

Comorbid Effects of Anxiety and Panic Disorder on Cardiovascular Diseases and Its Management Approach: A Review

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Abstract: Recent data indicate that psychological and emotional disorders may play an important role in the natural history of cardiovascular diseases. Studies indicate that anxiety and panic disorders in cardiac patient influences mortality and morbidity. Panic disorder, a subtype of anxiety disorder, has been associated with increased risk of fatal myocardial infarction and sudden cardiac death in epidemiological studies. Anxiety and panic attacks may accelerate different direct and indirect pathways involved in the pathogenesis of cardiovascular disorders such as lifestyle risk factors, hypertension, myocardial perfusion, autonomic nervous system or hypothalamus-pituitary-adrenal axis, and other inflammatory processes. Panic disorder seems to correlate particularly with sudden death: which suggests that it may be considered one of the main inducers of life-threatening arrhythmias, rather than to be linked to the development and progression of ischemic heart diseases.

Keywords: Panic disorder, anxiety, cardiovascular diseases, epidemiology, pathophysiology, treatment.

I. Introduction

Anxiety: Anxiety disorders are classified under Neurotic, stress-related and somatoform disorders, divided under many subcategories like generalized anxiety disorders, panic disorders and attacks, phobic anxiety disorders. Anxiety disorders include disorders that share features of excessive fear and anxiety and related behavioral disturbances. Fear is the emotional response to real or perceived imminent threat, whereas anxiety is anticipation of future threat.¹ Such situations create a confusing situation as symptomatology correlates cardiovascular disorders, generally of sudden onset. Sometimes the level of fear or anxiety is reduced by pervasive avoidance behaviors.²

Panic Disorder: Panic attacks feature prominently within the anxiety disorders as a particular type of fear response. Panic attacks are not limited to anxiety disorders but rather can be seen in other mental disorders as well. Thus, while the anxiety disorders tend to be highly comorbid with each other, they can be differentiated by close examination of the types of situations that are feared or avoided and the content of the associated thoughts or beliefs.¹

Anxiety in general, and specific disorders, such as generalized anxiety disorder or panic disorder, have been independently associated with increased risk of fatal myocardial infarction and sudden cardiac death in epidemiological retrospective population studies and prospective trials, both in healthy subjects.³

Co morbid Effects of Anxiety & Panic Disorder on Cardiovascular Diseases

Recently, acute and chronic mental stress and many psychiatric disorders have been accepted as a cause of cardiovascular disease.^{4,5} In post-myocardial infarction patients a higher level of anxiety is found as an important predictor of cardiovascular outcome.⁶ Panic disorder, a subtype of anxiety disorder, poses difficulty in diagnosis due to considerable overlap in symptoms between panic symptoms and cardiac symptoms.⁷ Previous studies demonstrated an increased prevalence of panic disorder in patients with coronary artery disease⁸. Epidemiological studies reveal patients with panic disorder possessed higher risk of fatal myocardial infarction and sudden cardiac death compared to normal population. In addition, increased risk of a fatal events were found in presence of higher levels of anxiety.^{3,9}

Although panic disorder is usually more common in people without CAD than with CAD, it is still seen in a significant portion of those with CAD.^{10,11,12,13,14} In fact, studies suggest more panic disorder in patients with CAD than without it among cardiac patients referred for esophageal motility studies.^{10,15}

Panic disorder is associated with several cardiac abnormalities.¹⁶ In addition to patients with panic disorder having elevated standing heart rates, 10% were found having arrhythmias.¹⁷ Panic disorder is

associated with increased left ventricular mass and diameter,¹⁸ and patients with panic disorder have poorer cardiovascular fitness as demonstrated by lower maximum oxygen consumption and decreased exercise tolerance.¹⁹

Patients presenting to the emergency department with panic attacks were found to have increased levels of B-type natriuretic peptide.²⁰ Conflicting studies concerning an association with idiopathic cardiomyopathy have been reported.²¹⁻²³ Case reports also have linked panic disorder to a descending aortic aneurysm²⁴ and pulmonary hypertension secondary to an atrial septal defect with pulmonic valve disease.²⁵ However, strong association is found between panic disorder and mitral valve prolapse (MVP). The panic-MVP relationship has been well documented,²⁶ but MVP may not likely be the source of chest pain.²⁷ The presence of MVP doesn't alter psychiatric comorbidity^{28,29} or treatment response,³⁰ but the source of the linkage needs further research. There is no supporting evidence for a MVP-to-panic sequence as proposed.³¹ Indirect linkages via autonomic vulnerability or dysfunction have also been proposed.³² Likely explanation might be that the decreased left ventricular volume due to tachycardia seen in panic disorder produces the MVP.³³ Studies suggesting that the MVP disappears with remission of the panic disorder supports this sequence.³⁴ Thus, anxiety and panic disorders have been linked to several forms of cardiac disorders. In fact, this association is seen in studies from the United States³⁵ and around the world.³⁶ Although a relationship with MVP is relatively common, an association with CAD would be the most significant.

Another study³⁷ found an association between panic attacks and both ischemic and non-ischemic chest pain among women undergoing holter monitoring. In fact, in a large managed care database, an association between diagnoses of panic disorder and coronary heart disease was found even after controlling for covariates.³⁸ Similarly, women enrolled in a different study demonstrated an association between panic attacks and coronary heart disease.³⁹ If this association is true, myocardial ischemia could cause panic attacks via increased catecholamines or cerebral carbon dioxide levels secondary to lactate.⁴⁰

Finally, a relationship between panic disorder and CAD could exist through a relationship between panic disorder and cardiac risk factors. While a separate study⁴¹ reported mild association with hypertension, diabetes, obesity, or hyperlipidemia, Other studies reported no association with BMI and reported no association with hypercholesterolemia^{42,43}. People with panic disorder frequently have a family history of CAD and have a higher number of risk factors than controls.⁴⁴

First, panic disorder is linked to elevations in both systolic and diastolic blood pressures.^{45,46} Hypertension is found to be associated with both panic disorder^{47,48} and panic attacks^{49,50}, which was consistent across primary care and cardiology settings. This association may explain why 9% to 32% of patients with chest pain and normal results of coronary angiograms have hypertension.⁵¹

Second, anxiety and panic disorders are associated with lipid abnormalities. Specifically, total cholesterol levels are increased in those with panic disorder.^{41,52} This is supported by studies documenting elevated cholesterol levels in 8% to 55% of patients with chest pain and normal coronary angiograms.⁵¹ In addition, the presence of panic attack in patients with chronic obsessive-compulsive disorder was associated with elevated triglyceride and decreased high-density lipoprotein (HDL) levels.⁵³ Conflicting gender differences in lipid patterns have been found. In one study, women with panic disorder frequently have elevated low-density lipoprotein (LDL) levels with decreased HDL levels, while male patients frequently have elevated triglyceride levels.⁵² However, one study⁵⁴ found elevated LDL levels in men in response to pentagastrin-induced panic attacks but not in women. But associations between panic disorder and lipid abnormalities are not always found⁵⁵ and, if found, are primarily seen in psychiatric settings and in studies with small sample sizes.

Management Approach To Anxiety Disorders And Cardiovascular Diseases

Proper management of anxiety disorders and cardiovascular events is of utmost importance in clinical setting. Traditionally, anxiety and panic disorders are treated with either cognitive behavioral therapy (CBT), pharmacotherapy (antidepressants, high-potency benzodiazepines), or both. A recent survey of family physicians found that, of their patients with panic disorder who were not referred to mental health providers, 73% received selective serotonin reuptake inhibitors (SSRIs), 23% received high-potency benzodiazepines, and 18% received CBT.^{56,57} Comparison of CBT in primary versus secondary care settings found a more rapid response in primary care settings.⁵⁸ In fact, previous studies have shown that, after 20 minutes of instruction in the emergency department, exposure therapy decreases depression, avoidance, panic attack frequency, and emergency department visits.⁵⁹ Thus, CBT may be useful in the management of panic disorder in the presence of CAD.

Pharmacotherapy for panic disorder in CAD patients is more complicated. Although TCAs are effective in panic disorder, their cardio toxicity precludes them as first-line agents in the presence of CAD. In fact, tricyclics use has been linked to the development of MI.⁶⁰ In addition, imipramine therapy for panic disorder increases cardiovascular mortality risk secondary to increased blood pressure and heart rate.⁵⁸

Benzodiazepines can also be considered. Alprazolam treatment of panic disorder actually decreases total cholesterol⁶¹ and catecholamine response to exercise.⁶² In addition, although alprazolam does not decrease the frequency or severity of angina attacks in CAD patients taking propranolol, it does decrease symptom severity and reduce nitroglycerin use.⁶³ Other potential cardiovascular benefits of low-dose benzodiazepines include decreased myocardial contractility and increased blood flow.⁶⁴ In fact, benzodiazepines were found to delay onset of exercise treadmill test-induced ischemia⁶⁵ and to reduce MI rate⁶⁶ in patients with CAD. However, benzodiazepines should generally not be used in elderly patients or those with a history of substance abuse or personality disorders.

II. Conclusion

Although both are independent etiology of chest pain, panic disorder and coronary artery disease may coexist, particularly in primary care settings. The panic attacks may cause the patient with coronary disease to seek care but could also provoke a cardiac event, if co-morbid. Distinguishing between the 2 disorders can be difficult when based on clinical criteria alone.⁶⁷ If one condition is recognized, a search for the other is to be done in particular patient subgroups. All patients with co-morbid panic disorder and CAD should be treated with exercise and smoking cessation. Treatment with a “safe” antidepressant, high potency benzodiazepines, or CBT depends on the presence of co-morbid anxiety, panic disorder and cardiovascular risk factors.

References

- [1]. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). American Psychiatric Association. 2013.
- [2]. Maurizio G, Abrignani, Nicolò R, Abrignani V, Raffa A, Salvatore N, et al. Panic disorder, anxiety, and cardiovascular diseases. *Clinical Neuropsychiatry* 2014; 11(5): 130-144.
- [3]. Kawachi I, Colditz GA, Ascherio A, Rimm EB, Giovannucci E, Stampfer MJ, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation* 1994;89:1992-7.
- [4]. Esler M. Heart and mind: psychogenic cardiovascular disease. *J Hypertens* 2009;27:692-5.
- [5]. Ketterer MW, Mahr G, Goldberg AD. Psychological factors affecting a medical condition: ischemic coronary heart disease. *J Psychosom Res* 2000;48:357-67.
- [6]. Frasure-Smith N, Lesperance F, Gravel G, Masson A, Juneau M, Bourassa MG. Long-term survival differences among low-anxious, high-anxious and repressive copers enrolled in the Montreal heart attack readjustment trial. *Psychosom Med* 2002;64:571-9.
- [7]. Jeejeebhoy FM, Dorian P, Newman DM. Panic disorder and the heart: a cardiology perspective. *J Psychosom Res* 2000;48:393-403.
- [8]. Fleet R, Lavoie K, Beitman BD. Is panic disorder associated with coronary artery disease? A critical review of the literature. *J Psychosom Res* 2000;48:347-56.
- [9]. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation* 2005;111:480-7.
- [10]. Kane FJ Jr, Strohle J, Harper RG. Noncardiac chest pain in patients with heart disease. *South Med J*. 1991; 84: 847-852.
- [11]. Cormier LE, Katon W, and Russo J, et al. Chest pain with negative cardiac diagnostic studies. *J Nerv Ment Dis* 1988;176: 351-58.
- [12]. Carney RM, Freedl KE, Ludbrook PA, et al. Major depression, panic disorder, and mitral valve prolapse in patients who complain of chest pain. *Am J Med*. 1990 89: 757-760.
- [13]. Dammen T, Ekeberg O, and Arnesen H, et al. Detection of panic disorder in chest pain patients. *Gen Hosp Psychiatry* 1999; 21: 323-32.
- [14]. Beitman BD, Basha I, Flaker G, et al. Atypical or non-anginal chest pain. *Arch Intern Med* 1987; 147: 1548-52.
- [15]. Katon W, Hall ML, Russo J, et al. Chest pain: relationship of psychiatric illness to coronary arteriographic results. *Am J Med* 1988; 84: 1-9.
- [16]. Taylor CB, King R, and Ehlers A, et al. Treadmill exercise test and ambulatory measures in panic attacks. *Am J Cardiol* 1987;60: 48-52.
- [17]. Goldberg R, Morris P, Christian F, et al. Panic disorder in cardiac out-patients. *Psychosomatic* 1990; 31: 168-173.
- [18]. Kahn JP, Gorman JM, King DL, et al. Cardiac left ventricular hypertrophy and chamber dilatation in panic disorder patients: implications for idiopathic dilated cardiomyopathy. *Psychiatry Res* April 1990; 32(1): 55-61.
- [19]. Schmi NB, Lerew DR, Santiago H, et al. Effects of heart rate feedback on estimated cardiovascular fitness in patients with panic disorder. *Depress Anxiety* 2000; 12: 59-6.
- [20]. Vural M, Akbas B, Acer M, et al. Blood B-type natriuretic peptide level increases in patients who complain shortness of breath and chest pain in the course of panic attack. *Int J Cardiol* April 2007;117(2): e82-e83
- [21]. Kahn JP, Drusin RE, Klein DF. Idiopathic cardiomyopathy and panic disorder. *Am J Psychiatry* 1987; 144: 1327-1330.
- [22]. Magni G, Borgherini G, Canton G. Idiopathic cardiomyopathy and panic disorder in cardiac transplant candidates. *Am J Psychiatry* 1988; 145: 902-903.
- [23]. Griez EJJ, Mammari N, Loirat JC, et al. Panic disorder and idiopathic cardiomyopathy. *J Psychosom Res* 2000; 48: 585-7.
- [24]. Benjamin AB, Adityanjee, Wright J. Aortic aneurysm in the differential for panic attacks. *Psychosomatics* 2000; 41: 282-283.
- [25]. Sietsema KE, Simon JI, Wasserman K. Pulmonary hypertension presenting as a panic disorder. *Chest* 1987; 91: 910-912.
- [26]. Katerndahl D. Panic and prolapse. *J Nerv Ment Dis*. 1993; 178(1): 539-544.
- [27]. Savage DD, Devereux RB, and Garrison RJ, et al. Mitral valve prolapse in the general population. *Am Heart J*. 1983; 106: 577-581.
- [28]. Mavissakalian M, Salerni R, Thompson ME, et al. Mitral valve prolapse and agoraphobia. *Am J Psychiatry*. 1983; 140: 1612-1614.
- [29]. Dager SR, Cowley DS, Dunner DL. Biological markers in panic states. *Biol Psychiatry*. 1987; 22: 339-359.
- [30]. Grunhaus L, Gloger S, Birmacher B. Clomipramine treatment for panic attacks in patients with mitral valve prolapse. *J Clin Psychiatry*. 1984 Jan; 45(1): 25-27.

- [31]. National Heart, Lung, and Blood Institute: Clinical and epidemiological issues in mitral valve prolapse. Proceedings of a National Heart, Lung, and Blood Institute Symposium. *Am Heart J.* 1987; 113: 1265–1332.
- [32]. Klein DF, Gorman JM. Panic disorders and mitral valve prolapse. *J Clin Psychiatry* 1984; 2: 14–17.
- [33]. Ballenger JC, Gibson R, and Peterson GA, et al. “Functional” MVP in agoraphobia/panic disorder. Presented at the 139th annual meeting of the American Psychiatric Association; May 10–16, 1986; Washington, DC.
- [34]. Gorman JM. Panic disorder; focus on cardiovascular status. Presented at the 139th annual meeting of American Psychiatric Association; May 10–16, 1986; Washington, DC.
- [35]. Korczak DJ, Goldstein BI, Levitt AJ. Panic disorder, cardiac diagnosis and emergency department utilization in an epidemiologic community sample. *Gen Hosp Psychiatry.* 2007; 29: 335–339.
- [36]. Ormel J, Von Korff M, and Burger H, et al. Mental disorders among people with heart disease—results from World Mental Health surveys. *Gen Hosp Psychiatry.* 2007; 29: 325–334.
- [37]. Smoller JW, Pollack MH, and Wassertheil-Smoller S, et al. Panic attacks, daily life ischemia, and chest pain in postmenopausal women. *Psychosom Med.* 2006; 68: 824–832.
- [38]. Gomez-Caminero A, Blumenthal WA, and Russo LJ, et al. Does panic disorder increase the risk of coronary heart disease? *Psychosom Med.* 2005 67: 688–691.
- [39]. Smoller JW, Pollack MH, and Wassertheil-Smoller S, et al. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women’s Health Initiative Observational Study. *Arch Gen Psychiatry* 2007; 64: 1153–1160.
- [40]. Gallerani M, Manfredini R, and Meloni D, et al. Can panic disorder be considered as an angina equivalent? [letter]. *Eur Heart J.* 1995 16(12): 2013–2014.
- [41]. Dammen T, Arnesen H, and Ekeberg O, et al. Panic disorder in chest pain patients referred for cardiological outpatient investigation. *J Intern Med.* 1999 245: 497–507.
- [42]. Bajwa WK, Asuis GM, and Sanderson WC, et al. High cholesterol levels in patients with panic disorder. *Am J Psychiatry.* 1992; 149: 376–378.
- [43]. Roy-Byrne PP, Stein MB, Russo J, et al. Panic disorder in the primary care setting: co-morbidity, disability, service utilization, and treatment. *J Clin Psychiatry.* July 1999 60(7): 492–499.
- [44]. Katerndahl D. Panic and plaques: panic disorder & coronary artery disease in patients with chest pain. *J Am Board Fam Pract* 2004; 17: 114–126.
- [45]. Bystritsky A, Maidenberg E, and Craske MG, et al. Laboratory psychophysiological assessment and imagery exposure in panic disorder patients. *Depress Anxiety* 2000; 12: 102–108.
- [46]. Katon WJ. Chest pain, cardiac disease, and panic disorder. *J Clin Psychiatry.* 1990; 51: 27–30.
- [47]. Davies SJC, Ghahramani P, and Jackson PR, et al. Association of panic disorder and panic attacks with hypertension. *Am J Med* 1999; 107: 310–316.
- [48]. Noyes R Jr, Clancy J, Hoehn PR, et al. Prognosis of anxiety neurosis. *Arch Gen Psychiatry* 1980; 37: 173–178.
- [49]. Katerndahl D, Trammell C. Prevalence and recognition of panic states in STARNET patients presenting with chest pain. *J Fam Pract* 1997; 45: 54–63.
- [50]. Goodwin RD, Hamilton SP. Panic attack as a marker of core psychopathological processes. *Psychopathology* 2001; 34: 278–288.
- [51]. Chambers JD, Bass C. Chest pain with normal coronary anatomy. *Prog Cardiovasc Dis* 1990; 33: 161–184.
- [52]. Hayward C, Taylor CB, and Roth WT, et al. Plasma lipid levels in patients with panic disorder or agoraphobia. *Am J Psychiatry* 1989; 146: 917–919.
- [53]. Agargun MY, Dulger H, Inci R, et al. Serum lipid concentrations in obsessive-compulsive disorder patients with and without panic attacks. *Can J Psychiatry* 2004; 49(11): 776–778.
- [54]. Perez-Parada J, Jhangri GS, Lara N, et al. Delayed increase in LDL cholesterol following pentagastrin-induced panic attacks. *Psychopharmacology.* 2007; 193: 333–340.
- [55]. Kim EJ, Yu BH. Increased cholesterol levels after paroxetine treatment in patients with panic disorder. *J Clin Psychopharmacol.* 2005 Dec; 25(6): 597–599.
- [56]. Taylor CB, Hayward C. Cardiovascular considerations in selection of antipanic pharmacotherapy. *J Psychiatr Res* 1990; 24 (2). 43–49.
- [57]. Katerndahl D, Ferrer RL. Knowledge about recommended treatment and management of major depressive disorder, panic disorder, and generalized anxiety disorder among family physicians. *Prim Care Companion J Clin Psychiatry.* 2004; 6(4): 147–151.
- [58]. Fortune L, Gracey D, Burke M. Effect of service setting on treatment outcome: a comparison between cognitive behavioral approaches within primary and secondary care. *J Ment Health.* 2005; 14(5): 483–498.
- [59]. Swinson RP, Soulios C, and Cox BJ, et al. Brief treatment of emergency room patients with panic attacks. *Am J Psychiatry.* 1992; 149: 944–946.
- [60]. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications. *Am J Med.* 2000; 108: 2–8.
- [61]. Shioiri T, Fujii K, and Someya T, et al. Serum cholesterol levels and panic symptoms in patients with panic disorder. *J Affect Disord.* 2000; 58: 167–170.
- [62]. Stratton JR, Halter JB. Effect of a benzodiazepine (alprazolam) on plasma epinephrine and norepinephrine levels during exercise stress. *Am J Cardiol* 1985; 56: 136–139.
- [63]. Mendels J, Chernoff RW, Blatt M. Alprazolam as an adjunct to propranolol in anxious outpatients with stable angina pectoris. *J Clin Psychiatry* 1986; 47(1): 8–11.
- [64]. Zeegers A, Van Wilgenburg H, Leeuwijn RS. Cardiac effects of benzodiazepine agonists and antagonists in the isolated heart. *Life Sci* 1998; 63: 1439–1456.
- [65]. Rossetti E, Fragasso G, and Xuereb RG, et al. Anti-ischemic effects of intravenous diazepam in patients with coronary artery disease. *J Cardiovasc Pharmacol* 1994; 24: 55–58.
- [66]. Wheatley D. The value of anti-anxiety drugs in the management of cardiac disease. *Acta Med Scand Suppl.* 1982; 660: 219–230.
- [67]. David A. The Association Between Panic Disorder and Coronary Artery Disease Among Primary Care Patients Presenting With Chest Pain: An Updated Literature Review. *Prim Care Companion J Clin Psychiatry.* 2008; 10(4): 276–285.