

Panic Attack and its Correlation with Acute Coronary Syndrome – More Than Just a Diagnosis of Exclusion

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Abstract

The panic attack is able to mimic the clinical presentation of an acute coronary syndrome (ACS), to the point of being clinically indistinguishable without appropriate investigations. However, the literature actually demonstrates that the 2 conditions are more related than just being differential diagnoses. Through a review of the literature involving epidemiological studies, randomised controlled trials, systematic reviews and meta-analyses found on a Medline search, the relation between panic disorder and ACS is explored in greater depth. Panic disorder, a psychiatric condition with recurrent panic attacks, has been found to be an independent risk factor for subsequent coronary events. This has prognostic bearing and higher mortality rates. Through activation of the sympathetic system by differing upstream mechanisms, the 2 conditions have similar presentations. Another psychiatric differential diagnosis would be that of akathisia, as an adverse effect to antidepressant medications. An overview on the investigations, diagnostic process, treatment modalities and prognoses of the two conditions is presented. Panic disorders remain under-diagnosed, but various interviews are shown to allow physicians without psychiatric training to accurately pick up the condition. Comprehensive multidisciplinary approaches are needed to help patients with both coronary heart disease and anxiety disorder.

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Introduction

Acute coronary syndrome (ACS) is a life-threatening condition which benefits from prompt evaluation and proper treatment, such that it would be considered negligent for a physician not to consider it as a possible diagnosis in any patient presenting with acute symptoms of chest tightness or discomfort, palpitations, dyspnoea, diaphoresis, nausea and vomiting.

One condition that is able to mimic this clinical presentation is the symptomatology of a panic attack (Table 1). Such attacks are commonly seen in panic disorder, which is a condition characterised by such attacks on a recurrent basis, but they have also been present in other anxiety disorders, depressive disorders and even psychotic conditions. Contrary to the notion that there are often clearly identifiable precipitants, the first panic attack in panic disorder is often completely spontaneous. This is a point emphasised by the

Diagnostic and Statistical Manual of Mental Disorders,¹ present in the most updated version as of 2000 (DSM-IV-TR). This makes it all the more indistinguishable from an ACS, at clinical presentation.

From a historical perspective, the origin of the word “panic” is complex.² The adjective word “panic”, derived from the Greek, stressed initially the intensity of a feeling of unjustified, individual or collective, fear, similar to the reaction provoked, according to the mythology, by the intervention of the God Pan.

The year was 1862 when the surgeon Jacob Mendes Da Costa had described a condition observed in soldiers during the American Civil War, with acute symptoms of left-sided chest pain, palpitations, breathlessness, sweating and fatigue in response to exertion, but without physical abnormalities on examination to explain a causative mechanism for the clinical presentation. This would later go on to be known as

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Table 1. Symptoms of a Panic Attack, Compared with Acute Coronary Syndrome

Panic attack	Acute coronary syndrome
1. Palpitations, pounding heart, or accelerated heart rate	1. Palpitations
2. Sweating	2. Diaphoresis
3. Trembling or shaking	3. Pain (usually described as pressure, squeezing/ burning sensation across the precordium and may radiate to the neck, shoulder, jaw, back, upper abdomen, or either arm)
4. Sensations of shortness of breath or smothering	4. Exertional dyspnoea
5. Feeling of choking	5. Nausea
6. Chest pain or discomfort	6. Decreased exercise tolerance
7. Nausea or abdominal distress	7. Atypical presentations in elderly and/or diabetic: <ul style="list-style-type: none"> • Fatigue • Syncope • Weakness • Lightheadedness • Altered mental status • Asymptomatic
8. Feeling dizzy, unsteady, lightheaded, or faint	
9. Feelings of unreality (derealisation) or being detached from oneself (depersonalisation)	
10. Fear of losing control or going crazy	
11. Fear of dying	
12. Numbness or tingling sensations (paresthesias)	
13. Chills or hot flushes	
(>4 of the above symptoms, as defined by the DSM-IV-TR1)	

Da Costa's Syndrome,³ while other names for this condition included "functional cardiovascular disease", "cardiac neurosis", "irritable heart" or "soldier's heart". Da Costa's reports showed that patients recovered from the more severe symptoms when removed from the strenuous activity or sustained lifestyle that had caused them to begin with.

It has been conventionally thought that psychiatric diagnoses of "functional" conditions, such as panic disorder, are only considered upon careful exclusion of "organic" causes to explain a patient's symptomatology. Today, even psychiatrists disapprove of the labels of mental illness as "functional" and physical illness as "organic", because of the increasing body of literature demonstrating the definite presence of a link between mental and physiological processes.

Existing literature has demonstrated definite links between coronary heart disease (CHD) and anxiety disorders, in general terms. A previous review article evaluating panic disorder in cardiology patients⁴ had concluded that panic disorder was prevalent and under-diagnosed in several cardiology populations, with atypical angina in the absence of heart disease having a high likelihood of being panic disorder as evidenced by a positive response to alprazolam.

Previous local data on panic disorder^{5,6} are available, but no correlates with cardiac conditions had been made.

This review seeks to evaluate the literature between ACS and panic attacks (with focus on anxiety disorders, and panic disorder in particular), as well as to explore the relation between the 2 conditions. The articles quoted were identified through searches of Medline, as of December 2009.

Findings

(i) Correlation in Epidemiology

Anxiety disorders (panic disorder in particular) have been considered as one of the psychosocial factors touted as possibly contributing to CHD. This has been thoroughly studied, but previous findings do not seem to indicate that is the case. A systematic review in 2003 by an Expert Working Group of the National Heart Foundation of Australia⁷ found that CHD did not have an independent causal associations with anxiety disorders or panic disorders. Increased risk in these groups were explained by conventional CHD risk factors such as smoking, dyslipidaemia and hypertension. Systematic review of prospective cohort studies⁸ in 2002 had a somewhat-equivocal finding, with 4 out of 8 studies of anxiety having a strong or moderate association with CHD.

Recent evidence has again drawn the 2 conditions of panic disorder and CHD closer than before. A recent nationwide population-based study in Taiwan⁹ had identified panic disorder as an independent risk factor for subsequent acute myocardial infarction. This was based on the findings that more subjects with panic disorder (1 in 21, as compared to 1 in 36 without panic disorder) had experienced an acute myocardial infarction within a year, with a 1.75 times higher adjusted hazard of an acute myocardial infarction being statistically significant. A recent Turkish study¹⁰ found higher scores on the Hamilton panic agoraphobia (HAM-PA) rating scale particularly common among patients with diabetes mellitus, hypercholesterolaemia, and cerebrovascular disease. Another recent study echoed this finding of panic attacks being an independent risk factor for cardiovascular morbidity and mortality¹¹ in community-dwelling post-menopausal women, based on a 10% prevalence of panic attacks which was associated with CHD over a mean follow-up of 5.3 years [hazard ratio (HR), 4.20; 95% confidence interval (CI), 1.76-9.99].

Given the presentation of panic attack being potentially indistinguishable from the ACS, it is already well-established that panic attacks are frequently the cause of non-cardiac chest pain. Even so, the rates of panic disorder might be high enough to surprise some. In patients with atypical/non-anginal chest pain, with normal angiograms, the prevalence of panic disorder has ranged from 34% (32 out of 94) to 57% (59 out of 103).¹²⁻¹⁴ This translates to at least 1 in 3 subjects presenting with what may be an ACS, actually having a panic attack. The ability to mimic symptoms of acute coronary insufficiency has led to costly and unnecessary medical evaluations and prolonged mismanagement of underlying panic. What is more intriguing is that some of the data highlights patients who demonstrate that both conditions actually can and do co-exist. Prospective evaluation of consecutive admissions to a university hospital coronary intensive care unit¹⁵ demonstrated that panic disorder was present in almost a third of the patients. Based on 15 with panic disorder out of 27 subjects with negative cardiac findings, the study concluded that there was a high prevalence of panic disorder among subjects in whom cardiac disease had been excluded. However, 4 of the 19 with panic disorder (21%) also demonstrated positive cardiac findings, including 2 who had myocardial infarctions. Big studies on walk-in patients going to the emergency department with chest pain would afford a better understanding of the breakdown of proportions of people with either or both conditions. In one such study involving 441 patients,¹⁶ 250 (57% of 441) of them were found to have non-cardiac chest pain, of whom 74 (30% of 250) had a documented history of CHD. In turn, there were 25 (34% of 74) of CHD patients who met the criteria for panic disorder. The conclusion of the study regarded panic disorder as highly prevalent in patients with CHD that were discharged with non-cardiac diagnoses. This conclusion was echoed in other various small-scale studies of patients with CHD, where rates of panic disorder have ranged from 11% to 27%.¹⁷⁻¹⁹

(ii) Pathophysiology (Fig. 1)

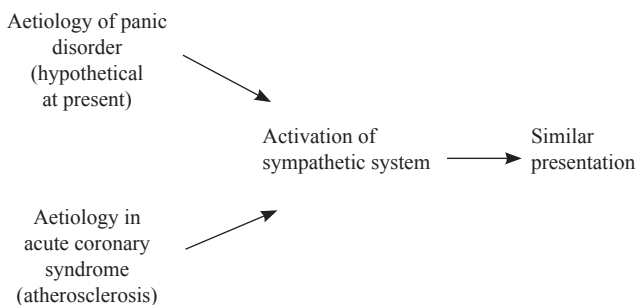


Fig. 1. Flowchart of the aetiology behind panic disorder and acute coronary syndrome, leading to a similar presentation.

The pathophysiology of ACS has been well described, with myocardial ischaemia mostly due to atherosclerotic plaques. These atherosclerotic plaques initially grow progressively, to cause clinically-significant symptoms at rest or with minimal exertion (unstable angina). Rupture of the coronary plaque with superimposed thrombosis results in occlusion of coronary vessels, leading to myocardial infarction where the myocardial tissue downstream of the occluded coronary vessel undergoes necrosis. The process of initiation, progression and complications of acute coronary arterial thrombosis can be related to Virchow’s triad for thrombogenesis, first described in 1856.²⁰ A minority of the cases, with normal or minimal narrowing of the coronary arteries, likewise experience symptoms of angina but this is due to vasospasm of a segment of an epicardial artery (Prinzmetal’s angina).

The pathophysiology of panic disorder remains less clearly defined, with various theories and proposed abnormalities/inefficiencies being non-mutually exclusive. These involve various neuronal regions (locus ceruleus model, neuroanatomic model) or neurotransmitter pathways (serotonergic, catecholamine/adrenergic, lactate, false suffocation carbon dioxide hypothesis, gamma-aminobutyric acid model). It remains with much to be elucidated. In particular, the neuroanatomic model²¹ involves the “fear network”, which has as its main point the central nucleus of the amygdala and includes the hypothalamus, the thalamus, the hippocampus, the periaqueductal gray region, the locus ceruleus and other brainstem structures.

At the biochemical level, panic attacks in individuals with panic disorder are thought to be due to metabolic acidosis as a compensatory response to chronic hyperventilation, where hypercapnic acidosis is responsible for the release of catecholamines (Fig. 1).²²

We today do not know as much as we would like to about the pathophysiology of panic, but it remains evident that there is activation of the sympathetic nervous system as a downstream mechanism. For that matter, activation of the sympathetic nervous system may be more relevant to generalised anxiety disorder (rather than panic disorder), which could help explain why generalised anxiety may sometimes be a sign present in the clinical presentation of ACS. Likewise, the pain and anxiety associated with a myocardial infarction also goes on to activate the sympathetic nervous system. This partly explains diaphoresis as one of the symptoms at presentation, as well as physiological consequences of systemic vasoconstriction, cardiac stimulation, activation of the renin-angiotensin-aldosterone system which enhances renal retention of water and sodium.

There are usually no acute implications of such sympathetic activation in the event of a panic attack when the coronary vessels are patent with adequate myocardial perfusion

present. This is in contrast with an increased myocardial demand in ACS, which could lead to arrhythmias and worsening of infarction with associated risks of morbidity. In the long run, however, the characteristic autonomic pattern found in patients with panic disorder, particularly the reduction in heart rate variability, are potential mediators of the cardiovascular impact of panic disorder.²³ This might, at least in part, explain some of the associations seen as above between the two conditions.

(iii) *Psychiatric Differential for Consideration*

One other psychiatric consideration of note in a presentation resembling an ACS, would be the activation syndrome. This might be poorly-characterised jitteriness or an anxiety syndrome (which may or may not involve panic attacks), in patients on antidepressant medications. Incidence rates published have been varied, from 4% to 65%.^{24,25} If a patient is able to volunteer the clinical history that they have been taking an antidepressant, then this possibility would have to be given due consideration.

(iv) *Investigations*

Two useful basic investigations in the diagnosis of ACS are the electrocardiogram (ECG) and the serum enzyme biomarkers. Dynamic T-wave changes and various ST elevation/depression are merely some of the features which may be detected on the ECG, but it is important to note that the unremarkable ECG cannot exclude the ACS. Various serum enzymes can serve as biomarkers for myocardial necrosis, with troponin I as the biomarker of choice due to it having the greatest sensitivity and specificity. Elevated serum levels of troponin I, detectable 3 to 6 hours after myocardial infarction, may even be considered diagnostic of the condition. This is because troponin is not usually found in the serum and usually released only in the event of myocardial necrosis. Another subunit of the troponin complex, troponin T, has a similar profile of release but may have false-positive results due to renal failure. Other markers include creatinine kinase-MB (CK-MB), with levels that rise within 4 hours after myocardial infarction, peaking at 18 to 24 hours, before subsiding over 3 to 4 days. Panic disorders cannot account for abnormal findings in the ECG and/or enzyme biomarkers; hence, more careful evaluation should be required if abnormalities should be present.

In psychiatric conditions, investigations are conventionally perceived only to be useful for exclusion of organic conditions. Examples would be the use of the thyroid function test to exclude possible hyperthyroidism and serum/urine toxicology to check for illicit substances which may result in anxiety or a panic attack, either directly or because of withdrawal. Psychiatric conditions are not routinely diagnosed by investigations, but some of the investigation

findings may also have bearing on the diagnostic process. A prolonged QT-interval on the ECG, for example, may be present in hyperventilation syndrome.

(v) *Diagnosis*

Certain considerations in the presenting history and physical findings may be useful to favour a diagnosis of panic disorders over the ACS. When asked, the subject may volunteer a history suggestive of agoraphobia, the fear of being in a situation traditionally involving public places and open spaces where help might not be available. Likewise, signs which may be observed in hypocalcaemia during hyperventilation such as Chvostek's sign (tapping the facial nerve at the angle of the jaw resulting in contraction of the ipsilateral face, usually seen as a twitch of the nose or lips) and Trousseau's sign (occlusion of the brachial artery, by inflating a blood pressure cuff around the arm beyond systolic blood pressure, inducing spasm of the hand and forearm with adduction of the fingers, flexion of the metacarpophalangeal joints and extension of the proximal and distal inter-phalangeal joints) may be noticed in the hyperventilation syndrome. The latter condition has been closely related to panic disorder. The presence of these factors makes the diagnosis of a panic disorder more likely, but they certainly do not negate the need to exclude an ACS.

Panic disorder and panic attacks often go unrecognised,²⁶ despite the 1.5% lifetime prevalence of panic disorder in the United States, due to them being seen in emergency departments, cardiac and other medical clinics.

Despite the pathophysiologic mechanisms mediating the association of anxiety disorders and cardiac symptoms being well-established, non-psychiatric physicians remain reluctant in diagnosing anxiety disorders in the population with recurrent chest pain but normal coronary arteries.²⁷

Perhaps emergency physicians are apprehensive about diagnosing patients with panic disorders, because they perceive that they do not have adequate training. However, an initiative to recognise and treat panic disorders in the emergency setting²⁸ demonstrated that no extra training was required. A mere screening measure and a 5-minute structured interview (Panic Disorder Module of the Structured Clinical Interview, SCID), allowed emergency physicians to reliably diagnose panic disorder and initiate the relevant pharmacologic treatment. Another test which may be employed is the Quick PsychoDiagnostics Panel (QPD),²⁹ which had reported favourable likelihood ratios (for both positive and negative) in the diagnosis of panic disorder.

(vi) *Treatment*

With the potential for mortality, ACS is a medical emergency which warrants management under close observation. Empirical treatment includes supplemental

oxygen, oral aspirin, intravenous glyceryl trinitrate and morphine. Beta-blockers and calcium channel blockers may be administered to reduce the risk of infarction. If ECG findings do not point towards an ST-segment elevation myocardial infarction (STEMI), administering intravenous heparin reduces the risk of progression of the infarction. In the event of a STEMI with onset less than 12 hours from point of assessment, myocardial salvage therapy is an option for consideration. Reperfusion may be attempted by either percutaneous coronary intervention (commonly known as coronary angioplasty) or thrombolysis (with streptokinase or recombinant tissue plasminogen activator). Beyond the acute phase, therapy with statins and other preventive measures such as modifications to lifestyle and diet also help to reduce the risk of further cardiovascular events and mortality rates.

At initial presentation, the panic attack may elicit the same level of concern from the emergency physician but upon excluding all other possible causes for the presentation, the physician's concerns can be allayed. Reassurance and advice on the regulation of breathing should be provided to the patient, with the comforting knowledge that the panic attack is mostly self-limiting. As a general guideline for treatment of psychiatric conditions, a holistic biopsychosocial approach is favoured. Treatment guidelines from the National Institute of Health and Clinical Excellence (NICE)³⁰ recommend the following treatment modalities, in descending order of evidence for the longest duration of effect: psychotherapy, pharmacological therapy and bibliotherapy. Cognitive behavioural therapy is the modality of choice for psychotherapy (and also the basis for bibliotherapy), while the serotonin-specific reuptake inhibitor (SSRI) is the first-line treatment for pharmacological therapy. Benzodiazepines are commonly used in the acute phase for panic attacks that do not respond to rest and reassurance, but the NICE guidelines explicitly mention that benzodiazepines should not be prescribed for the treatment of panic disorder.

(vii) Prognosis

ACS is regarded seriously by the physician, because of its life-threatening potential. It is a clinical syndrome encompassing a spectrum of conditions with varying severity, and consequently mortality rates. A third with STEMI die within 24 hours,³¹ while 15% with non-ST-segment elevation myocardial infarction (NSTEMI) die or experience re-infarction within 30 days.³² The presence of coronary artery disease should warrant the physician to be mindful of the development of psychiatric co-morbidities. In particular, approximately one-sixth of people recovering from myocardial infarction experience major depression while at least twice as many develop significant depressive symptoms soon after the myocardial infarction.^{33,34} This is a

particular cause for concern, as major depression is known to result in increased mortality and morbidity.³⁵

Panic attacks are often dismissed as a "false alarm" for an ACS. Without the prospect of immediate mortality, the panic disorder has a better outlook but even so, the panic attack is far from being purely "harmless" because of prognostic bearings in the long run. A study involving 34,000 male health professionals aged 42 to 77 years indicated that men with high levels on the Crown-Crisp index of phobic anxiety had a 6-fold increase in sudden deaths, unchanged after controlling for other risk factors.³⁶ The Nurses' Health Study found that among women (mean age, 54 years) with no history of cardiovascular disease, high levels of phobic anxiety were associated with increased risk of fatal CHD after 12 years of follow-up.³⁷ Mortality rates higher than the average population were found in male patients with panic disorder, due to cardiovascular causes.³⁸ Other psychiatric comorbidities may also develop as complications of panic disorder, and considerations should include alcohol or benzodiazepine abuse.

Conclusion

The panic attack may mimic an ACS, to the extent where it is clinically indistinguishable. However, they are far more than mere mutually-exclusive diagnostic entities, to be told apart by serum cardiac enzymes and the electrocardiogram. The presence of either condition warrants an adequate evaluation to ascertain if there might be a comorbid diagnosis, underlined by a common end-pathway of different pathophysiological mechanisms. The differential of akathisia as a side effect of antidepressant therapy also has to be considered. Comprehensive multidisciplinary approaches are needed to help patients with both CHD and anxiety disorder.

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