# Atypical or Nonanginal Chest Pain

## Panic Disorder or Coronary Artery Disease?

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**• Of 195 patients with atypical or nonanginal chest pain presenting in a cardiology clinic, 104 consented to be evaluated for anxiety disorders using a structured psychiatric interview. Thirty patients had histories of coronary artery disease (CAD). Fifty-nine patients in the sample (16 of those with CAD and 43 of those without CAD) fit diagnostic criteria for panic disorder (PD). Those without CAD and with PD were primarily women (mean age, 43 years) with predominantly nonanginal chest pain. Those patients with both CAD and PD were primarily men (mean age, 54 years) with predominantly atypical angina. Since PD has been shown to be readily responsive to pharmacologic intervention, this diagnosis should be considered in patients with atypical or nonanginal chest pain.**

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Several recent studies have suggested that at least one third of chest pain patients with angiographically normal coronary arteries have panic disorder (PD).[1-3] Studies have also suggested that physician impression of chest pain as atypical for angina was strongly associated with a normal coronary arteriographic study.[1,3-5] Diamond and Forrester[6,7] studied 28 948 patients described in the medical literature, each of whom had been assigned a chest pain category and had been evaluated by coronary arteriography. They determined the pretest probabilities that certain types of chest pain, when coupled with information about the patient's age and sex, would be associated with angiographically determined coronary artery disease (CAD). For example, a 35-year-old woman with chest pain atypical for angina has a 4% chance of having CAD, while a 65-year-old man with nonanginal chest pain has a 28% probability for CAD.[7]

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Since patients with angiographically normal coronary arteries tend to have atypical chest pain, and at least one third of them have been found to have PD, we hypothesized that cardiology outpatients with atypical or nonanginal chest pain and without CAD might also have a high probability of PD. We are unaware of any other studies of cardiology outpatients for PD. In addition, cardiologists have noted clinically that some patients with CAD continue to complain of chest pain that is not well explained by the heart disease itself. Often called "cardiac neurotics," this group appears anecdotally to include some patients with PD. Since the chest pain in these patients is often atypical, we hypothesize that patients with CAD who have either atypical or nonanginal chest pain might also have PD.

Therefore, we attempted to identify consecutive cardiology outpatients with atypical or nonanginal chest pain and to recruit them into an interview study for PD. The clinical relevance of this study is threefold as follows: (1) it might confirm the increasing evidence that many cardiology patients with chest pain have PD; (2) it would demonstrate the existence of such patients in the cardiology outpatient setting in addition to the inpatient postcatheterization setting; and (3) since PD is readily responsive to pharmacological intervention,[8] accurate diagnosis of these patients in cardiology clinics is likely to lead to successful treatment.

According to the 1985 proposed *Diagnostic and Statistical Manual of Mental Disorders III* (*DSM-III*),[9] PD is characterized by at least three attacks in three weeks of discrete periods of intense fear or discomfort, accompanied by at least four 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 (paresthesias); flushes (hot flashes) or chills; trembling or shaking; fear of dying; and fear of going crazy or doing something uncontrolled. In addition, the symptoms cannot be sustained by any organic factor (eg, hyperthyroidism, caffeinism, or amphetamine abuse).

Table 1.—Four Groups of Cardiology Outpatient Demographics: Panic Disorder (PD) and Coronary Artery Disease (CAD)

| | Group, No. (%) | | | | Significance* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PD(+)/CAD(+) (N=16) | PD(−)/CAD(+) (N=14) | PD(+)/CAD(−) (N=43) | PD(−)/CAD(−) N=30 | 1 vs 2 | 1 vs 3 | 1 vs 4 | 2 vs 3 | 2 vs 4 | 3 vs 4 |
| Age, y, SD | 54.4±11.1 | 57.0±12.1 | 42.5±18.6 | 46.8±16.2 | ... | ... | ... | .05 | ... | ... |
| Female | 7 (44) | 5 (36) | 33 (77) | 18 (60) | ... | ... | ... | .005 | ... | ... |
| Married | 9 (56) | 12 (86) | 28 (65) | 20 (67) | ... | ... | ... | ... | ... | ... |
| Social class I, II, III, IV | 3 (19) | 5 (36) | 9 (21) | 7 (27) | ... | ... | ... | ... | ... | ... |
| V, VI, VII, VIII, IX | 12 (75) | 8 (57) | 26 (60) | 19 (63) | ... | ... | ... | ... | ... | ... |
| Atypical angina | 13 (81) | 10 (71) | 14 (32) | 8 (29) | ... | .002 | .002 | ... | .005 | ... |

*Analysis of variance, followed by Tukey's test.

## PATIENTS AND METHODS

### Study Population

All clinical cardiologists at a university hospital were asked to identify outpatients with atypical or nonanginal chest pain. Each patient chart packet included a sheet requesting the patient's name, sex, age, type of chest pain (anginal, atypical, nonanginal, no chest pain), willingness to participate in the study, and willingness to be interviewed on the day of the cardiologist's evaluation. Typical angina was defined as substernal, exertional, and relieved by rest or nitroglycerine. Atypical angina was defined as having two of the three factors. Nonanginal chest pain was defined as having only one of these characteristics. Patients with and without CAD were included in the study. Coronary artery disease was defined by history of a positive cardiac catheterization or a history positive for myocardial infarction. Absence of CAD was defined by clinical cardiologists who used standard tests at their discretion. During the period from April 1985 through February 1986, 206 patients were identified.

### Interview

The Structured Clinical Interview for *DSM-III* (SCID) was developed by Spitzer and Williams[10] to approximate standard psychiatric clinical interviewing while retaining sufficient structure to maintain interrater reliability. The SCID-UP[11] was specifically developed for the diagnosis of PD, phobic avoidance (agoraphobia), social phobia, simple phobia, and major depression. To receive a diagnosis of PD, subjects were required to meet revised *DSM-III* criteria for PD[9] and to have had at least one panic attack per week for the past three weeks. This latter criterion ensured that subjects with PD would be experiencing an ongoing series of attacks rather than a single cluster. This more conservative criterion than the *DSM-III* criterion increases the likelihood that these subjects are in need of treatment.

Interviews were performed by one of two board-eligible clinical psychiatrists. Nine patients were seen by both interviewers. There was 100% agreement in their ratings of PD, agoraphobia, social phobia, simple phobia, and major depression. After each interview, the interviewer discussed his or her findings with the first author to minimize rater drift.[12]

### Self-Report Questionnaires

Each participant was asked to complete the following questionnaires at the time of the interview: (1) the Zung Self-Rating Anxiety Scale (SAS),[13] (2) the Beck Depression Inventory (BDI),[14] (3) the Marks-Mathew Fear Questionnaire,[15] and (4) the Brief Symptom Inventory (BSI).[16]

The SAS offers a well-accepted measure of anxiety. Ten of its 20 items are symptoms of panic attacks. Because depression is commonly found in patients with panic disorder,[17] the BDI provided a useful measure of this symptom complex. Since agoraphobia is also commonly associated with panic disorder,[9] the agoraphobia subscale of the Fear Questionnaire could serve to further define the PD group. The BSI provided subscales of anxiety, depression, and phobic anxiety by which to test the reliability of the other scales, as well as a subscale for somatization, another symptom dimension commonly found in patients with PD.[18] The BSI provided the General Severity Index (GSI) to be used as a single summary measure of current distress levels.

### Statistical Methods

To evaluate the relationship between the interview diagnosis of PD and categorical variables (eg, sex, type of chest pain, and other psychiatric diagnoses) $\chi^2$ analysis was used with the appropriate Fisher's exact test with Bonferroni's adjustment. Continuous variables (eg, mean group differences in age and self-report questionnaire means) were evaluated using two-tailed Student's $t$ test and analysis of variance (ANOVA) followed by Tukey's test. Statistical analysis system (SAS) software was used for the data analysis.

## RESULTS

One hundred four of the 195 (53%) potential subjects consented to participate. Of the subjects, 40 were men and 64 were women. They ranged in age from 16 to 86 years with a mean of 47.8 years. Forty-seven had chest pain that was atypical for angina, and 56 had nonanginal chest pain. One occasionally had atypical anginal chest pain and nonanginal chest pain at other times. Of the 91 nonparticipants, 39 were men and 52 were women, ranging in age from 19 to 84 years. Forty of these patients had atypical angina and 51 had nonanginal chest pain. There were no significant differences between the participants and nonparticipants with regard to sex, age, or type of chest pain. Only 15% of those patients who consented to participate agreed to be interviewed the day they were seen in cardiology clinic. Another 10% came to follow-up appointments. The rest were recruited to come in for the interview by telephone. The following reasons were given for not participating in the study: it was too far to travel (15%); the patient felt better since visiting the cardiologist (10%); and a lack of belief in psychiatry (10%). Another 25% could not be reached after several phone calls or did not have a phone. Among the others who refused to participate, a few stated that financial problems or conflict with work schedules made participation impossible. One potential subject died of a myocardial infarction shortly after being identified as eligible for the study.

Thirty of the 104 subjects had histories of CAD, 22 of whom had histories of cardiac catheterization with abnormal findings; eight had been treated for myocardial infarction. Of the remaining 74 subjects, 43 fit the diagnosis for PD and 31 did not. One of the 31 nonpanic, non-CAD

Table 2.—Differences in Scores on Self-Report Questionnaires Between Patients With and Without Panic Disorder (PD) and With and Without Coronary Artery Disease (CAD)

| | Group Score ± SD | | | | | Significance (*P*) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | PD(+)/CAD(+) (N=16) | PD(−)/CAD(+) (N=14) | PD(+)/CAD(−) (N=43) | PD(−)/CAD(−) (N=30) | ANOVA (*P*)* | 1 vs 2 | 1 vs 3 | 1 vs 4 | 2 vs 3 | 2 vs 4 | 3 vs 4 |
| Beck Depression Inventory | 12.4 ± 6.4 | 13.6 ± 8.3 | 13.4 ± 10.1 | 8.1 ± 5.8 | .0496 | ... | ... | ... | ... | ... | .05 |
| Zung Self-Rated Anxiety Scale | 52.0 ± 8.9 | 46.0 ± 9.5 | 51.8 ± 10.9 | 42.6 ± 9.6 | .0012 | ... | ... | .05 | ... | ... | .01 |
| Fear questionnaire | | | | | | | | | | | |
| Agoraphobia | 6.2 ± 6.6 | 6.7 ± 7.7 | 10.1 ± 9.4 | 4.3 ± 4.9 | .0148 | ... | ... | ... | ... | ... | .01 |
| Blood/injury | 8.3 ± 8.0 | 8.4 ± 7.3 | 12.6 ± 9.4 | 7.3 ± 5.5 | .0307 | ... | ... | ... | ... | ... | .05 |
| Social phobia | 10.7 ± 7.4 | 7.8 ± 6.2 | 13.9 ± 7.7 | 8.6 ± 6.1 | .0051 | ... | ... | ... | .05 | ... | .05 |
| Total score | 25.3 ± 14.1 | 23.0 ± 18.6 | 36.7 ± 20.8 | 20.2 ± 12.5 | .0009 | ... | ... | ... | ... | ... | .01 |
| Brief Symptom Inventory | | | | | | | | | | | |
| Somatization | 1.44 ± 0.54 | 0.87 ± 0.54 | 1.64 ± 0.61 | 0.79 ± 0.55 | .0001 | .05 | ... | .05 | .01 | ... | .01 |
| Depression | 0.82 ± 0.91 | 0.63 ± 0.65 | 0.85 ± 0.84 | 0.41 ± 0.54 | .0973 | ... | ... | ... | ... | ... | ... |
| Anxiety | 0.92 ± 0.80 | 0.61 ± 0.54 | 1.20 ± 0.88 | 0.56 ± 0.58 | .0026 | ... | ... | ... | ... | ... | .01 |
| Phobic anxiety | 0.43 ± 0.48 | 0.43 ± 0.54 | 0.72 ± 0.85 | 0.26 ± 0.53 | .0407 | ... | ... | ... | ... | ... | .05 |
| General Severity Index | 0.81 ± 0.54 | 0.63 ± 0.50 | 0.99 ± 0.60 | 0.47 ± 0.43 | .0010 | ... | ... | ... | ... | ... | .01 |

*ANOVA indicates analysis of variance.

subjects was found to have sleep apnea for which surgical treatment relieved her chest pain. She was therefore dropped from subsequent data analysis.

Four groups were formed based on the presence or absence of PD and the presence or absence of CAD. Forty-three were PD(+) (positive for panic disorder) and CAD(−) (negative for coronary artery disease). The following number of subjects in the PD(+)/CAD(−) group had at least one of these diagnostic evaluations: 41 had an electrocardiogram (ECG), 24 had Holter monitoring, 28 had an echocardiogram, 24 had treadmills (23 normal, one below normal exercise tolerance, and seven had coronary arteriography, all of which were normal or near normal—≤50% occlusion of a major artery). Sixteen subjects had PD(+)/CAD(+); 30 had PD(−)/CAD(−); and 14 had PD(−)/CAD(+). Table 1 describes the demographic variables of the four groups. Analysis of variance for age differences among the four groups was significant ($F=3.96$; $P<.01$). Using Tukey's multiple comparison test, the PD(−)/CAD(+) group was significantly older than the PD(+)/CAD(−) group. In the remaining categories, if the results of $\chi^2$ analyses were positive, Fisher's exact tests were conducted with Bonferroni adjustments to see where the differences occurred. On sex ($\chi^2=10.27$; $P<.025$), the PD(−)/CAD(+) group had more men than the PD(+)/CAD(−) group ($P<.005$). On chest pain type ($\chi^2=22.67$; $P<.005$), the differences were found between three pairs: PD(+)/CAD(+) vs PD(+)/CAD(−) ($P<.002$); PD(+)/CAD(+) vs PD(−)/CAD(−) ($P<.002$); and PD(−)/CAD(+) vs PD(−)/CAD(−) ($P<.005$). Atypical angina was significantly more frequent than nonangina among those with CAD(+). There were no significant differences in social class ($\chi^2=1.27$) or marital status ($\chi^2=3.12$).

In regard to other anxiety disorders, six of the PD(+)/CAD(−) group reported limited phobic avoidance, two of these subjects reported extensive phobic avoidance (agoraphobia), and one reported a social phobia; no other subjects fit criteria for social phobia. Simple phobias were reported by two subjects with PD(+)/CAD(+), four with PD(−)/CAD(−), and ten with PD(+)/CAD(−). Chi-square analysis showed no significant differences in simple phobias. The groups did not differ significantly in terms of current or at least one past major depression.

Table 2 compares the four groups on the self-report questionnaire, using ANOVA followed by Tukey's multiple comparison test where $F$ values reflect a probability below .05. The only significant difference between the two CAD groups was found on the somatization scale of the BSI. This scale also showed significant differences between the following three pairs: PD(+)/CAD(+) vs PD(−)/CAD(−); PD(−)/CAD(+) vs PD(+)/CAD(−); and PD(+)/CAD(−) vs PD(−)/CAD(−). In comparing the two groups without CAD, the PD(+) group scored significantly higher than PD(−) on all measures except the depression scale of the BSI. In addition, the PD(+)/CAD(+) group differed significantly from the PD(−)/CAD(−) group on the Zung Self-Rated Anxiety Scale. On the social phobia scale of the Fear Questionnaire, the PD(+)/CAD(−) group scored significantly higher than the PD(−)/CAD(+) group.

Because only seven of the 43 subjects with no history of CAD had angiographically normal coronary arteries, we calculated the probability that one randomly selected subject from the remaining 36 would have CAD. The calculations utilized the data of Diamond and Forrester,[7] who had calculated the preangiographically determined CAD probability based on sex and type of chest pain for the four decades 30 to 39 years, 40 to 49 years, 50 to 59 years, and 60 to 69 years. Since nine subjects were aged younger than 30 years and five subjects were aged older than 69 years, we made the following assumptions: for those subjects aged younger than 29 years, we used the 30- to 39-year figures and for those aged older than 69 years, we used the 60- to 69-year probability estimates. The mean probability that one randomly selected subject would have CAD was .10. However, these data were highly skewed toward the younger, lower probability end (SD ± .13), suggesting that the median (.04) might better represent this probability estimate. We therefore estimated that at least one member of the group ($36 \times .04 = 1.4$) had CAD that was undetected. In fact, after the data were analyzed, one patient was discovered to have CAD.

## COMMENT

The finding that 43 (59%) of 74 patients with atypical or nonanginal chest pain and no CAD had PD is remarkable. Even if one were to assume that all the nonparticipants had no CAD, making the denominator 74+91=165 and the percentage 43 (26%) of 165, this figure is still much higher than the 1.0% found in community studies,[19-21] and the 6.5% to 13.0% found in an outpatient primary care population.[22]

That more than 50% of patients with CAD and either atypical or nonanginal chest pain had panic disorder is also remarkable. If this finding is substantiated by future investigations, then cardiologists and general internists may use a new diagnostic option with possible treatment options for this often problematic population.

The self-report questionnaires showed significant differences on all but one scale in comparisons between PD(+)/CAD(−) and PD(−)/CAD(−) groups. However, they did not show as many significant differences within the CAD(+) group or in comparison of the two CAD(+) groups with the CAD(−) groups. The reason the PD(+)/CAD(+) group did not differ from the PD(−)/CAD(+) group may be because patients with medical illnesses tend to have high scores on measures of anxiety and depression. The PD(+)/CAD(+) did show some differences in the expected direction when compared with the PD(−)/CAD(−) group. The reason the differences were not greater is unclear.

One of the more intriguing questions generated by these findings concerns the pathophysiology of chest pain in PD. Chest pain is a common symptom of the disorder in psychiatric populations appearing in perhaps 60% of the patients (C. B. Taylor, MD, personal communication, September 1986). There are numerous hypothetical causes, including small-vessel disease, basal-membrane dysfunction, abnormal lactate metabolism, and abnormal hemoglobin dissociation curves. Support for any of these mechanisms has yet to be gained. We cannot conclude that PD "causes" chest pain, only that atypical and nonanginal chest pain are likely to be associated with PD. The data from Bass and Wade[1] and from Katon et al[3] show preliminary evidence that patients with typical angina are unlikely to have PD. We are currently undertaking a study of patients with CAD and typical angina to investigate this question further.

The findings of this study have limited validity because of three methodological considerations:

1. We were able to recruit only 53% of the total number of eligible patients. Informed consent,[23] for example, is one aspect of volunteer bias. Nevertheless, even if one were to assume that all those who failed to participate did not have PD, the percentage of patients would drop from 59 (57%) of 104 to 59 (30%) of 195, which is still a dramatically high figure.

2. Patients in the PD(+)/CAD(−) group may have had CAD. Only seven of these subjects underwent coronary arteriography to prove definitely their lack of CAD. The treadmill results of those subjects who underwent exercise ECGs may have been falsely negative.[24] Those subjects who only had resting ECGs could also have had CAD. Although the failure of all subjects to have undergone cardiac catheterization to rule out CAD is a methodological limitation, this limitation approximates general clinical practice. Especially for those younger women with nonanginal chest pain, CAD is quite unlikely, thereby making angiography a relatively high-risk diagnostic evaluation for a low probability of a positive finding. Using the pretest probabilities for CAD described by Diamond and Forrester,[7] we calculated the probability that a subject chosen at random from the 36 subjects with PD(+)/CAD(−) and no angiogram would have CAD. While the figure (.04) is low, the possibility remained that one member of this group could have had CAD. In fact, after these data were analyzed, one subject was found to have CAD. This uncertainty characterizes clinical practice.

3. Other possible causes of chest pain were not systematically ruled out. Again, the problem here is the accuracy of the clinical judgment of the cardiologists. Esophageal disease is a possible cause of chest pain in both CAD(+) and CAD(−) populations.[25,26] Coronary artery spasm is more likely in those patients with CAD(+).[27] Thyrotoxicosis, acute pericarditis, dissecting aortic aneurysm, pulmonary embolism, pleuritis, pneumonia, pneumothorax, costochondritis, arthritis, muscle spasm, thoracic outlet syndrome, and peptic ulcer disease may each cause chest pain. Given the nature of this study design, it is possible that one of these disorders was contributing to the chest pain of some of these patients. This limitation also applies to the PD studies of patients with angiographically normal coronary arteries,[1,3] since clinicians and researchers cannot do all possible tests on all patients.

Cardiologists have noted for many years that many of their patients have cardiac symptoms that do not appear to be of cardiac origin. In 1871, DaCosta[28] described the "irritable heart syndrome" that was subsequently assigned several names including "soldier's heart," "cardiac neurosis," and "neurocirculatory asthenia." In 1928, White and Jones[29] found that 10% to 14% of all cardiology patients seen in their New England sample had neurocirculatory asthenia. In 1941, Wood[30] presented an extensive review of DaCosta's syndrome, a recognized medical problem of the time.

Paralleling these developments in cardiology, in 1894, Freud[31] described a syndrome of morbid anxiety with anxious expectation as its central feature and termed it *anxiety neurosis.* In his view the syndrome manifested itself in two major ways: in one form, the patient suffered from a generalized or free-floating anxiety, and in the other, the patient experienced sudden upsurges of intense anxiety that did not have its origins in specific thoughts or in responses to specific environmental triggers. Some patients had both forms. Freud's description remained unchanged until the early 1960s when Klein[32] discovered that the panic attacks could be successfully treated with antidepressants without having any noticeable effect on the generalized anxiety often associated with the attacks.

The cause of PD remains unclear. Theories range from central dyscontrol of the locus ceruleus[33] to phobic misperception of physical symptoms.[34] Some believe that the laboratory infusion of sodium lactate as well as other substances, including caffeine and yohimbine, and the breathing of 5% carbon dioxide can trigger panic attack, while others have suggested that these are nonspecific effects.[34] There does appear to be a familial predisposition,[35] and the disorder in psychiatric populations appears to respond well to specific pharmacologic agents.[8] Imipramine hydrochloride has been the most frequently tested medication for panic disorder.[8] With careful cardiac monitoring[36] it and other antidepressants may be useful in the treatment of PD in patients with CAD, as well as those without. Alprazolam, too, may be useful in these populations,[37] but controlled trials of any antipanic medication for cardiology patients with chest pain and PD have yet to be reported. In anticipation of future trials, clinicians should consider PD in patients with atypical or nonanginal chest pain that cannot be explained by organic causes, since this diagnosis may imply specific treatments having a high likelihood of success.

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