

Reviews

Unexplained Chest Pain: When Is It Panic Disorder?

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Summary: Noncardiac chest pain is a common costly phenomenon in the cardiology setting. Recent research suggests that panic disorder, a highly distressful yet treatable anxiety disorder, occurs in a significant proportion of noncardiac chest pain patients. This article reviews research on the prevalence of panic disorder in patients seen in cardiology settings for unexplained chest pain. Financial, psychosocial, and historical aspects of noncardiac chest pain are described. Panic disorder and the potential consequences of its nonrecognition by physicians are examined. Current psychological and pharmacologic treatments are reviewed. Recommendations on the management of panic patients in the cardiology setting are provided.

Key words: panic disorder, noncardiac chest pain, coronary artery disease

Introduction

Chest pain is one of the most common symptoms prompting medical consultation.^{1,2} It is within the domain of cardiology to investigate a cardiovascular basis for this cardinal symptom of coronary artery disease (CAD)—a leading cause of death in North America. However, in more than 50% of patients suffering from chest pain, the pain does not have a cardiac cause.¹⁻⁵ Despite an excellent survival prognosis, 1- to 6-year follow-up studies suggest that between 34 and 70% of

these noncardiac patients continue to suffer from chest pain, repeatedly consult physicians, and report significant psychosocial disability (Table I).⁶⁻⁹

In addition to the physical suffering and psychosocial implications of noncardiac pain, the costs to diagnose and manage this pain syndrome are significant. Approximately 500,000 angiograms are performed annually in the United States; of these, 10 to 30% are negative. Since the cost of an angiogram is over \$2,000, it can be estimated that more than \$10,000,000 are spent each year to reach a negative diagnosis of coronary disease for chest pain sufferers.¹⁰ Kroenke and Mangelsdorff² reviewed patients' diagnostic yields and costs to discover an organic cause of chest pain not apparent on initial interview and physical examination in ambulatory care settings. Six percent of chest pain investigations yielded an organic cause not apparent on physical examination, and the associated costs were over \$4,000 per patient. A decade ago, the costs to manage noncardiac chest pain were approximately \$4,000 per year for each patient. This figure included 1.2 prescriptions per month, 2.2 emergency room or physician visits per year, and one hospitalization per year for further evaluation of the pain.¹¹

Physical Causes of Chest Pain

The most commonly reported physical causes of persistent chest pain in patients with otherwise normal coronary arteries are esophageal motility disorders, gastroesophageal reflux disease, mitral valve prolapse, microvascular angina, and abnormal visceral nociception. A multidisciplinary meeting of active investigators led to the publication of a review on unexplained chest pain in 1991.¹² Reviewers noted that, although several individual or combined physical abnormalities can be found in noncardiac patients, the majority of patients do not have a distinct physical cause for their pain. Moreover, even in the presence of observed physical abnormalities, medical treatments are often ineffective for some patients. Finally, psychiatric disorders occur in a significant proportion of patients with any of the physical conditions mentioned above.¹²⁻¹⁶ It is yet unclear if psychiatric disorders cause, result from, or simply parallel these conditions.

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TABLE I Summary of selected follow-up studies of patients with chest pain and normal coronary arteries

Year	Investigators (Ref.)	Sample size	Follow-up period	Findings
1979	Lavey and Winkle (6)	45	Mean 3.5 years	Continued chest pain (34%), use of medical services (79%) and disability
1980	Ockene <i>et al.</i> (7)	57	Mean 16 months	Chest pain (47%), unable-work (51%), believed bad heart disease (44%)
1984	Wielgosz <i>et al.</i> (8)	581	1 year	Chest pain (67%)
1986	Papanicolaou <i>et al.</i> (9)	1977	Median 6.3 years	Chest discomfort (70%), continued use of medical services, functional impairment and job disability

Psychological Correlates and Chest Pain: A Brief Historical Perspective

The contribution of psychological factors to chest pain has been suspected for more than a century. During the nineteenth century, there were several reports of a pain syndrome different from Heberden's angina pectoris, described in 1772.¹⁷ This new syndrome was particularly common during wartime among soldiers and was described by DaCosta in 1871.¹⁸ Although unsure of the causes for this chest pain syndrome, DaCosta suggested that it was due to a disordered innervation and, with a few exceptions, his patients were "functional." In 1892, Osler¹⁹ also acknowledged the difficulty in differentiating pain caused by a cardiac condition from that attributable to noncardiac factors. He described two distinct categories of chest pain: true angina and pseudoangina. In the latter category, he found that the patient population was comprised mainly of women in whom pain was characteristically periodic, nocturnal, accompanied by nervous symptoms, and vasomotor disturbances. He stated that treatment must be directed to the general nervous condition. With time, DaCosta's pain syndrome first diagnosed in soldiers became increasingly documented in the civilian population. In 1941, Wood²⁰ compared patients with heart disease with normal controls and concluded that a proper psychiatric diagnosis was almost always available. He believed that the cause of the pain was usually psychological, due to "misinterpretation of emotional symptoms, certain vicious circular patterns, the growth of a conviction that the heart is to blame, consequent fears of sudden death on exertion, conditioning, and hysteria."

Symptoms presented by many noncardiac patients as described by DaCosta, Osler, Wood, and others resembled what is known today as panic disorder (PD). As a result, recent research has focused on establishing the prevalence of this disorder in patients with chest pain. Panic disorder is a specific disabling anxiety disorder characterized by recurrent unexpected episodes of intense fear or discomfort associated with several somatic and cognitive symptoms²¹ (see Table II for diagnostic criteria). Its etiology is related to abnormal neurobiological functioning that involves a dysregulation of the noradrenergic, serotonin, and benzodiazepine systems.²² In addition to neurobiological etiology, panic patients have a well-documented tendency to catastrophically misinterpret their anxiety symptoms, which leads them into a cycle of anxiety → catastrophic

misinterpretation of the symptoms (e.g., "I am having a heart attack," "I am going crazy") → heightened anxiety level (panic attack).²³ It should be mentioned that researchers know more about effective treatments than about the specific etiology of PD, especially in terms of its neurobiological causes.²²

In this article we will review the studies that examined PD prevalence in patients with chest pain. We focused on studies conducted in the cardiology setting that used structured interview protocols (standard criterion) to diagnose PD. Omitted from this review is the research that examined the controversial relation between PD and mitral valve prolapse. This subject has been extensively reviewed elsewhere^{22, 24} and it is now generally accepted that mitral valve prolapse is not especially associated with PD.²²

Panic Disorder in Chest Pain Patients in the Cardiology Setting

The authors are aware of six original published PD prevalence studies in patients with chest pain in cardiology settings (Table III). Katon *et al.*²⁵ examined the prevalence of this disorder in 74 patients with chest pain without a previous history of CAD who were referred for coronary arteriography. Of patients with normal angiograms, 43% (12/28) met criteria for PD, compared with 6.5% (3/46) of patients with positive coronary arteriographies. Patients with chest pain and no significant CAD were more likely to be female, presented a higher number of autonomic symptoms associated with chest pain, and were more likely to describe atypical chest pain.

Beitman *et al.*²⁶ reported similar findings on a larger patient sample with normal angiographic results. Of the 94 patients consenting to participate, 32 (34%) exhibited PD. Because of its larger sample, this study strengthened Katon's finding that PD is highly prevalent in patients with normal coronary arteries. However, a limit to Beitman's study is that psychiatric interviewers were not blinded to angiographic results. Hence, the possibility of an experimenter expectancy effect, leading to a high PD prevalence, could not be excluded.

Beitman *et al.*²⁷ who observed that PD patients tended to present with atypical chest pain, focused on the prevalence of PD in this population. They found that 59 of 103 (57%) of cardiology outpatients with atypical or nonanginal chest pain met PD criteria. Of these 103 patients, 73 (70%) had no probable

TABLE II Diagnostic criteria for panic disorder (with or without agoraphobia)

- A. Both (1) and (2)
- (1) Recurrent unexpected panic attacks^a
 - (2) At least one of the attacks followed by 1 month (or more) of one (or more) of the following:
 - (a) Persistent concern about having additional attacks
 - (b) Worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, going crazy)
 - (c) A significant change in behavior related to the attacks
- B. Presence or absence of agoraphobia, i.e., anxiety about being in situations from which escape may be difficult in case of a panic attack, e.g., agoraphobic situations are commonly being in a crowd, on a bridge, traveling on a bus, subway, etc.
- C. Panic attacks not due to the direct physiologic effects of a substance (e.g., drug abuse) or general medical condition (e.g., hyperthyroidism)
- D. Panic attacks not better accounted for by another mental disorder such as social phobia, specific phobia, post-traumatic stress disorder, etc.

^aPanic attacks are defined as a discrete episode of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached their peak within 10 min: Palpitations, sweating, trembling or shaking, sensations of shortness of breath, feeling of choking, chest pain or discomfort, nausea or abdominal distress, feeling dizzy, feelings of unreality or of being detached from oneself, fear of losing control or going crazy, fear of dying, paresthesia, and chill or hot flushes.

CAD (diagnosed using test results ordered at the cardiologist's discretion). The results of this study are of interest as they suggest that atypical chest pain may imply an underlying panic syndrome. However, several methodological issues need to be addressed. First, patients were referred to the study by cardiologists and it is unclear whether only the more psychologically disturbed patients were referred. Second, less than half of the patients referred for psychiatric interview consented to participate. Finally, interviewers were not blinded to patient diagnoses. It is unclear if these issues contributed to the high observed prevalence.

Carter *et al.*²⁸ hypothesized that many chest pain patients admitted to the coronary care unit (CCU) for suspected myocardial infarction may suffer from PD, and estimated its prevalence in this setting. They found that one third of 62 consecutive patients met criteria for PD. Seventy-nine percent of patients with PD did not have clear evidence of CAD. Patients with PD displayed significantly higher scores on psychological scales and tended to have other comorbid psychiatric conditions such as agoraphobia and depression. Although this

study had a relatively small sample size, participation rate was high (85%) and the interviewers were blinded to medical diagnoses which strengthened the findings.

Carter *et al.*²⁹ recently investigated the prevalence of PD in consecutive referrals of patients with chest pain and without previous evidence of CAD to a nuclear medicine department for cardiac stress scintigraphy. Fifty patients (82%) participated; 28 patients (56%) met criteria for PD. Of the patients with PD, one had a positive stress scintigram. Although this study also had a small sample size and should be reproduced in different medical settings that may have different referral patterns for nuclear medicine testing, it suggests that PD is significantly prevalent in this cardiology setting. The authors concluded that the "salient question is not whether to evaluate patients with chest pain for PD, but at what point in their evaluation should it be considered."

Finally, in a recent study³⁰ attempting to improve upon the previous work's methodology, researchers from the Montreal Heart Institute examined the prevalence of PD in a sample of 441 consecutive patients consulting the ambulatory (walk-in)

TABLE III Panic disorder prevalence studies using structured interview protocols in patients with chest pain in the cardiology setting

Year	Investigators (Ref.)	Subjects	Sample size	Panic disorder prevalence (%)
1988	Katon <i>et al.</i> (25)	Referred for angiographic testing with no previous history of CAD	74	15/74 (20) in total sample 3/46 (6.5) in CAD + patients 12/28 (43) in CAD - patients
1989	Beitman <i>et al.</i> (26)	With normal angiograms (CAD-)	94	32/94 (34)
1987	Beitman <i>et al.</i> (27)	With atypical or nonanginal chest pain referred to study by cardiologists	103	59/103 (57)
1992	Carter <i>et al.</i> (28)	Consecutive admissions to the coronary care unit	62	19/62 (31)
1994	Carter <i>et al.</i> (29)	Consecutive referrals for cardiac stress scintigraphy with no previous history of CAD	50	28/50 (56%)
1996	Fleet <i>et al.</i> (30)	Consecutive patients consulting an ED of a cardiology hospital with chief complaint of chest pain	441	108/441 (24.5%)

Abbreviations: CAD = coronary artery disease, ED = emergency department.

emergency department (ED) with a chief complaint of chest pain. Approximately 25% (108/441) of patients met structured interview criteria for PD. Patients with PD displayed significantly higher panic-agoraphobia, anxiety, depression, and pain scores on state-of-the-art self-report scales than patients without PD. Moreover, 25% of patients with PD reported suicidal thoughts in the week preceding their ED visit compared with 5% of the patients without PD. Although 44% of the patients with PD had a history of CAD, 80% had atypical or nonanginal chest pain and 75% were discharged from the hospital with a final diagnosis of noncardiac chest pain. Of interest is that 98% of patients with PD were not recognized by cardiologists as suffering from this condition.

The previously described study strengthens the findings of the earlier research as it had a large sample size and a high participation rate (84%). Moreover, interviewers were blinded to the patients' medical diagnoses as well as to the study's specific hypotheses, and cardiologists were blinded to the results of the psychiatric interviews. The study also extends knowledge about the panic patient with respect to suicidal behavior and examines physician recognition of the disorder in the cardiology setting. However, one limitation of this naturalistic study is that the cardiovascular tests conducted were at the discretion of the attending cardiologists, who relied mainly on physical examination and noninvasive testing for most panic patients. Although this appears consistent with standard cardiology practice in Canada with respect to low-risk patients,⁵ it cannot be absolutely excluded that a small proportion of patients with PD had some symptoms better accounted for by undetected CAD.

In summary, between 25 and 57% of noncardiac or atypical chest pain patients in various cardiology settings suffer from PD. Although some of these results must be interpreted in light of the methodological issues described above, they underline the fact that cardiologists are highly likely to be confronted by this specific disabling anxiety disorder. The prevalence of PD in cardiology settings is significantly higher than the 6.5% rate reported in primary care populations and the 1 to 4% prevalence (with or without agoraphobia) reported in the general population. The following sections describe PD and summarize approaches to treatment.

Why Panic is Particularly Common in the Cardiology Setting

We can speculate on the reasons why panic prevalence is particularly high in patients with chest pain in the cardiology setting. One explanation is that most of the panic symptoms (10 of the 13 diagnostic symptoms) are somatic,²¹ not cognitive/psychological, leading the patient first to seek reassurance/care from nonpsychiatrist physicians rather than from mental health professionals. In turn, the cardiologist may particularly be targeted by these patients because seven of the panic symptoms are also symptoms of a cardiovascular disease: chest pain, palpitations, sweating, shortness of breath, feeling of choking, paresthesia, hot flushes. Among these

symptoms, chest pain may be the one of most concern for the panic patient and for the referring physician because it is a cardinal feature of a potentially fatal CAD. This combined with the fact that panic patients have an enduring tendency to focus on and to interpret their bodily sensations catastrophically can explain why they seek help from cardiologists upon feeling chest pain.^{23,31-33}

Panic Disorder: Underrecognized

Intuitively, the fact that several patients with PD are referred to cardiologists for evaluation of chest pain and that many subsequently undergo extensive cardiologic investigations suggests that panic is not a suspected cause for chest pain. If detection of PD in cardiology settings is as poor as recognition of various psychiatric conditions in primary care facilities,³⁴⁻³⁶ it is a cause for concern. Evidence from the Montreal Heart Institute, suggesting that PD goes unrecognized by cardiologists in 98% of patients with the condition, supports the intuition.³⁰

Possible Consequences of Nonrecognition

Diagnosis of noncardiac chest pain is often insufficient to reassure the PD patient.³⁷ Without an appropriate explanation and treatment, the discharged PD patient suffers chronically.^{38, 39} With subsequent attacks, the panic patient repeatedly seeks medical services, making PD one of the psychiatric disorders associated with the highest rate of ED or general medical services utilization.⁴⁰⁻⁴³

Undetected and untreated, PD may lead to increased psychiatric morbidity. For example, approximately 50% of PD patients develop agoraphobia within the first year of their initial attack.³⁷ Major depression and substance abuse often co-occur with PD, and panic patients may be at particular risk of suicidal behavior.⁴⁴⁻⁴⁷

Panic as a Risk Factor for Cardiovascular Mortality

Although most studies of PD patients in the cardiology setting have focused on patients with noncardiac chest pain, there is growing body of evidence suggesting that panic or phobic anxiety results in an increased risk of cardiovascular mortality. Coryell *et al.*^{48,49} reported that men with PD are at higher risk of cardiovascular mortality. Weissman *et al.*⁵⁰ reported that persons meeting lifetime criteria for PD in the New Haven portion of the Epidemiological Catchment Area study were twice as likely to report having suffered from a stroke as patients with other psychiatric disorders. A recent prospective study of 33,999 U.S. male health professionals free of cardiovascular disease at onset uncovered that phobic anxiety, a common characteristic of PD patients, was a strong predictor of sudden cardiac death.⁵¹

The mechanisms by which panic is associated with cardiovascular complications are unknown. It is unclear whether associated cardiovascular disease and complications are direct results of PD through slightly abnormal cardiovascular function in these patients or indirect consequences of engaging in high risk factor health habits. Patients with PD tend to have slightly elevated blood pressures and higher submaximal exercise treadmill heart rates compared with controls.⁵² One study also indicated that PD patients have higher serum cholesterol levels compared with patients with depression and with normal controls.⁵³ Patients with PD may also indirectly increase their likelihood of developing CAD through poor health habits such as smoking and drinking. Finally, PD patients may avoid exercise as exertion increases the cardiovascular symptoms they tend to fear.

Recognizing PD early in the medical consultation process may be beneficial to avoid unnecessary diagnostic investigations and to prevent further psychiatric and medical morbidity. Detection may be especially rewarding in light of the fact that proven effective treatments for PD do exist.

Treatments

Psychotropic medications and cognitive-behavioral interventions are the most widely studied treatments for PD. Improvement of the patient's condition with either or both of these treatment modalities is usually noticed fairly quickly (within 6 to 8 weeks or less), bringing relief to 70 to 90% of patients suffering from PD (with or without agoraphobia).⁵⁴⁻⁵⁶ A brief description of these treatments follows.

Pharmacotherapy

Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOs), and benzodiazepines have been the most widely studied psychotropes. Their efficacy has been established in double-blind placebo-controlled investigations.⁵⁷ Recent investigations with selective serotonin reuptake inhibitors (SSRI) suggest that this group of medication also has antipanic benefits.⁵⁸⁻⁶⁵

A recent meta-analysis of treatments for PD (with and without agoraphobia) suggested that antidepressants were the most effective pharmacologic intervention.⁵⁵ However, the side effects of TCAs—amphetamine-like stimulation in early stages of treatment and weight gain in prolonged therapy—are common reasons for treatment discontinuation.⁵⁷ Night time insomnia and daytime lethargy, along with dietary restrictions, have led to possible underuse of MAOs.⁵⁷ Although lower initial dosages may minimize some side effects of TCAs and MAOs, the more favorable side effect profile of SSRIs has made them a potential first-line pharmacologic treatment, especially for older patients at risk of cardiovascular complications.^{57,65} However, it should be noted that the antipanic action of most antidepressants takes at least 4 to 6 weeks.

In contrast to antidepressants, benzodiazepines provide almost immediate relief for PD patients. However, potential for abuse and dependence does not make benzodiazepines the treatment of choice for long-term therapy. To avoid addiction, some clinicians⁵⁷ suggest adding an antidepressant to the drug regimen several weeks after the initial symptoms have resolved with benzodiazepine treatment, and then slowly tapering the benzodiazepine dose.

Cognitive-Behavioral Interventions

Cognitive and behavioral techniques are also effective in the treatment of PD whether used alone or in combination. These include the reinterpretation of misinterpreted bodily sensations, applied and deep muscle relaxation training, breathing training, as well as exposure to panic-provoking cues. Margraf *et al.*,⁵⁶ in a review of methodologically robust cognitive-behavioral panic treatment studies, reported that about $\geq 80\%$ of patients receiving combined cognitive-behavioral treatments achieved a panic-free status as well as strong and clinically significant improvement in general anxiety, panic-related cognitions, depression, and phobic avoidance. Furthermore, these gains were maintained at a 2-year follow-up.

Managing Panic in the Cardiology Setting

Long-term management of the panic patient may be complex and unpractical for the cardiologist. We recommend that efforts be invested in the detection of a possible panic syndrome, initial management of the panic attacks, and referral to mental health professionals for further evaluation and long-term management (Fig. 1).

Detection of a panic syndrome is relatively simple and extremely rewarding. Once cardiologic investigation suggests a low probability for a cardiac-related chest pain, the patient should be reassured of this and a series of questions asked. First, specific questions about the somatic and cognitive symptoms of panic, particularly fear of bodily symptoms, as previously described in this article, should be asked. Second, the patient should be questioned about agoraphobic avoidance, such as travel restrictions and symptoms associated with specific situations. Finally, patients should be asked about recent stressful life events (job loss, separation, loss of a loved one, etc.). To validate the interview further, brief self-report questionnaires can be used to establish the probability of a panic syndrome.^{66,67}

Once the cardiologist has established a probable panic syndrome, the patient should be informed. A brief description of panic attacks should be provided and the patient should be reassured that effective treatment exists. Pollard and Lewis⁶⁸ provided a straightforward verbatim of information physicians can provide to patients who had experienced a panic attack. Patients should be discharged with a short-term, nonrenewable prescription for a benzodiazepine, along with a referral to a mental health professional.

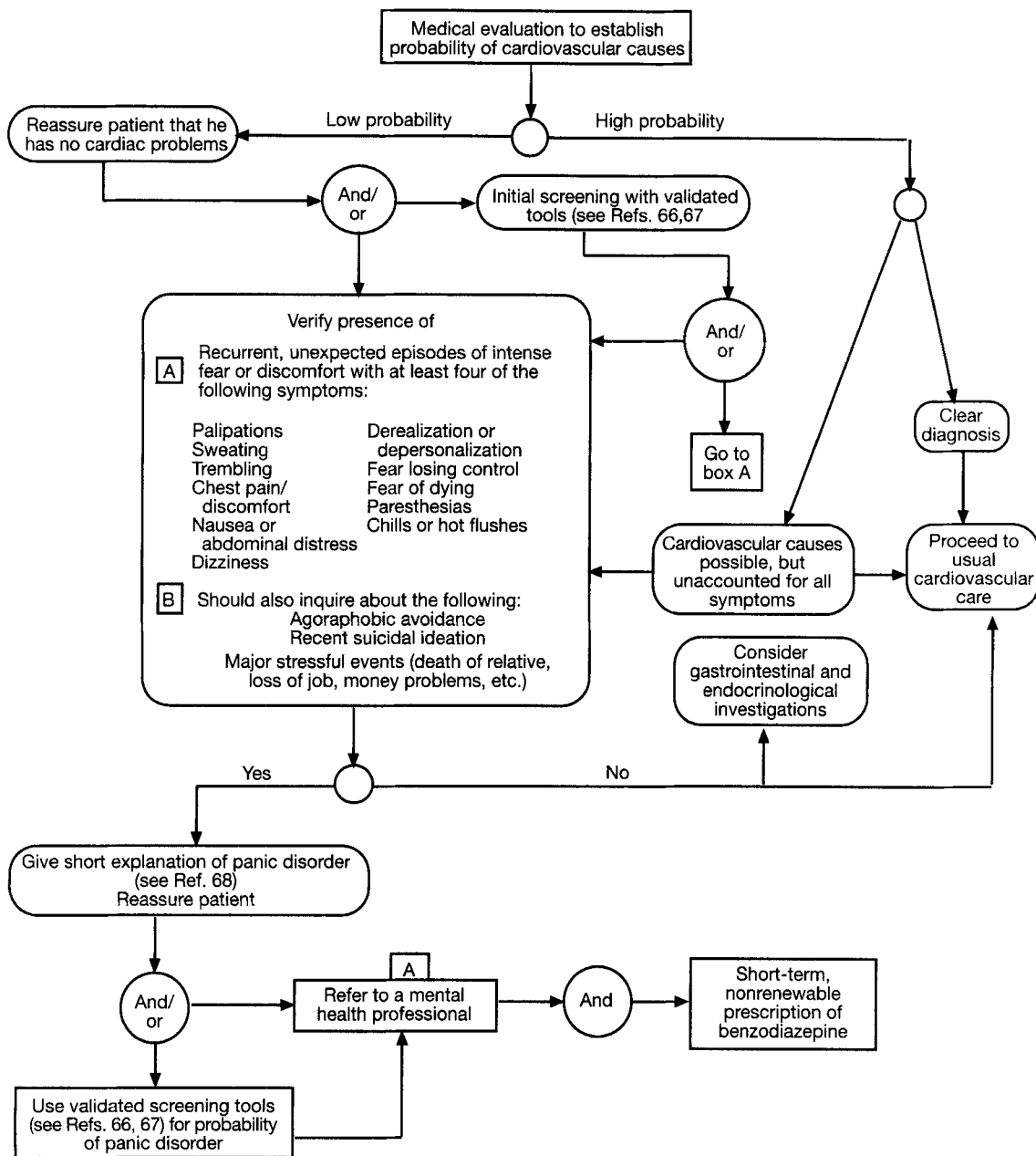


FIG. 1 Step-by-step procedure to facilitate recognition of possible panic disorder in patients with chest pain.

Conclusion

Panic disorder is a highly prevalent, serious, yet treatable disorder in patients with noncardiac chest pain. One of the major problems lies in the low rate of detection of PD by physicians, leading to repeated medical consultations, significant health care costs, increased psychiatric and possibly medical morbidity. Because simple reassurance of noncardiac chest pain may not suffice to relieve the patient, cardiologists should inquire about a probable panic syndrome, inform the patient, and refer him/her to mental health professionals for further evaluation and specific therapy.

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