetime history for other psychiatric disorder, medication use, treatment sought, and work status). We did not obtain similar data at baseline. As shown in Table 2, those in the panic disorder group reported greater disability on all measures. Because of the multiple comparisons and potential for an inflating α, we use the conservative α level of .01 to indicate statistical significance.

Chest Pain.—Beginning with measures of chest pain, Table 2 shows that, compared with the no panic disorder patients, significantly more panic disorder patients had experienced chest pain in the past week (72% vs 33%), chest pain during rest (67% vs 23%), and chest pain during sleep (30% vs 0%). These differences remain significant after α adjustment for multiple comparisons (.01). Also, although only approaching statistical significance, panic disorder patients were nearly three times more likely to report that their chest pain had worsened since their normal catheterization at baseline (22% vs 7%) (χ^2 [2, N = 59] = 5.31, P < .07).

Patients' Self-view of Disability.—Table 2 shows that panic disorder patients view themselves as significantly more disabled than do no panic disorder patients. Thirty-one percent of the panic disorder group reported that their health had deteriorated since catheterization as compared with 3% in the no panic disorder group. Similarly, a significantly greater proportion of the panic disorder group reported worsening ability to perform physical activity (27% vs 4%) and difficulty doing tasks ranging from "ordinary" to "nearly everything" (47% vs 19%). Of those who reported a moderate to strong belief that they were suffering with heart disease, 31% were in the panic disorder group, while only 8% were in the no panic disorder group; however, this difference did not reach the conservative α value of P < .01.

Other Psychiatric Disorders.—Although study groups were formed based on the presence or absence of panic disorder, the extent to which patients reported other psychiatric conditions during the follow-up period is a further measure of disability. Restricting our assessment to major depression and alcohol abuse, we found that those in the panic disorder group reported these conditions more often than did other patients. Statistical comparisons, however, demonstrated that these differences were not significant (depression: χ^2 [1, N = 72] = 2.68, P < .10; alcohol abuse: χ^2 [1, N = 64] = 3.23, P < .07).

Use of Medications.—A greater proportion of those in the panic disorder group reported the current use of cardiologic medications (ie, diuretics, β-blockers, digitalis derivatives, antiarrhythmics, other antihypertensives, and nitrate derivatives) than did those in the no panic disorder group (58% vs 39%); however, these differences only approached statistical significance (χ^2 [1, N = 72] = 2.72, P < .10). A similar trend is shown in Table 2 for patients' use of psychiatric medications (ie, primarily benzodiazepines and antidepressants 33% vs 16%), where group differences again approached statistical significance (χ^2 [1, N = 65] = 2.75, P < .10).

Medical Treatment Sought—Few significant group differences in medical treatment sought over the follow-up period were noted. This finding may reflect, in part, the very high rates of treatment sought for both groups (ie, a "ceiling effect"). Table 2 shows that about 94% of both groups sought additional medical services for their symptoms during the follow-up period. Although more of those with panic disorder sought psychiatric help (22% vs 5%), and were rehospitalized (42% vs 27%), these differences were not statistically significant.

Work Status.—Panic disorder patients appeared to be somewhat more unable to work than others in terms of their work status; however, relevant group differences did not reach statistical significance. As seen in Table 2, panic disorder patients were more likely to have changed their job or work activities due to their symptoms since baseline (21% vs 7%) (χ^2 [1, N = 65] = 2.56, P < .11), but were no more likely to report being unemployed (does not include homemaker or retired, 39% vs 33%). Of those who were employed, however, Table 2 shows that those in the panic disorder group missed more days of work specifically due to their symptoms in the preceding year than did other patients (mean, 16 vs 2 days). This finding must be viewed with caution, however, because only 40 of the 72 patients responded to this question, and the group differences did not reach the conservative α level of .01.

Specific Activity Scale.—In addition to the patients' self-reports of exertional limitations, we utilized the SAS in order to derive a more standardized measure of exertional capacity. Sub-

stantially fewer panic disorder patients were classified in the 0 and 1 categories of the SAS (lower classification numbers indicate a greater symptom-free exertional capacity) as compared with other patients. In order to evaluate the statistical significance of these differences, we contrasted the study groups in terms of the proportion who were classified in either category 0 or 1 on the SAS vs those classified at 2 to 4 on the SAS using a χ^2 test. Results of this analysis showed that those in the panic disorder group were significantly more likely to be classified in the 2 to 4 range of the SAS (lower capacity for symptom-free exertion) than were those in the no panic disorder group (68% vs 38%) ($\chi^2[1, N=62] = 6.29$, $P<.01$).

Psychological Measures.—We evaluated whether the study groups differed on self-report and continuous measures of psychological and social functioning (Table 3). We first subjected these measures (ie, Brief Symptom Inventory [psychological distress], Marks-Mathews Fear Questionnaire [fears and phobias], Zung Self-rating Anxiety Scale [state anxiety], and SAS-SR [social functioning]) to a multivariate analysis of variance, followed by evaluation of univariate analyses of variance where indicated. The multivariate analysis of variance produced a significant multivariate statistic ($F[4,35] = 3.04$, $P<.05$), indicating that the analyses of variance for the dependent measures could be evaluated separately.

As Table 3 shows, univariate analyses were significant for each dependent variable with the exception of fears and phobias (Marks-Mathews Fear Questionnaire). These findings indicate that panic disorder patients reported more social dysfunction (SAS-SR) and were more symptomatic with regard to general psychological distress (Brief Symptom Inventory) and state anxiety (Zung Self-rating Anxiety Scale).

Table 3.—Functional Status at Follow-up for Those With and Without Panic Disorder (Continuous Psychological Measures)

Psychological Measure	Panic Disorder (n=36)	No Panic Disorder (n=36)	F Value
Social Adjustment Scale score			
Mean	2.08	1.69	5.99*
SD	0.70	0.53	...
Zung Self-rating Anxiety Scale score			
Mean	44.19	37.32	13.40†
SD	8.17	3.21	...
Marks-Mathews Fear Questionnaire score			
Mean	25.43	23.55	0.08
SD	19.30	22.29	...
Brief Symptom Inventory score			
Mean	37.03	19.50	7.78‡
SD	27.49	10.01	...

*$P<.05$.
†$P<.001$.
‡$P<.01$.

COMMENT

This study indicates that over a 3- to 4-year follow-up of patients with NCA, those with panic disorder report more continuing chest pain, worsening of health, greater reduction in exertional capacity, poorer social adjustment, more anxiety symptoms, and more psychological distress than do those without panic disorder. There were no significant differences between the two groups in the use of cardiac and psychiatric medications or visits to physicians; however, a clear statistical trend in the data suggested that the use of these drugs was more common for patients with panic disorder. Similarly, while it is well established that many patients with NCA continue to report chest pain, along with social and work disability, this study suggests that it is those with panic disorder who account for a disproportionately large degree of these continuing difficulties.

The small sample size may have reduced the significance of many of the differences found. Furthermore, disability due to panic attacks was present in the group without panic disorder, since 18 (50%) of this group met criteria for panic attacks, but the attacks were not frequent enough to meet panic disorder criteria (four attacks in 4 weeks). This may also have reduced the significance of the differences between the two groups.

Panic disorder has been shown to be effectively treated in pharmacologic[27] and cognitive-behavioral therapy trials.[28] While these studies were conducted in psychiatric samples, other evidence suggests that panic disorder in patients with NCA is also responsive to standard antipanic treatment. We made no systematic efforts to judge the treatment adequacy of the panic disorder patients in this study, except to find that only 22% sought psychiatric treatment and that nearly one of three was taking benzodiazepenes and/or antidepressants. Without such treatment, group differences probably would have been greater.

On the other hand, the finding that only one of three of the panic disorder patients was taking medications likely to be useful for treating their panic symptoms reflects the following three obstacles to panic disorder treatment in patients with NCA whom we have observed clinically: (1) these patients tend to resist psychiatric labels, (2) their primary care physicians tend to miss the panic disorder diagnosis, and (3) angiologists do not include panic disorder in their differential diagnosis. All patients were offered the opportunity to ask about their psychiatric diagnosis and the treatment options. For details about diagnostic and treatment approaches to patients with NCA, see Beitman[30] and Cannon.[31]

A further limitation of this study is the lack of assessment for several other potentially relevant psychiatric disorders that may have contributed to the group differences. Among these disorders are hypochondriasis, somatization disorder, and various personality disorders. These disorders would be likely to increase the disability of panic disorder patients. The marginally significant findings of increased depression and increased alcoholism in the panic disorder group also suggest the possibility that other, co-occurring disorders may explain some of the disability seen in panic disorder patients. However, any patient with one psychiatric disorder is twice as likely as someone with no psychiatric disorder to have another psychiatric disorder.[32] Furthermore, approximately 50% of panic disorder patients report a lifetime history of major depression,[33,34] and alcoholism may be increased among panic disorder patients.[35] Therefore, panic disorder is likely to be associated with other disorders that may increase patients' disability.

The findings of this study may not generalize to other populations. In our hospital, 7% of patients undergoing cardiac catheterization at the time of this study had 30% or less stenosis. It remains unclear to what degree our findings apply to the approximately 10% of cardiac catheterization patients who have "near-normal" coronary arteries (30% to 50% stenosis), who are somewhat more likely to develop coronary

artery disease.[11] Future studies need to contrast patients with normal vs near-normal epicardial arteries, who together constitute up to 25% of patients undergoing cardiac catheterization.[1,2]

In addition to panic disorder, other medical diagnostic entities have been suggested to explain the chest pain in patients with NCA, including esophageal motility disorders and gastroesophageal reflux[36] and microvascular angina.[37] Studies have indicated that there is considerable overlap between both esophageal disorders and microvascular angina and psychiatric disorders, including panic disorder.[38-40]

As indicated earlier, as many as 150 000 individuals undergoing cardiac catheterization for chest pain in the United States each year are found to have normal or near-normal epicardial arteries. According to our findings, 34% will fit panic disorder criteria at the time of catheterization,[16] and as many as 50% will show a lifetime diagnosis for panic within a 3- to 4-year period following catheterization. Because much evidence indicates that panic disorder is highly treatable, the correct diagnosis and appropriate treatment is likely to greatly reduce patient morbidity and public health costs.

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