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Panic Disorder, Cardiology Patients, and Atypical Chest Pain

Bernard D. Beitman, M.D., Vaskar Mukerji, M.D.,† Greg Flaker, M.D.,‡ and Imad M. Basha, M.D.§*

Cardiologists have long recognized that many patients with chest pain may not suffer from demonstrable organic disease. However, many of these patients continue to experience chest pain and become disabled. Such patients have received a variety of diagnoses and no apparently consistent treatment. With the clearer understanding by psychiatrists of the entity now known as panic disorder has come the opportunity to better characterize and treat those cardiology patients who have chest pain that has no apparent organic cause. In this chapter we review the history of these cardiology patients and the extent to which cardiologists have come to understand panic disorder. We then present the findings from the University of Missouri Panic/Cardiology Project, which has investigated the epidemiology of panic disorder in cardiology patients whose chest pain cannot be explained by standard medical diagnostic procedures.

CHEST PAIN WITH ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES

Prevalence

Approximately 10 to 30 per cent of patients referred to coronary arteriography for chest pain are found to have normal or nearly normal coronary arteries.[16, 22, 26, 29] The Registry Committee of the Society of Cardiac Angiography[30] reported that of 41,204 patients referred for coronary arteriography

*Associate Professor, Department of Psychiatry, University Hospital, University of Missouri, Columbia, Missouri
†Assistant Professor, Division of Cardiology, University Hospital, University of Missouri, Columbia, Missouri
‡Associate Professor, Division of Cardiology, University Hospital, University of Missouri, Columbia, Missouri
§Assistant Professor, Department of Psychiatry, University Hospital, University of Missouri, Columbia, Missouri

because of presumed coronary artery disease (CAD), 20 per cent had normal arteriograms. Similarly, 25 per cent of patients screened for the Coronary Artery Surgery Study (CASS) had normal or only slightly abnormal coronary arteriograms.[18] If about 500,000 cardiac catheterizations are performed annually in the United States for the evaluation of chest pain,[20] it can be estimated that about 100,000 of these show normal coronary arteries. Of 706 consecutive patients who underwent cardiac catheterization because of symptomatic chest pain, Bertrand et al.[10] found the incidence of normal coronary arteriograms to be as high as 89 per cent in patients with atypical angina and 29 per cent in patients with typical angina. In the same study among 395 consecutive patients with nonsignificant coronary stenoses on arteriography, 221 (56 per cent) had presented with atypical angina, 93 (24 per cent) with rest angina, and 81 (20 per cent) with exertional angina with or without rest angina.

Prognosis

Several studies have shown that the syndrome of angina with normal coronary arteries carries a favorable prognosis for longevity. Proudfit et al.[28] followed a series of 521 patients at the Cleveland Clinic for a period of 10 years. The patients were divided into three groups, with 357 having completely normal coronary arteriograms, 101 having mild disease (<30 per cent narrowing), and 63 having moderate disease (30 to 50 percent narrowing). Coronary events occurred in 2.1 per cent of those with normal arteriograms, 13.8 per cent of those with mild narrowing, and 33 per cent of those with moderate coronary narrowing. Isner et al.[13] at the Tufts–New England Medical Center followed a group of 121 patients with angiographically normal or nearly normal coronary arteries for 1 to 11 years (mean, 4.3 years). They noted only a 2.5 per cent incidence of sudden death and a 3.4 per cent incidence of acute myocardial infarction. The CASS registry shows a 7-year survival rate of 96 per cent in patients with normal coronary arteriograms.[17] These figures reflect a highly favorable prognosis for longevity in this group of patients.

Despite the excellent prognosis for survival, most patients with chest pain and normal coronary arteries suffer considerable disability. Papanicolaou et al.[26] followed 1977 patients with chest pain and normal coronary arteries or insignificant coronary artery disease for a mean period of 6.3 years. Seventy per cent of these patients continued to experience chest pain, and 50 per cent were unable to exert themselves. Ockene et al.[25] followed a series of 57 patients with angiographically normal coronary arteries for a period of 6 to 37 months. They also noted that 70 percent of the patients continued to experience chest pain, 47 per cent described their usual daily activities as limited by chest pain, and 51 per cent claimed that they were unable to work because of their symptoms. Forty-four per cent continued to believe that they had heart disease, although their overall use of medical facilities decreased. In a similar study, Lavey and Winkle[21] followed 45 patients with chest pain and normal coronary arteriograms for a mean period of 3.5 years. Seventy-nine per cent of those whose activities were initially limited by cardiac symptoms continued to be limited to the same or a greater degree at the time of follow-up. Eighty-two per cent con-

tinued to see physicians because of cardiac complaints. Thus, the demonstration of anatomically normal coronary arteries produced no relief in chest pain or symptom-related morbidity for most of these patients.

One probable advantage of cardiac catheterization in these patients is a decrease in the rehospitalization rate. Several studies have reported that the rehospitalization rate for chest pain complaints in these patients ranges from 3 to 27 per cent.[13, 21] In a series of 72 consecutive patients with chest pain and normal coronary arteries, Faxon et al. found that only 24 per cent became pain-free after the procedure.[12] However, hospitalization for all patients decreased significantly, resulting in a significant decrease in estimated hospital costs.

It appears that the catheterization procedure is not "therapeutic" for these patients, and reassurance is usually unsuccessful in relieving the patients' symptoms. As the patient continues to complain of chest pain, the cardiologist may consider repeating coronary arteriography after a period. Marchandise et al.[22] at the Montreal Heart Institute performed repeat catheterizations in patients with nonsignificant coronary artery disease over a mean interval of 42 months. They noted no progression in CAD in patients with initially normal arteriograms. However, among patients with less than 50 per cent stenosis of at least one major coronary artery, 27 per cent showed progression of disease. These data suggest that some of the patients who have minimal irregularities in their coronary vessels may be in the process of developing more significant coronary artery disease and may need to be reassessed by a cardiologist periodically if symptoms persist. But repeat catheterizations in patients with totally normal coronary arteriograms are unlikely to yield new data and may subject the patients to unnecessary risk. As an extreme example of the risk involved, Shah and coworkers[31] have reported a patient with Munchausen's syndrome and normal coronary arteries who underwent repeated cardiac catheterizations leading to the loss of a limb. As these patients continue to complain of chest pain, the physician is often at a loss to decide on adequate follow-up care.

Etiology

Chest pain in patients with normal coronary arteries may be of cardiac or noncardiac origin. The common cardiac causes encountered include chest pain due to coronary artery spasm, pericardial disease, valvular disease (mitral valve prolapse, etc.), and occasionally hypertensive heart disease. Except for coronary artery spasm, these causes can usually be identified in the clinical setting. Coronary artery spasm occurs in only 10 per cent of this population. The common noncardiac causes of chest pain are esophageal, rheumatologic, pulmonary, and occasionally abdominal disease. Among these, esophageal disorders are frequently the most difficult to establish as the etiology for the patient's discomfort. In addition to the conditions mentioned above, a number of other hypotheses, cardiac and noncardiac, have been suggested to explain the chest pain in these patients, including myocardial perfusion defect, microvascular angina, abnormal lactate metabolism, and abnormal hemoglobin dissociation. None of these hypotheses have proven useful in explaining the chest pain in most patients with angiographically normal coronary arteries.

PANIC DISORDER IN PATIENTS WITH ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES

As suggested in the previous section, patients with angiographically normal coronary arteries have a low risk of cardiac death and a low risk for nonfatal myocardial infarction. To a person with severe chest pain the absence of coronary artery disease should be reassuring. Nevertheless, a significant percentage of these patients continue to be disabled by their chest pain, which interferes with normal work and social functioning.[21, 25, 26]

Bass and Wade[4] found that 37 per cent of patients with normal or nearly normal coronary arteries had anxiety neurosis. Since patients with angiographically normal coronary arteries seem to score high on measures of hypochondriasis[36] and since anxiety neurosis was the DSM-III precursor of panic disorder,[1] Mukerji et al.[23] hypothesized that a significant percentage of patients with angiographically normal coronary arteries were likely to have panic attack symptoms. They retrospectively examined the charts of 123 patients with angiographically normal coronary arteries. Forty per cent of this group described attacks of four symptoms (including chest pain) consistent with the symptoms of panic attacks. In a study conducted concurrently with ours, Katon et al.[15] found that 12 of 28 patients (43 per cent) with normal coronary arteries fit DSM-III criteria for panic disorder.

We sought to test the hypothesis that a significant number of patients with angiographically normal coronary arteries have panic disorder.[5] Patients with chest pain undergoing cardiac catheterization at the University of Missouri Hospital were considered for the study if they were found to have normal coronary arteries. Patients with any coronary lesion causing 30 per cent stenosis or greater were excluded from the study. While stenosis of 70 per cent or less is generally considered "normal" or "hemodynamically insignificant," patients with 30 to 50 per cent stenosis show more coronary events and higher cardiac mortality than those with 0 to 30 per cent stenosis.[28] Therefore, 30 per cent or less is a more conservative definition of hemodynamically insignificant occlusion. Also excluded were patients with valvular heart disease (including mitral valve prolapse), cardiomyopathy, congenital heart disease, hypertensive heart disease, pericardial disease, or any other possible cause of chest pain. The 33 subjects who consented to participate (15 male and 18 female) ranged in age from 24 to 71 years, with a mean of 50.2 years. The patients were interviewed and the questionnaires administered the evening of the catheterization day or the next morning.

The Structured Clinical Interview for DSM-III-Upjohn version (SCID-UP) developed by Spitzer and Williams[34] was administered by clinical psychiatrists trained in its use. To receive a diagnosis of panic disorder the subject had to meet revised DSM-III criteria[38] for panic disorder and to have had at least one panic attack per week for the past 3 weeks. This frequency criterion is more conservative than that of DSM-III-R[2] and increases the likelihood that the patient is in need of treatment because of the ongoing repetitive nature of the attacks. Panic attacks were defined as "discrete periods of discomfort or fear" accompanied by at least four of the following symptoms: shortness of breath, choking or smothering sensations, palpitations, chest pain or discomfort, sweating, faintness, dizziness, deper-

sonalization or derealization, numbness or tingling (paresthesias), flushes or chills, trembling or shaking, fear of dying, fear of going crazy or doing something uncontrolled. During at least some of the attacks most of the symptoms needed to be experienced within 10 minutes of the beginning of the first symptom. The SCID-UP also provided for the diagnoses of social phobia, simple phobia, and current and past episodes of major depression. An additional diagnosis, current simple panic,[14] was added for subjects who had at least one panic attack in the 3 weeks prior to the interview but did not have one attack in each week.

Eleven of the 33 subjects (33 per cent) fit the criteria for panic disorder, and 8 (24 per cent) fit the criteria for simple panic. None reported a social phobia, and one reported a simple phobia. Nine (27 per cent) reported a lifetime prevalence of at least one major depressive episode. Six (18 per cent) reported a past history of at least one major depressive episode, and five (15 per cent) reported having a current major depressive episode. All five with current major depression also had simultaneous panic disorder. Two of these five also reported having had a past major depressive episode. Two of the eight with simple panic reported at least one past episode of major depression.

Three groups were formed—panic disorder ($N = 11$), simple panic ($N = 8$), and no panic attacks ($N = 14$). The three groups did not differ with regard to age or sex. Panic disorder: 7 (64 per cent) women with a mean age of 46.6 ± 13.8 years. Simple panic: 5 (62 per cent) women with a mean age of 52.0 ± 14.1 years. No panic: 6 (43 per cent) women with a mean age of 51.8 ± 12.0 years. The three groups did not differ in lifetime prevalence of major depression.

The results of this study confirm the hypothesis that panic disorder occurs frequently in patients with chest pain of uncertain origin and normal coronary arteries. Since this diagnosis is rarely considered by angiologists, most patients are simply reassured that "nothing physical" is wrong with them and sent home. While this reassurance is no doubt sometimes helpful, follow-up studies of patients with angiographically normal coronary arteries demonstrate significant social and vocational distress. A great many of these patients deserved but were not given a diagnosis that has a high probability of successful treatment outcome.

PANIC DISORDER IN CARDIOLOGY OUTPATIENTS WITH ATYPICAL OR NONANGINAL CHEST PAIN

As suggested in the previous sections, several studies have found that at least one third of chest pain patients with angiographically normal coronary arteries have panic disorder. Studies have also suggested that physician impression of chest pain as atypical for angina was strongly associated with a normal coronary arteriographic study.[4, 15, 23, 35]

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 panic disorder, we hypothesized that cardiology outpatients with atyp-

ical or nonanginal chest pain and without coronary artery disease might also have a high probability of panic disorder.

In addition, cardiologists have noted clinically that some patients with coronary artery disease continue to complain of chest pain that is not well explained by the heart disease itself. Often called "cardiac neurotics," they appear anecdotally to include some with panic disorder. Since the chest pain in these patients is often atypical, we hypothesized that coronary artery disease (CAD) patients with either atypical or nonanginal chest pain might also have panic disorder. Therefore we attempted to identify consecutive cardiology outpatients with atypical or nonanginal chest pain and to recruit them into an interview study for panic disorder.[6]

All clinical cardiologists at a university hospital were asked to identify for this study outpatients with atypical or nonanginal chest pain. Typical angina was defined as substernal, exertional, and relieved by rest or nitroglycerine. Atypical angina was defined as having two of these three factors. Nonanginal chest pain was defined as having only one of these characteristics. Patients with and without CAD were included in the study. CAD was defined by history of a positive cardiac catheterization or a history positive for myocardial infarction. Absence of coronary disease was defined by clinical cardiologists who utilized standard tests at their discretion. Two hundred and six patients were identified. The SCID-UP[34] was again used. There was 100 per cent agreement in the ratings of the two interviewing psychiatrists regarding panic disorder, agoraphobia, social phobia, simple phobia, and major depression in nine subjects.

One hundred and four of the 195 (53 per cent) potential subjects consented to participate. Of the subjects, 40 were male and 64 were female. They ranged in age from 16 to 86, with a mean of 47.8 years. Forty-seven had chest pain atypical for angina and 56 had nonanginal chest pain. One sometimes had atypical and at other times nonanginal chest pain.

Thirty of the 104 subjects had coronary artery disease. Twenty-two of this group had histories of cardiac catheterization with abnormal findings; 8 had been treated for myocardial infarction. Of the remaining 74 subjects, 43 fit the diagnostic criteria for panic disorder and 31 did not. One of the 31 nonpanic, non-CAD group was found to have sleep apnea, the surgical treatment of which relieved her chest pain. She was therefore dropped from subsequent data analysis.

Four groups were formed based on the presence or absence of panic disorder (PD) and the presence or absence of coronary artery disease (CAD). Forty-three were PD(+) (positive for panic disorder) and CAD (−) (negative for coronary artery disease). Of the 30 CAD(+) subjects, 16 were PD(+).

The female (%) and age ± SD distributions were as follows: PD(+)/CAD(+): 7 (44 per cent), 54.4 ± 11.1 years; PD(−)/CAD(+): 5 (36 per cent), 57.0 ± 12.1 years; PD(+)/CAD(−): 33 (77 per cent), 42.5 ± 18.6 years; PD(−)/CAD(−): 18 (60 per cent), 46.8 ± 16.2 years. The PD(−)/CAD(+) group was significantly older than the PD(+)/CAD(−) group (57 versus 43 years). The PD(−)/CAD(+) group had significantly more males than the PD(+)/CAD(−) group, 9 (66 percent) versus 10 (23 percent). On chest pain type, the significant differences were found among three pairs: PD(+)/CAD(+) versus PD(+)/CAD(−), PD(+)/CAD(+) ver-

sus PD(−)/CAD(−), and PD(−)/CAD(+) versus PD(−)/CAD(−). Atypical angina was significantly more frequent than nonangina among those with CAD(+).

With regard to other anxiety disorders, 6 of the PD(+)/CAD(−) group reported limited phobic avoidance; 2 of this group reported extensive phobic avoidance (agoraphobia), and 1 reported a social phobia. No other subjects fit criteria for social phobia. Simple phobias were reported by 2 with PD(+)/CAD(+), 4 with PD(−)/CAD(−), and 10 with PD(+)/CAD(−).

The finding that 43 patients out of 74 (59 per cent) with atypical or nonanginal chest pain and no CAD had panic disorder is remarkable. Even if one were to assume that all the nonparticipant patients had no CAD, making the denominator 74+91=165 and the percentage 43/165 (26 per cent), this figure is still much higher than the 1.0 per cent found in community studies[24, 37] and the 6.5 to 13.0 per cent found in an outpatient primary care population.[14]

That more than 50 per cent 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 utilize a new diagnostic option with possible treatment options for this often problematic population.

The 43 subjects with PD and without CAD were further analyzed. Nineteen of 43 had a lifetime history of major depression.[7] Eight had agoraphobic symptoms,[8] and 12 reported no fear during their last major panic attack.[9]

PHARMACOTHERAPEUTIC TREATMENT OF PANIC DISORDER IN CARDIOLOGY PATIENTS WITH CHEST PAIN

In psychiatric populations panic disorder has been shown to be responsive to three classes of psychoactive medications including several polycyclic antidepressants, the monoamine oxidase inhibitors, and at least two high-potency benzodiazepines, alprazolam[3] and clonazepam.[27] Certain specific psychotherapeutic interventions[19, 33] also may be effective. A significantly positive treatment trial of chest pain patients with panic disorder would confirm the validity of the epidemiologic findings.

Subjects were recruited from cardiology outpatients with atypical or nonanginal chest pain who were without evidence of coronary artery disease and from cardiology inpatients with chest pain and angiographically normal coronary arteries. Patients admitted to the trial all met revised DSM-III criteria[38] for panic disorder. In addition, they had to have had at least one panic attack per week with at least three symptoms for the past 3 weeks. (Also, all had to have at least one four-symptom attack.) Patients were between the ages of 18 and 60, suffered no serious or uncontrolled medical illnesses, did not fit the criteria for DSM-III major depression within the past 5 years (unless it was judged clinically to be secondary to panic disorder), and had no history of alcohol or drug abuse in the past 6 months. All previous possibly psychoactive medications, including beta and calcium channel blockers, were discontinued at least 7 days before beginning the trial.

After the screen, each subject was instructed in the use of the panic attack diary and kept it for 1 week without medication. Only those who had at least one three-symptom panic during the baseline week were continued on into the drug trial. All subjects entered the open-label trial of alprazolam with an initial dose of 0.5 mg per day. To be considered evaluable a patient was required to have taken medication for at least 3 weeks. The acute phase of the trial lasted 8 weeks.

During the study, subjects were rated on the Hamilton Anxiety Scale (HAM-A), the Hamilton Depression Scale (HAM-D), and the Physician's Global Impression Scale. Patients recorded work and social functioning on a 1-to-5 scale. A count of the number of panic attacks experienced in the past week was also recorded at each visit, based upon the daily diaries the patients were instructed to keep. The total number of panic attacks was the sum of situational and unexpected attacks. Situational attacks were defined as those attacks occurring when the subject was in or about to be in a situation likely from his/her experience to bring on an attack. Unexpected attacks were those occurring with little or no provocation, that is, when not in a situation likely to bring on an attack. Three or more symptoms were required for an episode to be recorded as a panic attack.

Twenty patients with chest pain and panic disorder without evidence of significant CAD were evaluable, having each completed at least 3 weeks on medication. Thirteen were women and seven were men. Their mean age age was 35.8 ± 9.0 years. All were Caucasian. Five subjects dropped out before completing the acute phase. Therefore, 15 were considered study completers. Responders were defined as those evaluable subjects who reported a 50 per cent or greater reduction in their panic frequency between baseline and their final week in the acute trial. Fifteen of the 20 (75 per cent) met this criterion.

The mean number of panic attacks from baseline to week 8 dropped from 12.80 ± 7.14 to 6.53 ± 6.45 ($p<0.01$). However, the number of limited symptom attacks increased by a mean of approximately 1 over the 8-week trial, from 9.46 ± 11.60 per week to 10.47 ± 14.21 ($p<0.84$). Statistically significant decreases were recorded in physician-rated measures of anxiety (Hamilton Anxiety Scale), depression (Hamilton Depression Scale), and global functioning (Physician's Global Impression Scale). Patients rated themselves significantly improved in their work and social functioning. Each of these measures reached significance after week 1 and stayed significant for the 8-week acute phase. Subject reports of chest pain episodes decreased in a marginally significant way.

This open-label trial of alprazolam in cardiology patients with chest pain and panic disorder without evidence of CAD suggests that this and possibly other pharmacotherapeutic interventions may be useful in this population. It is also of interest that subject reports of chest pain episodes decreased in a marginally significant way. This finding suggests that alprazolam might be useful specifically for this troublesome symptom.

The next step in this process is a double-blind, placebo-controlled trial of one or two of the commonly accepted medications used for the treatment of panic disorder. Should this next study confirm the findings reported in this nonblind study, then vigorous attempts should be undertaken to train primary care physicians and cardiologists in the recognition of the panic

disorder spectrum. Without accurate diagnosis patients often go from physician to physician looking for an answer, usually running up costs for nonconclusive evaluations. They sometimes become convinced that they have an unnamed disorder and experience increasing social and work morbidity, as has been shown in patients with angiographically normal coronary arteries,[26] at least one third of whom have panic disorder.[3] Accurate diagnosis will be likely to lead to effective treatment with a consequent reduction in social and work morbidity and in medical care costs.

CONCLUDING COMMENTS

If many patients with panic disorder can be correctly diagnosed by cardiologists, then unnecessary procedures will not be performed and patients are likely to be adequately treated. However, two important questions remain: (1) Do cardiology patients with chest pain and panic disorder respond to the same treatments that psychiatric patients with panic disorder find useful, as suggested by our uncontrolled trial? We are in the planning stages of a placebo-controlled, double-blind study to answer this question. (2) What will it take for nonpsychiatric physicians to accurately diagnose panic disorder? An index of suspicion is, of course, required but insufficient. They will need to be trained to make diagnoses not only of panic but also of other anxiety disorders and of major depression and dysthymia. They will need to gain some understanding of the relationship between anxiety disorders and affective disorders, since treatment response is likely to be influenced by their coexistence.

These developments appear to be heralding an increasingly stronger relationship between psychiatry and the rest of medicine because, as the inner workings of the brain are becoming better known, physicians are gradually recognizing that the organs of their specialties are very much influenced by the brain's activities.

SUMMARY

Although patients with angiographically normal coronary arteries have low mortality, several studies have indicated that their social and work morbidity is high. Panic disorder appears to be a major contributor to the continuing chest pain in this population. There are also many chest pain patients appearing in cardiology clinics who also do not have heart disease but who are not given the opportunity to be evaluated for psychiatric disorders. Among those presenting with atypical or nonanginal chest pain, panic disorder represents a likely etiologic consideration. The fact that such patients do exist in cardiology populations is further substantiated by an open-label trial of alprazolam which demonstrated a positive effect in patients selected from those with atypical chest pain and no heart disease found to fit panic disorder criteria. These findings strongly support the increasing affiliation between cardiology and psychiatry and reinforce the belief that many problems of the heart may be problems of the mind/brain.

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Department of Psychiatry
Clinic 6, University Hospital
University of Missouri
Columbia, Missouri 65212