Anxiety Disorders and the Syndrome of Chest Pain With Normal Coronary Arteries: Prevalence and Pathophysiology

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Recurrent chest pain in the presence of normal coronary arteries is a common and perplexing problem in primary care medicine and cardiology and is associated with significant morbidity and health care utilization. A series of carefully controlled prospective studies conducted over the past decade have suggested a strong association between this syndrome and the presence of anxiety disorders. Thirty percent to 50% of patients with recurrent chest pain and normal coronary arteries meet criteria for panic disorder. Generalized anxiety disorder may also be associated with this syndrome. In contrast, major depression seems strongly associated with the syndrome only when it presents as a comorbidity with panic disorder. Reluctance of nonpsychiatric physicians to diagnose and treat anxiety disorders in this population may reflect a lack of knowledge of the well-established pathophysiologic mechanisms that can mediate the association of anxiety disorders and cardiac symptoms. We propose a conceptual framework, derived from the neurologic literature and from recent studies using positron emission tomography and intravenous procaine challenge, which links anxiety and subjective cardiovascular symptoms to abnormal activity in neural circuits involving the anterior limbic system of the brain. This neuropsychiatric model of the role of anxiety disorders in the pathophysiology of chest pain in patients with normal coronary arteries is proposed to strengthen the rationale for the identification and treatment of anxiety disorders in this population by nonpsychiatric physicians.

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Chest pain is one of the most common complaints presenting in medicine and must always be taken seriously. Many causes of chest pain, such as myocardial ischemia, pulmonary embolism, and pneumothorax, are life threatening. In primary care and even in cardiology, however, most cases of chest pain are not related to ischemia or other potentially serious disorders. In fact, even in patients with chest pain sufficiently suggestive of ischemia to warrant invasive testing using coronary angiography, 20% to 40%[1,2] of studies turn out to be normal. In populations undergoing noninvasive testing, the rate of negative studies may be 50%[3,4] or higher. This presents two significant problems for clinicians. First, negative studies represent a major cost to the health care system. A conservative estimate of the annual cost of negative angiograms alone is $750 million. In addition, patients with chest pain and normal coronary arteries (referred to hereafter as the normal coronary artery chest pain syndrome) pose a diagnostic and management dilemma. Overall, such patients have an excellent cardiac prognosis, yet they frequently experience recurrent pain and distress, show persistent functional and occupational disability, and become persistent high utilizers of health care resources.[5,6]

During the past decade, a number of carefully conducted studies have indicated a high prevalence of psychiatric disorders among populations of patients with the NCA chest pain syndrome. In this article, we review the results of these studies and clarify the relationship between the presence of panic disorder, major depression, and generalized anxiety disorder (GAD) and the clinical syndrome of recurrent chest pain but normal coronary arteries. We will then discuss the difficulty that many physicians have had integrating the results of these studies into their clinical practice, with particular reference to the need to educate nonpsychiatric physicians about the likely pathophysiologic basis of cardiovascular symptoms in patients with psychiatric disorders. Our goal will be to provide a rational basis for the aggressive treatment of

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NCA patients for whom a psychiatric disorder is present, with the aim of improving the care of these patients and reducing the high morbidity and cost associated with this syndrome.

PANIC DISORDER AND THE NCA SYNDROME

Chest pain is one of the B symptoms of panic in the DSM-IV diagnostic criteria for panic disorder. Estimates of the prevalence of chest pain as part of the symptom complex of panic disorder have varied from 22% to over 70% of patients.[7,8] Since aspects of the presentation and the pattern of chronicity and disability in the NCA chest pain syndrome are similar to those seen in panic disorder, it is not surprising that the prevalence of panic disorder in NCA patients has been a major focus of investigation.

The first study attempt to prospectively assess NCA chest pain patients for psychiatric disorders was undertaken in the United Kingdom by Bass et al.[9] These investigators evaluated 99 consecutive patients undergoing coronary angiography. Overall, among patients with no objective evidence of coronary artery disease (CAD), 37% met criteria for the International Classification of Diseases-Ninth Revision (ICD-9) diagnosis of anxiety neurosis (encompassing both panic disorder and GAD). In contrast, only 6% of patients who were positive for CAD had this psychiatric disorder. In a similar study that used DSM-III diagnoses, Cormier et al.[3] at the University of Washington evaluated 98 chest pain patients with no previous cardiac history who had been referred for either treadmill cardiac stress testing or coronary angiography. In this study, equal numbers of patients had positive and negative cardiac studies, and 47% of the NCA patients had panic disorder (vs. 6% of CAD positive patients). Beitman and colleagues[10] evaluated a large series (N = 94) of outpatients with chest pain who had angiographically normal coronaries and found that 34% of these patients met strict criteria for panic disorder (at least one attack per week for the 3 weeks prior to the assessment). In a study of chest pain patients in the acute care setting, Carter et al.[11] evaluated 62 consecutive patients whose cardiac presentation was so convincing that they were actually admitted to a university hospital Coronary Care Unit (CCU) to rule out myocardial infarction. A total of 19 patients (31%) had panic disorder. Of the 27 patients without evidence of CAD, 15 (55%) had panic disorder, versus 4 (11%) of 35 CAD positive patients. At the other end of the spectrum of acuity, Carter et al.[4] studied 50 consecutive patients referred for cardiac stress scintigraphy to rule out coronary disease. Patients were included only if they had no previous documented cardiac disease, and retrospective chart analysis indicated that the majority of the patients' pain pattern was atypical for angina. Twenty-seven (63%) of the 43 patients with negative studies had panic disorder versus 1 (14%) of 7 CAD positive patients.

Since panic disorder is a descriptive diagnosis, a number of studies have been conducted to establish whether NCA patients with panic disorder actually have the same syndrome as those seen in psychiatric settings. In the majority of the studies cited above, the demographics and comorbidities of panic disorder patients with NCA chest pain syndrome parallel those of panic disorder patients in other settings. NCA patients with chest pain tend to be younger, more often female, and have much higher rates of comorbid agoraphobia and major depression than those who do not have panic disorder.[3,9,10] When the family proband interview method was used, the expected increased rate of a family history of panic disorder in first-degree relatives of NCA chest pain panic disorder patients has been observed.[12] Two small studies that used sodium lactate infusion or 35% CO_2 inhalation[12] to challenge NCA chest pain panickers showed the expected increased occurrence of panic symptoms, measured using the Acute Panic Inventory, in this group compared with controls. Finally, Carter et al. (Maddock RJ, Carter CS, Tavano-Hall, et al. Manuscript submitted) have reported that patients with chest pain and panic disorder undergoing myocardial stress scintigraphy showed resting hypocapnia as well as lower pCO_2 values throughout the procedure and that baseline hypocapnia was strongly predictive both of the presence of panic disorder and of the absence of coronary disease.

These studies suggest that in a variety of clinical settings and across the spectrum of acuity, patients who have chest pain and normal coronary arteries have a 30% to 60% likelihood of meeting DSM-III-R criteria for panic disorder. Demographic patterns, comorbidity findings, and the results of validating studies suggest that the diagnosis of panic disorder is valid in these patients. These striking findings have major implications for the diagnosis and treatment of patients with the NCA chest pain syndrome.

MAJOR DEPRESSION AND THE NCA CHEST PAIN SYNDROME

Several of the above studies of psychopathology among chest pain patients in cardiological settings evaluated patients for the presence of major depression. In the initial study by Bass et al.,[9] it was reported that the groups of patients with and without CAD did not differ in rates of major depression. In contrast to this finding, Cormier et al.[3] found that 23% of 49 NCA patients had only major depression (in the absence of panic disorder), versus a surprisingly low 6% of the 49 CAD positive patients. In the outpatient study of Bass et al.,[9] 12% of 94 post angiography NCA patients had major depression; however, 9 of these 11 patients had comorbid panic disorder. In the study by our own group of patients admitted to the CCU, 22% of 27 NCA patients had major depression, but, again, 5 of these

6 patients had comorbid panic disorder. Finally, in the Carter et al.[4] study of patients undergoing cardiac stress scintigraphy, we found that 16% of 43 NCA patients had major depression, but in all cases this was comorbid with panic disorder. The results of these studies suggest that when major depression is associated with the NCA syndrome, it is mostly as a comorbidity with panic disorder, and we would conclude that these patients' cardiac symptomatogy is related to the pathophysiologic processes of panic disorder rather than depression.

GAD AND THE NCA SYNDROME

Despite the operationalization of the diagnostic criteria for GAD in the DSM-III-R, there are surprisingly little data related to the prevalence of this disorder in patients with the NCA chest pain syndrome. In the Bass et al. study,[9] 37% of the NCA chest pain syndrome patients had anxiety neurosis. It is unknown what proportion of these patients would have met criteria for GAD. In a study of 56 patients referred for cognitive behavioral therapy to treat the NCA chest pain syndrome,[13] roughly equal proportions had GAD and panic disorder (22% and 27%, respectively). In a study that administered structured interviews to a group of 50 "pure" GAD patients who had been prescreened for psychiatric comorbidities, Carter and Maddock found that 48% reported histories of chest pain.[14] Eighty-seven percent of these 24 patients indicated that their chest pain was definitely not panic related, and a high proportion (62%) of patients reported that they tended to experience their pain during periods of excessive worry. The overall pattern of medical utilization associated with cardiac symptoms was similar in this sample of GAD patients to that of a group of patients with panic disorder. In contrast to these findings, in the only study to date to evaluate chest pain patients prospectively, (while blind to the patients' cardiac status), Carter et al.[4] for GAD found that although 35% of 43 NCA patients had this diagnosis, in every case GAD was present as a comorbid diagnosis with panic disorder. Hence, we conclude that while there are some data to suggest that there is an independent association between GAD and the NCA chest pain syndrome, further prospective studies in a variety of clinical settings are needed to clearly establish the clinical significance of this association.

SUMMARY OF FINDINGS TO DATE

The studies summarized above suggest that anxiety disorders are highly prevalent in patients with the NCA chest pain syndrome. On the basis of these results, the standard of care for this patient group should include an evaluation for the presence of anxiety disorders in all patients for whom coronary disease is excluded, since 30% to 50% of these patients will have panic disorder. Because only a small percentage of patients with chest pain and a diagnosis of panic disorder ultimately turn out to have coronary artery disease, some patients with chest pain, particularly those with atypical pain, an absence of risk factors for coronary disease, and a panic disorder diagnosis, should be considered for a trial of anxiolytic therapy before the physician proceeds with invasive cardiac testing.[3] However, despite the availability of these data, panic disorder remains vastly underdiagnosed in these populations.[4] We believe that this is because nonpsychiatric physicians are not aware of the well-established pathophysiologic mechanisms that can mediate the association of anxiety disorders and cardiac symptoms. In the absence of such a pathophysiologic understanding, nonpsychiatric physicians are understandably cautious in labeling as "psychiatric" the striking symptoms of a possibly serious somatic disease. In the section below, we propose a framework for understanding the relationship between anxiety and somatosensory symptoms such as chest pain. Our goal is to link the results of the descriptive and validation studies described above with a model of abnormal physiology in neural systems representing emotional responses. In doing so, we seek to strengthen the rationale for identifying and treating anxiety disorders in patients with the NCA chest pain syndrome.

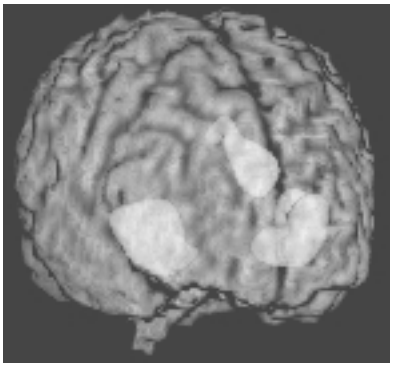
A PATHOPHYSIOLOGIC EXPLANATION OF CHEST PAIN IN PATIENTS WITH ANXIETY DISORDERS

There is no evidence that the chest pain experienced by patients with panic disorder is related to myocardial ischemia. In a systematic study of panic disorder patients, treadmill stress testing and ambulatory cardiac monitoring showed no evidence of cardiac ischemia despite the frequent occurrence of chest pain.[15] In the Carter et al.[4] study of cardiac stress scintigraphy patients, we also observed reports of chest pain during the test while the myocardial scan showed no abnormality.

In the absence of a myocardial cause, any plausible pathophysiology must, therefore, focus upon the central nervous system. For some physicians, this possibility is difficult to accept. This should not be the case, however, since CNS disease is frequently associated with perceptual and somatosensory symptoms. One dramatic example of this is temporal lobe epilepsy (TLE). The aura of seizures arising from the temporal lobes consists of cardiovascular, gastrointestinal, and emotional responses, most notably fear. These symptoms are clearly related to abnormal electrical activity in anterior limbic structures, notably the insular cortex, the anterior cingulate, and the amygdala. Similarities between the phenomenology of panic disorder and TLE have been emphasized by several authors,[16,17] and abnormal metabolic activity in limbic structures has been reported in panic disorder patients undergoing positron emission tomography (PET) studies.[18,19]

In studies conducted in our laboratory, a limbic system excitant, procaine hydrochloride,[20] was administered intravenously to young healthy normal subjects to explore the relationship between limbic structures and the somatic symptoms of panic. We found that robust activation of anterior limbic structures (see Figure 1) was accompanied by prominent paniclike symptoms that included cardiovascular symptoms such as palpitations and chest discomfort (Servan-Schreiber D, Perlstein W, Cohen J, et al. Manuscript submitted). Since there were no observed changes in heart rate or blood pressure during the time of the scan, these responses are presumed to correspond to the direct activation of somatosensory areas in limbic regions (such as the insular cortex).[21] The observations that seizure foci in the anterior limbic system can produce paniclike somatosensory symptoms in TLE and that pharmacologic activation of this neural system produces similar subjective symptoms provide a framework for understanding the relationship between abnormal limbic physiology in panic disorder and the somatosensory symptoms, such as chest pain, that can result in referral for cardiological evaluation.

Figure 1. PET Activation Map Rendered Upon Perspective View of MRI Scan of Normal Human Brain*



*Region of activation shown is all pixels in which rCBF was significantly greater ($p < .001$) after i.v. procaine than after placebo administration. Robust, bilateral activation is seen in the following anterior limbic structures: amygdala, insular cortex, and anterior cingulate cortex.

CONCLUSION

Anxiety disorders are major etiologic factors in the NCA chest pain syndrome. To communicate the relevance of anxiety disorders to the diagnosis and treatment of disorders such as the NCA chest pain syndrome, we need to educate our nonpsychiatric colleagues regarding the probable pathophysiologic basis of these symptoms. NCA chest pain is not cardiac; it reflects CNS dysfunction. The occurrence of cardiovascular symptoms and anxiety during the aura of TLE, and during intravenous procaine challenge, suggests that, in anxiety disorders, these symptoms reflect abnormal activity in anterior limbic circuits. Patients who have recurrent unexplained chest pain and normal coronary arteries should be evaluated for the presence of an anxiety disorder. Adoption of this practice by cardiologists and primary care physicians will result in improved treatment for this disabling condition and is likely to result in substantial savings to the health care system. Prospective studies implementing this approach to clinical pathways for chest pain diagnosis and management are strongly indicated.

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